

A NEW APPROACH TO IMPROVING THE CONTROL OF TYPE 1 DIABETES

Ruaan Pelzer

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Supervisor: Prof. E.H. Mathews

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ABSTRACT

Title: A new Approach to Improving the Control of Type 1 Diabetes

Key Terms: Basal insulin; blood glucose control; bolus calculation; bolus insulin; equivalent teaspoons sugar; ets; glycaemic control; insulin regime; insulin suggestion; long acting insulin; short acting insulin & Type 1 diabetes.

Blood glucose management in Type 1 diabetes is crucial in preventing several diabetic complications. Blood glucose management is a complex task requiring diabetics to carefully administer the correct dosages of insulin by taking their blood glucose levels, food consumption, exercise, stress, illnesses and several other factors into account.

Improved bolus calculation greatly aids in controlling blood glucose levels within a tight range. This study investigates how the ets-concept (Equivalent Teaspoons Sugar-concept) can be used to develop products to calculate insulin boluses. A cellular phone based software application was developed to calculate insulin boluses using the ets-concept. This product was tested in a clinical trial.

A blood glucose characterization procedure was also developed to characterize the blood glucose response of a Type 1 diabetic to carbohydrate ingestion and insulin administration. The characterization procedure was used during the clinical trial to characterize patients in order to customize the bolus calculation products for the specific diabetic user.

SAMEVATTING

Titel: A new Approach to Improving the Control of Type 1 Diabetes

Sleutel terme: Tipe 1 diabetes; bolus-insulien; kortwerkende-insulien; basale-insulien; langwerkende-insulien; ets; ekwivalente teelepels suiker; bloedsuikerbeheer; bolus berekening; insulien skedule berekening & insulien voorstelle.

Diabetiese komplikasies by Type 1 diabetese kan slegs voorkom word deur behoorlike bloedsuiker beheer toe te pas. Dié beheer is 'n kompleks en ingewikkelde taak. Diabetese moet daaglik besluit oor hoeveel insulien om toe te dien deur hul bloedsuikervlakke, voedsel inname, oefening, stres, siektes en ander faktore in ag te neem.

Akkurate berekening van insulien-bolusse is belangrik vir goeie bloedsuiker beheer. Hierdie studie het gebruik gemaak van die ets-konsep (Ekwivalente Teelepels Suiker-konsep) om insulien-bolus-berekeningsprodukte te ontwikkel. 'n Selfoon sagteware program was ontwikkel om insulien bolusse mee te bereken. Hierdie produk is verder getoets in 'n kliniese toets.

'n Bloedsuiker karakteriseringsprosedure is ook ontwikkel om die bloedsuiker-respons van Tipe 1-diabetese te meet vir beide koolhidraat inname en insulien toediening. Hierdie nuwe prosedure is gebruik gedurende die kliniese toets. Die waardes wat daarmee bereken is, is gebruik om die bolus berekeningsagteware in te stel vir die spesifieke diabeet wat dit gebruik het.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	1
ABSTRACT	2
SAMEVATTING.....	3
TABLE OF CONTENTS.....	4
NOMENCLATURE	7
LIST OF FIGURES AND TABLES.....	8
1 INTRODUCTION.....	2
1.1 THE NEED FOR THIS STUDY.....	2
1.2 CURRENT SYSTEMS	3
1.3 OBJECTIVES AND SCOPE OF STUDY	7
1.4 OUTLINE OF THE STUDY.....	7
1.5 CONTRIBUTIONS OF THIS STUDY	8
1.6 CONCLUSION.....	9
1.7 REFERENCES	10
2 IMPORTANCE OF BLOOD GLUCOSE CONTROL IN DIABETES	14
2.1 INTRODUCTION.....	14
2.2 DIABETES	14
2.3 TYPE 1 DIABETES	15
2.4 IMPORTANCE OF TIGHT GLYCAEMIC CONTROL	16
2.5 BASAL INSULIN VS. BOLUS INSULIN	22
2.6 PRE-REQUISITES FOR INSULIN-BOLUS CALCULATION.....	25
2.7 SUMMARY	27
2.8 REFERENCES	27
3 DERIVATION OF ENERGY EQUATIONS	32
3.1 INTRODUCTION.....	32
3.2 HISTORICAL IDEAS ON ENERGY FROM CARBOHYDRATES ARE WRONG	32
3.3 A MORE CORRECT WAY OF ESTIMATING METABOLIZED ENERGY FROM CARBOHYDRATES	34
3.4 TRUE METABOLIC EFFICIENCY OF CARBOHYDRATES.....	36
3.5 RELATIONSHIP BETWEEN INSULIN RESPONSE AND INGESTED CARBOHYDRATES	39
3.6 INSULIN IS A FUNCTION OF ENERGY.....	44
3.7 SUMMARY	45
3.8 REFERENCES	45
4 DERIVATION OF THE ETS-INSULIN-BOLUS EQUATIONS	49
4.1 INTRODUCTION.....	49
4.2 BLOOD GLUCOSE RESPONSE OF TYPE 1 DIABETIC TO INGESTED CARBOHYDRATES.....	49

4.3	BLOOD GLUCOSE RESPONSE OF TYPE 1 DIABETIC TO BOLUS-INSULIN	51
4.4	BLOOD GLUCOSE RESPONSE OF TYPE 1 DIABETIC TO ENERGY EXPENDITURE.....	53
4.5	BLOOD GLUCOSE RESPONSE OF TYPE 1 DIABETIC TO STRESS OR ILLNESS	55
4.6	INSULIN-BOLUS CALCULATION ALGORITHM.....	56
4.7	BLOOD GLUCOSE CHARACTERIZATION OF TYPE 1 DIABETICS.....	59
4.8	CONCLUSION.....	59
4.9	REFERENCES	60
5	DEVELOPMENT OF THE ETS-INSULIN-BOLUS CALCULATOR.....	63
5.1	INTRODUCTION.....	63
5.2	OBJECTIVES AND ADVANTAGES OF THE SYSTEM	63
5.3	USER REQUIREMENT STATEMENT	64
5.4	SOFTWARE APPLICATION	67
5.5	PDA VS. CELLPHONE BASED BOLUS CALCULATOR.....	89
5.6	SLIDE RULE BASED BOLUS CALCULATOR	90
5.7	INTELLECTUAL PROPERTY	92
5.8	SUMMARY	93
5.9	REFERENCES	93
6	IMPROVED BLOOD GLUCOSE CHARACTERIZATION	96
6.1	INTRODUCTION.....	96
6.2	EQUIPMENT	96
6.3	MEASUREMENT OF ETS (FOOD) SENSITIVITY	97
6.4	MEASUREMENT OF INSULIN SENSITIVITY	99
6.5	CHARACTERIZATION PROCEDURE AND VERIFICATION	101
6.6	CONCLUSION.....	103
6.7	REFERENCES	103
7	ETS-INSULIN-BOLUS CALCULATOR CLINICAL TRIAL.....	105
7.1	INTRODUCTION.....	105
7.2	PROBLEM AND HYPOTHESIS.....	105
7.3	PROTOCOL, QUESTIONNAIRES AND PIC'S.....	106
7.4	EXECUTION OF THE CLINICAL TRIAL.....	109
7.5	CLINICAL RESULTS	109
7.6	CONCLUSION	118
7.7	REFERENCES	119
8	CLOSURE.....	121
8.1	INTRODUCTION.....	121
8.2	SUMMARY OF CONTRIBUTIONS.....	121
8.3	RECOMMENDATIONS FOR FURTHER WORK	123
8.4	NOVELTY OF THIS STUDY.....	123
8.5	CLOSURE.....	124

APPENDIX A: PRELIMINARY PATENT.....	125
APPENDIX B: CLINICAL TRIAL PROTOCOL	183
APPENDIX C: PATIENT INFORMED CONSENT FORM.....	201
APPENDIX D: PRE-TRIAL QUESTIONAIRRE	205
APPENDIX E: POST-TRIAL QUESTIONAIRRE.....	209
APPENDIX F: ETS-INSULIN-BOLUS CELLPHONE USER'S GUIDE.....	213
APPENDIX G: CLINICAL DATA.....	241

NOMENCLATURE

Abbreviations

AACE	American Association of Clinical Endocrinologists
AADE	American Association of Diabetic Educators
ADA	American Diabetes Association
AUC	Area Under the Curve
CGMS	Continuous Glucose Monitoring System
DCCT	Diabetes Care and Complications Trial
EASD	European Association for the Study of Diabetes
ets	Equivalent Teaspoons Sugar
GI	Glycaemic Index
GL	Glycaemic Load
GUI	Graphical User Interface
II	Insulin Index
IP	Intellectual Property
MRC	Medical Research Council
NIDDK	National Institute of Diabetes, Digestive and Kidney Diseases
PCT	Patent Cooperation Treaty
PDA	Personal Digital Assistant
PIC	Patient Informed Consent
PIL	Patient Information Leaflet
R&D	Research and Development
RDA	Recommended Daily Allowance
SAMA	South African Medical Association
SAMAREC	South African Medical Association Research Ethics Committee
TDD	Total Daily Dose
WHO	World Health Organization

LIST OF FIGURES AND TABLES

Figure 1: Typical plasma insulin concentration for a Type 1 diabetic on a basal-bolus insulin regime.....	24
Figure 2: Relationship between mass loss and “isocaloric” kCal ingested for 9 different foods (kCal calculated in the conventional way).....	34
Figure 3: Relationship between mass loss and <i>ets</i> Cal.....	36
Figure 4: Measured insulin response as a function of mass of carbohydrates (CHO) consumed	39
Figure 5: Measured insulin response as a function of the glycaemic index (GI) of the consumed food	40
Figure 6: Measured insulin response as a function of <i>ets</i> consumed	40
Figure 7: Main menu interface of <i>ets</i> -insulin-bolus calculator	68
Figure 8: Logbook interface of <i>ets</i> -insulin-bolus calculator	72
Figure 9: Flow diagram for algorithm to navigate through food database.....	73
Figure 10: Interface for entering the time of a meal	74
Figure 11: Interfaces for navigating through the food and beverage database	74
Figure 12: Interfaces for food and beverage database search function.....	75
Figure 13: Flow diagram for algorithm to search for a specific food or beverage item	76
Figure 14: Interface for entering CHO content of a food or beverage item.....	77
Figure 15: Flow diagram for algorithm to add a food or beverage item not present in the food and beverage database.....	77
Figure 16: Interfaces for selecting the type and duration of exercise activity	79
Figure 17: Flow diagram for algorithm to add exercise activities to the logbook database	79
Figure 18: Interface for entering a blood glucose value.....	80
Figure 19: Flow diagram for algorithm to enter a blood glucose level.....	80
Figure 20: Interface for entering time of insulin-bolus calculation	84

Figure 21: Interface for entering pre-prandial blood glucose level.....	85
Figure 22: Interface for confirming values used for insulin-bolus calculation	85
Figure 23: Interface for displaying insulin bolus suggestion	87
Figure 24: Flow diagram for calculating totals from the logbook database and initial safety check.....	88
Figure 25: ets slide rule device for insulin-bolus calculation.....	90
Figure 26: Main parts of the ets-insulin-bolus slide rule	90
Figure 27: Medtronic CGMS	97
Figure 28: Blood glucose response for ets food sensitivity measurement	98
Figure 29: Blood glucose response for insulin sensitivity measurement	100
Figure 30: Pre-trial HbA1c levels of Type 1 diabetic test subjects.....	110
Figure 31: Post-trial HbA1c levels of Type 1 diabetic test subjects	111
Figure 32: Pre- and post-trial HbA1c levels of Type 1 diabetic test subjects	111
Figure 33: Reduction in HbA1c levels of Type 1 diabetic test subjects	112

CHAPTER 1

INTRODUCTION

Millions of Type 1 diabetics struggle daily to control their blood glucose levels. Although there are a few systems available to assist them with this task, these systems are complex and have not gained popularity amongst diabetics. This study focuses on a new and innovative way of calculating insulin dosages.

1 INTRODUCTION

1.1 The need for this study

Worldwide millions of diabetics struggle daily to control their blood glucose levels. This is a very difficult task especially for Type 1 diabetics. Their bodies are not able to produce the essential hormone insulin. These diabetics have to administer insulin daily in order to stay alive [1]. They also have to calculate and administer the correct insulin dosages in order to avoid several diabetic complications.

The World Health Organization (WHO) estimates that there are more than 170 million diabetics worldwide and it is predicted that this figure will double within the next 10 years. In South Africa alone there are more than eight hundred thousand diabetics [2]. Approximately 10% of the diabetic population is Type 1 diabetics. This means that there may be up to eighty thousand Type 1 diabetics in South Africa.

What makes this condition so difficult to manage, is that the diabetics have to balance their insulin with their food intake, exercises, stress and various other factors in order to control their blood glucose levels. At the same time, they should also take into account how their own bodies respond to all these above-mentioned factors [3,4]. Administering incorrect insulin dosages leads to several short and long-term complications [5,6]. In severe cases, insulin over dosage can be fatal.

Blood glucose control is a complicated engineering control problem. Type 1 diabetics are faced with this challenge daily without having any control systems knowledge -- most diabetics are neither scientists nor engineers. Many diabetics therefore follow rigid meal plans together with fixed insulin regimes [1]. This passive approach is not the best option, since it doesn't take pre-prandial blood glucose levels into account. This makes it difficult to adjust insulin dosages if necessary.

Most diabetics follow a more active approach that is based on a combination of experience from trial and error and information gathered from their medical doctors, dieticians and other sources. This approach may work well for some diabetics, but for many others it only sends their blood glucose levels on a roller coaster ride [3].

There is a definite need among Type 1 diabetics for a system or procedure that will allow them to control their blood glucose levels more accurately. Such a system or procedure should be easy to use, or it will not be used at all. Some commercial systems that have been available for a long time which will be discussed later have not been able to prove themselves due to their complexity, high cost and lack of user friendliness.

The diabetic market is very large [2]. Various major companies are actively doing R&D in this field. These companies, which include Novo Nordisk, LifeScan, Medtronic, Bayer, Roche, Lily, Sanofi Aventis, Smiths Medical etc., [7] are all competing in this lucrative market. From a business point of view, there is a definite opportunity for an accurate and easy-to-use system to promote improved glucose control amongst Type 1 diabetics.

1.2 Current systems

The first step toward conquering diabetes was taken in 1921 when Banting discovered (or isolated) the hormone insulin. This discovery gave hope to many Type 1 diabetic sufferers who were facing certain death [8]. Since then a lot of research and development has made the management of diabetes much easier. These developments include: different types of insulin with different timing profiles [9], more accurate equipment to measure blood glucose levels [10] and also more accurate systems to administer precise dosages of insulin [11].

All these developments are very important to manage Type 1 diabetes. The optimization of insulin dosages however, still remains a problem [12]. It is very difficult for most diabetics to estimate an appropriate insulin bolus by taking into account their pre-prandial blood glucose levels, food intake and exercise activities. *The main focus of this study is to address this problem.* A system was developed to calculate insulin boluses for Type 1 diabetics in order to promote better blood glucose control.

The ideal management tool would be an artificial pancreas. The predictable high cost of such a system means that it will be too expensive for most diabetics, especially those in developing countries (The insulin pump [13] and CGMS [14] which are both indispensable components

of this system, costs¹ between R11400 to R23000 for the pump and R25000 for the CGMS in South Africa and requires a R500 blood glucose sensor replacement every 3 days). Initial prototypes of this system have already been developed and tested by Medtronic [15,16] who received FDA approval for this integrated glucose regulating device in April 2006. The next generation insulin pump that is expected to be launched soon, integrates the pump and CGMS into one device, but unfortunately it is not yet a closed loop control system. Therefore the user still has to decide how much insulin should be administered.

A malfunctioning close-looped system administering insulin can indeed pose a severe safety risk to the patient. Insulin over dosage can be fatal. In the light of the risk and high cost of such systems there still seems to be a market for a manual insulin dosage calculation tool.² There are a few systems available to Type 1 diabetics to help them control their blood glucose levels. These are essentially all based on the carbohydrate counting concept.

Carbohydrate Counting

Carbohydrate counting uses a carbohydrate-to-insulin ratio to determine how many units of bolus-insulin to administer for a certain amount of carbohydrates. Carbohydrate counting is not a new concept. References in literature to carbohydrate counting appeared soon after the discovery of insulin in 1921.

Initially dieticians proposed an exchange system, where a fixed number of insulin units were administered for a fixed amount of carbohydrates [18]. Different types of foods and portions with the same amount of carbohydrates could then be exchanged for another while keeping the insulin-bolus dosage the same. This led to very rigid meal plans.

More recently, rules such as the 450-rule to determine the carbohydrate-to-insulin ratio, were introduced. This method is, however, based on the assumption that the average person eats 450 grams of carbohydrates per day (calculated using a daily energy requirement average for the average person). To calculate a bolus, the diabetic divides the number of grams of carbohydrates in a meal by the estimated carbohydrate-to-insulin ratio. The result indicates the number of bolus-insulin units to administer.

¹ Prices based on a 2005 Quotation by Medtronic, South-Africa.

² Most diabetics today cannot afford an insulin pump. Not all medical aids cover the cost of an insulin pump.

The bolus should then also be further adjusted to compensate for blood glucose levels prior to the meal, which may be too high or too low. If this blood glucose level prior to the meal is too high, the bolus should be increased, while the opposite should be done for low blood glucose levels. The problem here is that the diabetic needs to know by how many units of insulin the bolus should be adjusted.

It takes a lot of trial and error to eventually establish a good insulin regime for the patient. The estimation of the carbohydrate-to-insulin ratio, using an estimated figure of 450 grams of carbohydrates, is not practical. It is evident that better patient characterization is necessary for such a system to work.

Counting the grams of carbohydrates is also a difficult task [17] – one has to investigate the often-confusing³ labels of food items to be consumed. In addition the diabetic also has to take the portion sizes of the different meal items into account. It is an almost impossible task to estimate the amount of carbohydrates in some meals, especially for those prepared at home or in a restaurant, where nutritional information for those meals is hard to find.

The carbohydrate-counting method of calculating insulin boluses is difficult and has not proven to be very popular with the Type 1 diabetics so far. A more user-friendly system is therefore needed. Some of the bolus-calculation tools that have been developed and patented are discussed below.

Medtronic Bolus Wizard

The Medtronic Bolus Wizard [20] is a software application that is used in conjunction with the Medtronic Minimed insulin pump [13]. This application is in essence a carbohydrate counting device that makes calculations a bit easier [21]. Unfortunately, it does not provide the diabetic with a database to look up carbohydrate quantities. This means that the diabetic still has to guess how many grams of carbohydrates there are in a plate of food.

The advantages of this system include time specific blood glucose target levels. This means that different control levels can be specified for different times of the day. It also takes into account blood glucose levels prior to the meal (usually also the same time that the insulin-bolus is administered).

³ US Legislation requires food stuffs to be adequately labeled showing all macronutrients. In South-Africa many products on the shelves give no indication regarding their nutritional value. Furthermore product claims such as “Fat free” or “Diabetic friendly” can lead to wrong conclusions being made by diabetics.

A drawback of this system, however, is that it is only available to users of the Minimed insulin pump as an optional upgrade, which makes an already expensive system even more expensive. This implies that the system is only available to the small group of diabetics that are using this specific insulin pump.

It should also be mentioned that the Medtronic Bolus Wizard was retrofitted to Medtronic's existing pump design, which was not initially designed to calculate insulin boluses. Limited navigational abilities of the device, in conjunction with a small and limited display area, makes the device difficult to use.

DANA Magic™ Bolus Calculator

This bolus calculation device [22] is similar to Medtronic's Bolus Wizard. It uses carbohydrate counting to calculate insulin-boluses. It is also intended for use with an insulin pump. Since it is important to accurately determine the amount of carbohydrates [23] in a meal, the Magic™ Bolus Calculator therefore also provides a limited food database.

Other patented inventions

There are several patented inventions that claim to calculate insulin boluses. These devices all use carbohydrate counting in order to calculate insulin-boluses. Although the algorithms used, and the physical implementations, are slightly different, they all have the same function. The following U.S. patents are relevant:

- U.S. Patent number 6,691,043, "Bolus Calculator" [24];
- U.S. Patent number 6,554,798, "External infusion device with remote programming, bolus estimator and/or vibration alarm capabilities" [25] and
- U.S. Patent number 6,641,533, "Handheld personal data assistant (PDA) with a medical device and method of using the same" [26].

It should be noted at this stage that the bolus-calculation system that was developed and tested in this study, does *not* utilize carbohydrate counting and is therefore both different and novel when compared with these other patented inventions. (Novelty is a requirement for patent registration.)

1.3 Objectives and scope of study

The main objective of this study was to develop a system that allows a Type 1 diabetic, following a basal-bolus-insulin regime, to calculate reasonably accurate insulin boluses. A secondary objective of this study was to test this system on Type 1 diabetics, in order to verify the accuracy, ease-of-use and practicality of the system.

The scope of this study therefore includes the following:

- The development of an insulin-bolus calculation system for Type 1 diabetics following a Basal-Bolus insulin regime.
- Improving on the current, but outdated, carbohydrate counting concept to calculate insulin boluses by rather using the ets (Equivalent Teaspoons Sugar) concept.
- The development of a new improved characterization procedure to measure the insulin and ets sensitivity of a specific diabetic patient. These sensitivity values are important to customize the ets-bolus system for the specific diabetic patient – every patient's blood glucose level responds differently to insulin and ets uptake and expenditure.
- An initial clinical trial or pilot study was designed and conducted to establish whether this system's accuracy and practicality was acceptable for everyday use.

1.4 Outline of the study

This study document consists of eight chapters.

Chapter 2 discusses the importance of blood glucose control for Type 1 diabetics. Aspects such as insulin administration, dosage optimization and other needs of these diabetics are also discussed.

Chapter 3 is used to derive several important relationships in the human energy system. A new energy unit called ets (equivalent teaspoons sugar) is introduced. Thereafter simple relationships between ets and different elements of the human energy system are established.

Chapter 4 is used to derive equations that allow insulin dosage calculation, including both bolus and basal insulin. This is crucial to the design of a system to establish good blood glucose control in Type 1 diabetics.

Chapter 5 describes the products developed by using the research discussed in Chapters 3 and 4. These products include an insulin bolus calculation software application implemented on a cellular phone and PDA. A simple bolus calculation slide rule that was developed is also discussed.

Chapter 6 shows how patients can be characterized in terms of their blood glucose response to ingested food and insulin administered. These procedures are necessary in order to customize the insulin dosage calculation products mentioned in Chapter 5.

Chapter 7 deals with the clinical trial of the ets insulin bolus calculator. The design, execution and results of the clinical trial are discussed.

Chapter 8 is the closure of this study.

1.5 Contributions of this study

The systems developed in this study are based on the ets-concept (Equivalent Teaspoons Sugar) that was developed by Prof E.H. Mathews. Dr. C.P. Botha [27] used this concept during the research and development of the simulation model of the human energy system. Initial equations were derived by Mathews to calculate the insulin requirements of both healthy and diabetic patients.

The author of this thesis contributed to this study by completing the following tasks.

- The development of a new Type 1 diabetic patient characterization procedure. This procedure is used to determine the ets and insulin sensitivities of patients. It was used (and therefore tested) in the ets-insulin-bolus clinical trial. This procedure utilizes Medtronic's new technology namely CGMS (continuous glucose monitoring system) that recently became available. Although the procedure is slightly costly, it helps to establish a good initial insulin regime for the diabetic patient. The focus in this study

is patient specific characterization rather than using estimated values (e.g. the 450 rule [3]).

- The derivation of several equations to calculate the bolus-insulin needs for Type 1 diabetics, based on information received including food intake, exercise, pre-prandial blood glucose level of the patient as well as the ets- and insulin-sensitivity values of the diabetic patient during different times of the day.
- The development of an insulin-bolus calculation algorithm and implementation thereof in a software application that can be downloaded onto a cellular phone. This software application allows the diabetic user to calculate insulin boluses. For ease-of-use, food and exercise databases were integrated into this application.
- A protocol to conduct a clinical trial to test the accuracy and ease of use of the ets-bolus-insulin software application was written and submitted to an ethical committee. All supporting documentation, including a patient informed consent form (PIC), pre- and post-trial questionnaires, as well as a users manual for the system that was being tested, was also written and submitted to the committee by the author.
- Design, planning and execution of the clinical trial entitled “Glycaemic control of Type 1 diabetics using the ets concept” in conjunction with the medical practice of Dr. L. Johnson at the Montana Hospital in Pretoria.
- A preliminary patent to protect the intellectual property of the ets-bolus-insulin calculation system was written and registered with the help of patent attorneys DM Kisch in Sandton, Johannesburg.

1.6 Conclusion

This chapter has shown that there is a large market of diabetics that struggle to manage their blood glucose levels. There is a definite need for an improved bolus calculation system to promote better glycaemic control for Type 1 diabetics. It was shown that there are insulin-bolus calculators available, but also that these are based on the carbohydrate counting method and are neither very accurate, nor user-friendly. There is therefore a definite business

opportunity for the development, testing and commercialization of an improved insulin bolus calculation system.

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CHAPTER 2

IMPORTANCE OF BLOOD GLUCOSE CONTROL IN DIABETES

This chapter discusses the need for tight glycaemic control in Type 1 diabetes. A closer look is taken at the blood glucose control problem, diabetes complications and prevention thereof. The basal-bolus insulin treatment option is discussed, as well as the requirements to improve on this treatment option.

2 IMPORTANCE OF BLOOD GLUCOSE CONTROL IN DIABETES

2.1 Introduction

Diabetes is a serious condition, which when not properly diagnosed and treated, causes several short and long term complications. The pancreas of a Type 1 diabetic does not secrete the essential hormone insulin needed for blood glucose regulation. The diabetic therefore has to administer insulin to lower blood glucose levels.

Furthermore, the diabetic has to take into account the current blood glucose state, the effect that a specific meal will have on blood glucose levels and several other factors such as emotional stress, exercise and illnesses, when calculating an appropriate insulin dosage.

This chapter takes a closer look at diabetes, blood glucose regulation and the need for tight glycaemic control. Furthermore, diabetes complications and different approaches to controlling blood glucose levels will also be discussed. The problems with insulin-bolus calculations are discussed as well as several different pre-requisites to address this problem. These requirements will then be addressed in the chapters to follow.

2.2 Diabetes

There are mainly two types of diabetes, i.e. Type 1 diabetes and Type 2 diabetes. The early stage of Type 2 diabetes is often called pre-diabetes while diabetes during pregnancy is called gestational diabetes. Although all these types of diabetes result in elevated blood glucose levels that must be managed, there are many differences between them.

Type 1 diabetes is a condition where the pancreas does not produce insulin. Insulin is an essential hormone that plays a key role in blood glucose regulation. Without insulin present, blood glucose levels cannot be lowered. This condition will eventually be fatal. Type 1 diabetes is treated with insulin administration to control blood glucose levels. Type 1 diabetes accounts for roughly 10% of all diabetic cases worldwide.

Type 1 diabetes was formerly known as Insulin-Dependant-Diabetes-Mellitus (IDDM) or “Juvenile Onset Diabetes”. These are less correct descriptions of the condition, since Type 2 diabetics can *also* be dependant on insulin and can *also* be diagnosed with Type 2 diabetes at an early age.

Type 2 diabetes is a condition where the pancreas either does not produce *enough* insulin, the cells do not effectively respond to the action of the insulin, or a combination of both. This condition also leads to elevated blood glucose levels and should be treated with a combination of the correct diet, exercise, oral agents (medication) and insulin. About 40% of all diabetics will need insulin treatment at some stage of their lives.

Type 2 diabetes is most prevalent in older adults. However, it is recently being diagnosed increasingly in adolescents as well, in particular where obesity plays a role. Obesity is often the result of a sedentary lifestyle and poor eating habits.

Gestational diabetes is a form of diabetes that is mostly diagnosed during late stages of pregnancy and affects about 4% of all pregnant women. Gestational diabetes usually clears up after the pregnancy. There seems to be a tendency for women who had gestational diabetes during one or more pregnancies, to develop Type 2 diabetes at a later stage in their lives.

This study focuses primarily on Type 1 diabetes. Although this type of diabetes only accounts for about 10% of the diabetes population, their blood glucose control is much more complex and critical than that of most Type 2 diabetics. New methods were investigated to improve the insulin regimes of Type 1 diabetics in order to promote better blood glucose control. **Any reference to diabetes in this study implies Type 1 diabetes unless otherwise stated. Therefore any reference to a diabetic implies a diabetic with Type 1 diabetes unless otherwise stated.**

2.3 Type 1 Diabetes

Type 1 diabetes is far less common than Type 2 diabetes. This condition begins when the beta cells in the pancreas responsible for producing insulin become severely damaged. These cells are usually destroyed by the body’s own immune system. Destructive antibodies are produced by the immune system in order to destroy these cells.

When less than about 10% of these beta cells remain, blood glucose levels start becoming dangerously high. When this happens, the diabetic will quickly develop the severe Type 1 diabetes symptoms. If this condition is not diagnosed and treated soon enough, the diabetic may develop a serious life threatening condition called ketoacidosis.

This inability of the pancreas to produce insulin therefore requires the Type 1 diabetic to administer appropriate insulin dosages to mimic the insulin secretion of the pancreas. A slow and steady supply of insulin (called basal, long acting or background insulin) is required to allow cells to receive glucose for energy utilization (by unlocking the cells). Secondly, a faster supply of insulin (bolus, short acting or rapid insulin) is needed to store glucose originating from carbohydrates in meals. Lastly, insulin is also needed to lower blood glucose levels by storing any other excess blood glucose.

Type 1 diabetes treatment therefore requires an active approach from the diabetic patient to manage his/her disease. This is done by frequently monitoring blood glucose levels, making decisions regarding insulin dosages, living a healthy lifestyle (e.g. correct diet, physical activity and reducing stress) and regularly visiting an experienced medical care provider. Blood glucose levels should be carefully controlled to prevent diabetic complications.

The most difficult part of managing Type 1 diabetes is to achieve good control over blood glucose levels. This is a very involved task. Good blood glucose control requires experience, guidance (e.g. proper education of diabetes), motivation, persistence and a certain level of intellect. Blood glucose (glycaemic) control should not be neglected and therefore the next section discusses the importance of tight glycaemic control.

2.4 Importance of tight glycaemic control

There are currently several methods available to monitor glycaemic control. At present glycosylated hemoglobin (HbA_{1c}) is the most acceptable method seeing that these levels are strongly related to diabetes complications. Unfortunately HbA_{1c} levels do not give real time information on specific hyperglycaemic and hypoglycaemic events. It rather gives an indication of the average blood glucose control over the past 2-3 months [1].

The relationship between HbA_{1c} and mean blood glucose levels is shown in Table 1[2].

HbA _{1c}	Mean blood glucose (mmol/l)
4 %	3.6 mmol/l
5 %	5.6 mmol/l
6 %	7.5 mmol/l
7 %	9.4 mmol/l
8 %	11.4 mmol/l
9 %	13.3 mmol/l
10 %	15.3 mmol/l
11 %	17.2 mmol/l
12 %	19.2 mmol/l

Table 1: Relationship between HbA_{1c} and mean blood glucose levels

Currently the American Association of Clinical Endocrinologists (AACE) [3] guidelines for diabetes control is an HbA_{1c} level below 6.5%, while the ADA guidelines states HbA_{1c} lower than 7% to be desirable [4]. Few of the trial subjects who participated in the clinical trial discussed in Chapter 7 initially had HbA_{1c} levels within either of these target ranges.

A low HbA_{1c} doesn't necessarily indicate good glycaemic control. A diabetic may, for example, experience frequent undesirable hypoglycaemic and hyperglycaemic excursion but still have an HbA_{1c} level within the target range. This is because HbA_{1c} gives an indication of the average blood glucose level over time.

To help diabetics improve their blood glucose level through monitoring, there are a few options available. These include glucose measurements from urine or blood samples. The use of urine samples are less accurate, inconvenient and also outdated. Several blood glucose-monitoring devices are available on the market. These devices use a small blood sample, usually obtained from pricking a finger to measure the glucose level.

More recently, continuous glucose monitoring systems (CGMS) became available. These systems monitor the blood glucose level by taking glucose measurements every few minutes and storing this information. They are of great value and provide the diabetic or medical caretaker with a lot of additional information on which treatment decisions can be based [6].

The CGMS system is able to detect hyperglycaemic and hypoglycaemic excursions that may have been missed by taking isolated finger prick measurements.

Unfortunately, CGMS systems are very expensive and are therefore mostly used only by medical professionals. Most diabetics therefore are still left with finger-prick-type glucose monitors to control their blood glucose levels. Diabetics should test their blood glucose levels frequently to help them make decisions to control their blood glucose levels. Table 2 gives an indication of ideal vs. acceptable blood glucose values.

Blood glucose target	Ideal	Acceptable
Fasting	4-6 mmol/l	3-7 mmol/l
1 hour after meal	5-8 mmol/l	4-10 mmol/l
2 hours after meal	5-8 mmol/l	4-8 mmol/l
3 hours after meal	3-6 mmol/l	3-7 mmol/l
Hemoglobin (A _{1c})	6%	7%

Table 2: Ideal vs. acceptable blood glucose levels [7]

An incorrect insulin regime will result in blood glucose levels frequently falling outside of these acceptable target ranges. Some diabetics also deliberately control their blood glucose levels at higher than acceptable values, in fear of inducing hypoglycaemia through insulin over-dosage. These diabetics will have high HbA_{1c} levels. A lot of motivation and persuasion is often necessary to convince them otherwise.

Abnormal blood glucose levels fall into two categories [7]:

- Hypoglycaemia: less than the normal blood glucose level of less than 3.3 mmol/l or
- Hyperglycaemia: greater than the normal blood glucose level, i.e. greater than 7.8 mmol/l.

The exact diagnostic threshold values for these conditions vary slightly between different literature sources. Abnormal glucose levels are not desirable, causing several diabetes complications that are referred to as hyperglycaemic and hypoglycaemic complications. Obviously, the further blood glucose levels go from normal, the higher the risk and rate of development of complications.

Hyperglycaemic complications

Prolonged hyperglycaemia causes several long and short-term complications [8]. Here is a non-exhaustive list of some common hyperglycaemic complications.

- Cardio-vascular-disease (CVD): A study conducted by Haffner and Cassels [9] has found that hyperglycaemia considerably increases the risk factor for CVD and mortality from CVD.
- Micro vascular complications: The risk for developing neuropathy increases in patients whose HbA1c levels are higher than 7% (indicative of frequent hyperglycaemia) [10]. A study conducted by Reichard [11] has found that this risk is reduced in insulin dependent diabetics whose HbA_{1c} levels are below 7% due to intensified insulin treatment.
- Reduction in lens transparency: Kato et al. [12] found that the accumulated effect of hyperglycaemia is related to reduced lens transparency in patients with Type 1 diabetes.
- Retinopathy: The DCCT found a relationship between glycaemic exposure (HbA1c) to the risk of development and progression of retinopathy [13].
- Central nervous system (CNS) complications: Hyperglycaemia is one of the major causes of CNS complications in diabetics [14].
- Cancer risk: Several studies have found that hyperglycaemia increases the risk for several types of cancer [15].
- Ketoacidosis: Severe cases of ketoacidosis (fatty acids are broken down and used for energy instead of glucose, a result of too little insulin causing hyperglycaemia) may lead to a diabetic coma [16]. This condition can also be caused by infection, illness or severe emotional stress [7].
- Peripheral neuropathy: Hyperglycaemia increases the risk for neuropathy especially in lower extremities such as the feet causing conditions such as diabetic foot. In severe cases this may result in feet and legs being amputated [18].
- Hyperglycaemia causes reduced renal function of kidneys [19].

Most of these hyperglycaemic complications are long-term complications. Ketoacidosis occurs with hyperglycaemia and is usually the result of a lack of insulin. This is a very serious short-term complication. Hyperglycaemia is caused by several factors including stress, illness and incorrect insulin dosages (basal insulin dosage too low and/or bolus dosages too little for specific meals).

The blood glucose counter regulation system is responsible for the release of glucose into the blood from the glycogen stores (glucogenesis). This happens in response to counter regulation hormones such as glucagon, adrenalin and cortisol. When cells lack insulin, they are not able to receive glucose to utilize for their energy needs.

Signals are then sent to the counter regulation system to release more glucose into the blood. The real problem here is *not* a lack of glucose for energy, but rather a lack of *insulin* to promote the utilization of glucose for energy. This raises the blood glucose level further. The blood glucose level may continue to rise, while cells remain unable to utilize the glucose.

Hypoglycaemic complications

Hypoglycaemia affects the normal functioning of the brain and rest of the CNS both acutely and in severe cases chronically [20]. Mild hypoglycaemia can usually be self-treated, while severe hypoglycaemia requires external help to rectify the low blood glucose level. Acute hypoglycaemic excursions cause cognitive impairment. Hypoglycaemia can cause comas and convulsions.

Severe hypoglycaemia may even cause permanent cognitive impairment. Frequent hypoglycaemic events reduce the quality of life of a diabetic e.g. may lead to loss of employment or the ability to drive [21,22]. Unfortunately, frequent hypoglycaemic excursions affect the awareness of diabetics for hypoglycaemia, making it increasingly difficult for the diabetic to act when hypoglycaemia occurs [23]. Hypoglycaemia therefore also reduces the efficiency of the blood glucose counter regulatory system.

Although both hypoglycaemic and hyperglycaemic events are serious, hypoglycaemic events happen quickly and unexpectedly. Type 1 diabetics are therefore usually more scared of hypoglycaemia than hyperglycaemia, and therefore many of them will rather try to control their blood glucose level at a higher than acceptable level than to risk hypoglycaemia. Hypoglycaemia is often caused by insulin overdose; therefore care should be taken when calculating insulin dosages.

Diabetes Care and Complications trial (DCCT)

The DCCT was conducted over 10 years from 1983 to 1993 by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK). The study showed that tight glycaemic control slows the onset and progression of eye, kidney, and nerve diseases caused by diabetes

[5,8,13,22]. According to the findings *any* sustained lowering of blood glucose helps, even if the person has a history of poor control.

The key findings demonstrated that by reducing blood glucose levels eye disease risk is lowered by 76%, kidney disease risk by 50% and nerve disease risk by 60%. Furthermore, the DCCT used intensive management of diabetes. The elements of intensive management include: testing blood glucose levels four or more times per day, four daily insulin injections or the use of an insulin pump, adjusting of insulin dosages according to food intake and exercise, a diet and exercise plan and monthly visits to a health care team.

Blood glucose counter-regulatory system

The blood glucose counter regulatory system is a safeguarding mechanism to prevent hypoglycaemia. Its primary purpose is to help maintain a normal blood glucose level by preventing blood glucose levels from falling too low, thereby protecting the CNS. Several counter regulation hormones are released when blood glucose levels fall too low. These hormones then trigger the release of blood glucose from glycogen stores to raise the blood glucose level.

The primary counter regulation hormone is glucagon secreted by the pancreas when blood glucose levels fall below 3.8 mmol/l [24,25]. Other counter regulation hormones include:

- Adrenalin; secreted by the adrenal glands when blood glucose levels fall below 3.8 mmol/l [24],
- Growth hormone; secreted by the pituitary gland when blood glucose levels fall below 3.7 mmol/l [26] and
- Cortisol; secreted by the adrenal glands when blood glucose levels fall below 3.2 mmol/l [25].

These counter regulation hormones are often secreted even though blood glucose levels are *not* low. Emotional stress, for example, causes cortisol secretion, while adrenalin is a flight or fight hormone that is secreted when a person gets a fright, is shocked or endangered.

Unfortunately, because Type 1 diabetics are prone to hypoglycaemia, the efficiency of the counter regulatory system decreases with time as a lot of stress is put upon this system. Type

1 diabetics therefore gradually lose most of their counter regulation ability over time, making them even more prone to hypoglycaemic excursions.

The benefits of tight glycaemic control have been proven in many clinical trials [16,5,8,13,16,22]. Diabetic complications can only be eliminated by improving the glycaemic control of the diabetic. To improve the glycaemic control of a Type 1 diabetic the following issues should be addressed:

- Blood glucose levels should be monitored frequently to establish the current glycaemic state in order to make decisions regarding the type and measure of the corrective action that is needed.
- The insulin dosages should be matched to meals while taking pre-prandial blood glucose levels into account.
- Basal insulin dosages should be optimized and not lead to hypoglycaemia during prolonged fasting periods (e.g. during sleep) but also not lead to hyperglycaemia caused by under dosage.
- The effects that exercise has on blood glucose levels should be accounted for.
- Other factors such as emotional stress and/or illness should also be accounted for.
- The diabetic patient should be made aware of the risks of bad glycaemic control and be educated to improve this control. Cooperation from the diabetic is necessary and therefore a support structure should be there to motivate, guide and assist the diabetic patient.

2.5 Basal insulin vs. bolus insulin

Insulin is needed for several metabolic functions. It controls the glucose entry into cells, helps regulate the production and release of fats as energy fuel, and also controls the entry of certain amino acids, that create enzymes and structural proteins, into cells. For the purpose of blood glucose regulation, the control of glucose entry into cells by insulin is either to promote storage of glucose in a cell or to allow glucose to enter a cell to be utilized for energy.

Basal insulin

The cells in the human body constantly require energy for metabolic functions. Therefore insulin is constantly being released by the pancreas to allow blood glucose to enter these cells. The release rate of the insulin is carefully regulated. The glucose is then utilized for energy in

these living cells. Increased activity in cells will therefore require more glucose and hence more insulin. Type 1 diabetics therefore have to administer slow releasing insulin to mimic this function.

Long acting, basal or background insulin has a slow release rate and usually stays active for up to 24 hours. Table 3 shows several long and intermediate acting insulins with their onset, duration and peak times. These insulins, with slow but gradual release rates, allow the cells to receive glucose to be utilized for energy.

	Onset (h)	Peak (h)	Effective duration (h)
Long Acting			
Ultralente	6-10	10-16	18-20
Insulin glargine (Lantus)	2-4	peak less	24
Insulin detemir (Levemir)	2-4	-	20
Intermediate Acting			
NPH	2-4	4-10	10-16
Lente	2-4	4-12	12-18

Table 3: Long and intermediate acting insulin [28]

Basal insulin regimes should be established by taking the activity level, weight and insulin sensitivity of the diabetic patient into account. Increased activity levels, will require more glucose for energy and therefore also more insulin. If the daily basal insulin dosage is too high, the diabetic will be likely to encounter hypoglycaemic excursions. Many diabetics experience hypoglycaemia early in the morning while sleeping. The excess basal insulin causes blood glucose to be stored and therefore causes blood glucose levels to fall.

Basal insulin dosages that are too low cause elevated blood glucose levels. Because there is not enough insulin to allow glucose to enter cells to be utilized for energy, the glucose remains in the blood. The cells, however, need the glucose for energy and signals are sent to the blood glucose counter regulatory system to release more glucose into the blood for energy. This condition causes the diabetic to feel tired. During periods of high-energy expenditure (e.g. during intense exercise) blood glucose levels will rise very high if there is insufficient insulin.

There are different options available to establishing basal insulin regimes. These include:

- prescribing a single daily shot of long acting insulin such as Lantus with an effective duration of 24 hours (see Figure 1);
- prescribing a twice daily shot of intermediate acting insulin with an effective duration of 10-18 hours;
- prescribing a combination insulin mix of intermediate acting insulin and rapid or regular insulin for use at meal times; or
- using an insulin pump that automatically controls the release of insulin 24 hours a day.

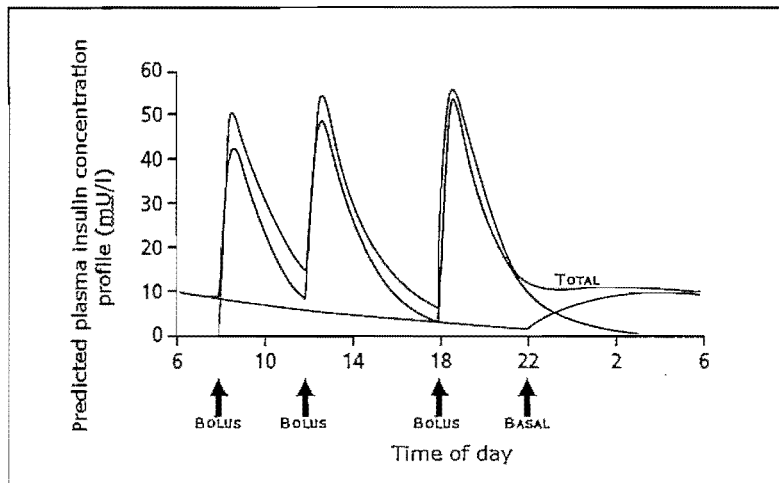


Figure 1: Typical plasma insulin concentration for a Type 1 diabetic on a basal-bolus insulin regime

Bolus insulin

Insulin is also needed to store excess blood glucose in cells (glycogenesis). Blood glucose should be stored in glycogen storage cells after glucose is absorbed into the blood as a result of carbohydrate digestion. Blood glucose should also be stored when blood glucose levels are too high. There are several reasons why this may happen, such as excessive secretion of counter regulation hormones (e.g. cortisol is secreted during periods of emotional stress).

Bolus insulin is usually administered shortly prior to a meal. Rapid acting or short acting insulin can be used. There are different brands with different onset, peak and duration times. Some trial-and-error is needed to choose a suitable bolus insulin. There are also several mixes available that combine regular insulin (bolus insulin) with intermediate insulin (basal insulin).

Table 4 shows several rapid and short acting insulins suitable for bolus insulin use.

The bolus insulin's release rate should be slow enough to prevent blood glucose levels from falling too low before carbohydrates from the meal are absorbed into the blood as glucose, but also be fast enough to prevent blood glucose levels from staying elevated for prolonged periods of time.

	Onset (h)	Peak (h)	Effective Duration (h)
Rapid acting			
Insulin lispro	< 0.3 - 0.5	0.5 - 2.5	3 - 4
Insulin aspart	< 0.25	0.5 - 1.0	1 - 3
Short acting			
Regular	0.5 - 1	2 - 3	3 - 6

Table 4: Rapid and short acting insulin suitable for bolus insulin administration

Bolus insulin dosage calculation should take into account the effect that the meal will have on the blood glucose level, the pre-prandial blood glucose level, the effect that the active insulin still left in the blood will have as well as the insulin sensitivity of the patient. Too much insulin bolus will result in hypoglycaemia, while too little bolus insulin will result in hyperglycaemia. Both of these conditions are undesirable and may lead to several complications.

The calculation of the insulin bolus is unfortunately a very difficult task. It has to be calculated for every meal, by taking several different factors into account. The next section investigates some of the requirements that are needed to calculate insulin bolus dosages.

2.6 Pre-requisites for insulin-bolus calculation

Insulin-bolus calculation should be done prior to any meal, which contains a substantial amount of carbohydrates, usually the three major meals of the day. Although a bolus can be administered for snacks between meals, it is usually not done by diabetics taking shots (insulin administration by using a syringe or insulin pen) because of the inconvenience. Diabetics using insulin pumps, however, often administer boluses for all meals and in-between snacks.

Bolus-calculation should take the following into account:

- Preprandial (prior to meal) blood glucose level: this level may be too high (hyperglycaemia), too low (hypoglycaemia) or within the target range.
- The meal: the effect of the meal on the blood glucose level of the diabetic depends on the type and quantity of carbohydrates in the meal, the ratio of carbohydrates, protein and fat to each other, as well as the fiber content of meal. As mentioned earlier, it is also a difficult task to estimate the amount of carbohydrates in a specific meal. This estimation is crucial to the calculation. A controversial factor, namely the Glycaemic Index (GI), also plays a role.
- Sensitivity to carbohydrates: the blood glucose response to carbohydrate intake is different for different persons and should be accounted for.
- Sensitivity of the diabetic to insulin: blood glucose response to insulin administration is different for different persons. Some diabetics are very insulin sensitive while others are very insulin resistant (insensitive to insulin).
- Energy expenditure affecting the blood glucose level: if exercise is to be performed shortly after a bolus administration, energy will be expended in the form of blood glucose that may either lower or raise the blood glucose concentration.
- Residual effect of previous insulin administration: there might still be active insulin left in the body which will lower the blood glucose level.

It is therefore clear that the calculation of the insulin-bolus is an involved and complex task. By taking all these factors into account, the diabetic has to calculate a number of short acting insulin units. From a control-systems engineering point of view, the first step should be to quantify the effect that each one of these factors will have on the system (blood glucose level) in isolation and then to try to derive a model which incorporates all these factors.

It is, however, very difficult to relate all these factors to each other. Food intake is quantified in terms of portion size, weight, grams of carbohydrates, proteins and fats, calories or kilojoules. Energy expenditure is quantified in terms of calories or kilojoules, which is derived from the intensity and duration of the exercise while taking into account the physical characteristics of the person exercising. Blood glucose levels are measured in mmol/l while insulin is measured in units.

Mathews [30] addressed this problem by establishing a universal energy unit that can be used to quantify energy in the human energy system. Glucose is the primary energy source of the human body so it would have been logical to consider glucose as an energy source. However, for several reasons, including ease of use, it was decided to rather use another form of sugar, namely sucrose (table sugar), as reference.

This energy unit was called *ets* which is short for Equivalent Teaspoons Sugar. Although it quantifies energy in terms of sucrose and not glucose, the conversion between the units is relatively easy. The next chapter will take a closer look at why and how the *ets* energy unit was derived.

2.7 Summary

Type 1 diabetes is a serious life-threatening condition if not properly managed. Hypoglycaemia (low blood glucose) and hyperglycaemia (high blood glucose) are both caused by bad blood glucose control, and can lead to short and long term complications, many of which are very serious. It is a difficult task to establish a suitable insulin regime for the specific patient and a need therefore exists for easier and more accurate systems that will enable Type 1 diabetics to improve their blood glucose control.

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CHAPTER 3

DERIVATION OF ENERGY EQUATIONS

Glucose is the primary source of energy in the human energy system. Glucose is used by living cells for their energy. It is important to first understand how the human energy system works, before attempting to address the blood glucose control problem. In this chapter several important equations are derived to help simulate the flow of energy in the human energy system.

3 DERIVATION OF ENERGY EQUATIONS

3.1 Introduction

The human energy system is very complex and even today it is still not completely understood. All the different complex subsystems, and the ways in which they interact with each other under different circumstances, make it a very difficult system to analyze. Furthermore, there are also interpersonal differences in physiology. When addressing problems of the human energy system, these differences in physiology should be accounted for in order to customize the treatment for the specific patient.

This chapter investigates how our understanding of energy in the human energy system can be improved. A thorough understanding of what happens to a healthy energy system will help to address the problems of a non-healthy system (e.g. diabetic person where the pancreas is not functioning properly). The focus of this chapter will be on energy, specifically the dependency on insulin for energy management and the way in which energy becomes available through digestion. Mathematical equations will be derived to characterize these quantities.

In Chapter 2 it was mentioned that the first step to understanding the human energy system would be to isolate the different elements. In this chapter a closer look will be taken at energy in the human body, where it comes from, how it is measured and how it is utilized. The equations derived in this chapter aim to simplify the human energy system to allow the simulation of the energy flow.

3.2 Historical ideas on energy from carbohydrates are wrong

Mathews [1] conducted a study to investigate the energy available from carbohydrates to a living body compared with the energy being measured in a bomb calorimeter. Over the past 100 years it has been assumed that the energy available from food for carbohydrates, proteins and fats are approximately 4, 4 and 9 kilocalories per gram respectively [2,3].

The conversion process in the digestive system is quite different from the way in which a bomb calorimeter measures energy. The hypothesis that these two processes will release different amounts of energy was therefore tested.

Nine groups, each consisting of eight healthy Sprague Dawley rats, were investigated. All rats were of the same age and fully-grown. They received the same kilocalories per body mass, determined by the following energy equation for recommended daily allowance (RDA) for rats [4]:

$$\text{RDA}[\text{kCal}] = 0.45 \times \text{body mass}^{0.75} \quad (1)$$

Each of the groups received different foods containing a high percentage of carbohydrates, namely:

1. Barley,
2. Provita,
3. Strawberry Pops,
4. Chickpeas,
5. Toasted Muesli,
6. ProNutro Flakes,
7. Special K,
8. All Bran Flakes and
9. Nutrific.

The energy content of the foods was measured with a bomb calorimeter. The mass loss/gain for each group was measured weekly for three weeks.

As the energy supplied to the rats (calculated in the conventional way) is their RDA, it is expected that the mass of the rats should not change. However, if there is a small mass loss/gain, (for example due to an error in Equation 1), this loss/gain should be the same for each group, since they all received the same amount of kCal per body mass.

The results in Figure 2, however, show that *all* the groups actually lost mass, some dramatically. The results also show that these losses were *not* the same for the different groups consuming different types of “isocaloric” food.

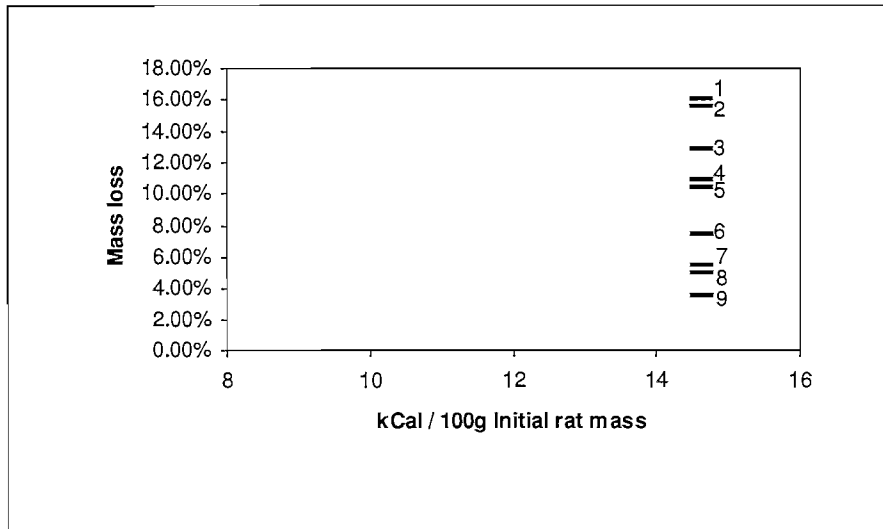


Figure 2: Relationship between mass loss and “isocaloric” kCal ingested for 9 different foods (kCal calculated in the conventional way)

The first conclusion is that contrary to conventional belief, a living creature cannot extract the full 4kCal of energy per gram of CHO. A second conclusion is that the amount of energy extracted differs for different types of CHO.

The implications of this experiment are far reaching. Incorrect calculation of carbohydrate energy raises questions about historical diets. The accuracy of the carbohydrate counting concept should therefore also be questioned.

3.3 A more correct way of estimating metabolized energy from carbohydrates

A better method than the bomb calorimeter based measurements used during the past century is needed to calculate the carbohydrate (CHO) energy available to a living creature (see section 3.2) [5]. The energy available from different CHOs can differ vastly. Based on these results, it is suspected that a metabolic conversion efficiency factor (η) of the body should be introduced to and applied to each different CHO.

The energy E_{CHO} [kCal] converted from a CHO with a metabolic conversion efficiency of η_{CHO} and a mass of m_{CHO} [g], including fiber, can be given by Equation (2). All losses,

including energy needed for digestion, incomplete digestion, gas production etc. are accounted for in η_{CHO} . Section 3.4 discusses how η_{CHO} can be measured.

$$E_{CHO} [kCal] = \eta_{CHO} m_{CHO} [g] 4 [kCal / g] \quad (2)$$

The energy content in any CHO should preferably be expressed by a unit that is easy to understand for the layperson, such as a teaspoon of sugar. Other advantages for choosing this unit are described in more detail in reference 6.

Equation (2) can be reformulated for one teaspoon of sugar (5g) to give the following:

$$E_{TeaspoonSugar} [kCal] = \eta_{Sugar} 5 [g] \times 4 [kCal / g] \quad (3)$$

The energy from each different CHO (E_{CHO}) can now be related to equivalent teaspoons sugar (ets). This is done by dividing Equation (2) by Equation (3) for sugar to find the amount of ets in any CHO, namely ets_{CHO} .

$$ets_{CHO} = \frac{E_{CHO}}{E_{Teaspoon Sugar}} = \frac{\eta_{CHO} m_{CHO} \times 4 [kCal / g]}{\eta_{Sugar} m_{Teaspoon} \times 4 [kCal / g]} = \frac{\eta_{CHO}}{\eta_{Sugar}} \frac{m_{CHO}}{5} \quad (4)$$

Using the glycaemic index (GI) [7], Mathews [8] proved that $\eta_{CHO} = GI/100$. Measured values for η_{CHO} for most of the important CHOs are therefore already available.

Using Equation (3) and keeping in mind that $GI_{sugar} = 65$, thus having a metabolic conversion efficiency (η) of 0,65, the equivalent energy in one teaspoon sugar (ets) is 13kCal as calculated using Equation (3)).

$$E_{TeaspoonSugar} [kCal] = \text{one } ets [kCal] = 0,65 \times 5 \times 4 = 13 [kCal]. \quad (5)$$

Now that the energy available from any CHO can be expressed in terms of ets (Equations (4) and (5)), a new way of calculating energy available to the body is proposed. This new energy value is called $etsCal$, to avoid confusion with standard kCal. It is calculated by the following equation:

$$\begin{aligned}
 etsCal = & 13[kCal/ets] \times ets_{CHO} + \\
 & 9[kCal/g] \times Mass_{Fat}[g] + \\
 & 4[kCal/g] \times Mass_{Protein}[g]
 \end{aligned}
 \tag{6}$$

Figure 3 was constructed from experimental data obtained from the experiment mentioned in section 3.2. A linear relationship is found between the *ets* Cal values of a food containing CHO and the % mass loss with a resulting Pearson's R^2 value of 0.68. This shows that the *etsCal* equation is more representative of the energy conversion of CHO in a body than the constant 4kCal/g historically used. It is predicted that similar efficiency factors can be found for both proteins and fats.

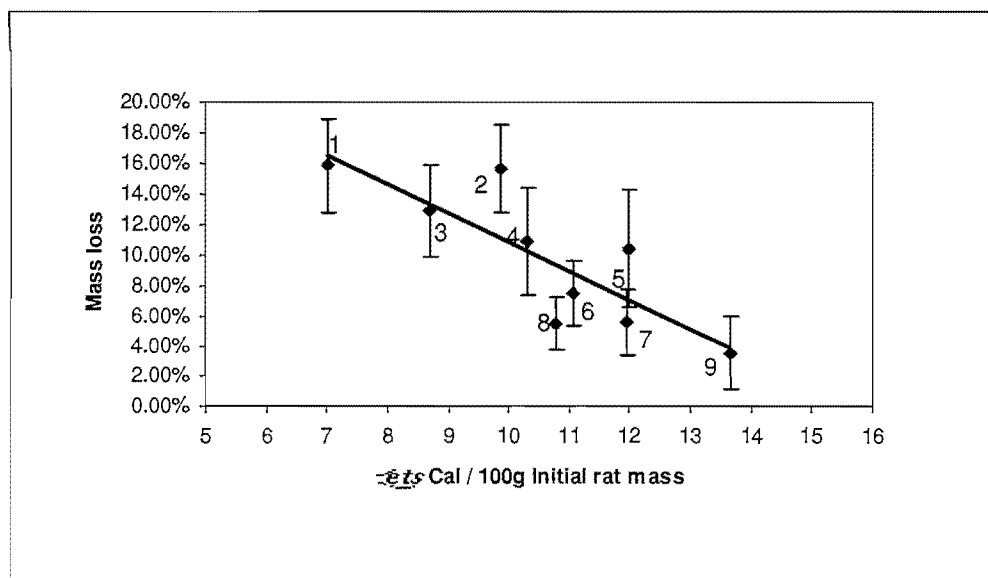


Figure 3: Relationship between mass loss and *ets* Cal

3.4 True metabolic efficiency of carbohydrates

It was shown by Mathews [9] that the conventional method of measuring energy available to a living body through digestion is not correct. Section 3.3 proposed a better way of estimating the energy from CHO. In order to accomplish this, the true metabolic efficiency of the specific CHO should be found.

Only CHO in a meal is directly metabolised into blood sugar during digestion. The “metabolic conversion efficiency” (η_{CHO}) of CHO estimates the amount of energy which is converted into blood sugar by a typical person. All losses, including energy needed for digestion, incomplete digestion, gas production, etc. are accounted for in η_{CHO} . This value can

be measured (as discussed later) and is a property of the meal. It depends on many factors including the content of dietary fibre, fat and protein in the meal therefore also the Glycaemic Index of the meal.

Energy from CHO which can be utilised by a person (E_{CHO} [KJ]) in the form of blood sugar is then a function of:

- the mass of CHO (including fibre) in the meal (m_{CHO} [g]);
- the full energy content per mass of the CHO (k_{CHO} [KJ/g]) measured outside the body by means of a bomb calorimeter; and
- the metabolic conversion efficiency (η_{CHO}) of the meal which accounts for how efficient the energy can be extracted inside the body.

The correct equation for CHO energy in a meal which can be utilised inside the body (E_{CHO}) is then shown by:

$$E_{CHO} = \eta_{CHO} m_{CHO} k_{CHO}. \quad (7)$$

Efficiency of metabolising the effective CHO from a meal (Equation (7)) into blood sugar varies between different people. This personalised CHO efficiency can be represented by the term f_{CHO} . (Remember that f_{CHO} is a function of a specific person, while η_{CHO} is a function of a meal.) The total energy absorbed in the blood for a specific person is then given by

$$E_{Absorb} = f_{CHO} E_{CHO} = f_{CHO} \eta_{CHO} m_{CHO} k_{CHO}. \quad (8)$$

As E_{Absorb} [KJ] is the CHO energy converted into blood sugar for a specific person, E_{Absorb} can also be found by means of blood sugar measurements for that specific person. First the response curve for blood sugar concentration ($\int BS(t) dt$) should be integrated over a period during which the blood glucose rises above basal level. This period is usually in the order of 120 minutes and is the period used in Glycaemic Index (GI) methodology [10]. The resulting integral value is called Area Under the Curve (AUC).

AUC now gives the concentration of blood sugar in [mmol/l].min. To find the total amount of extra glucose in the blood due to the meal, the concentration should be multiplied by the total

volume of blood of the person (Vol) [l] Finally, E_{Absorb} [KJ] is then found by multiplying by e [KJ / mmol] , the energy value of glucose and dividing it by the integration period of 120 minutes.

$$E_{Absorb} = \frac{Vol.e}{120} \int_{t_0=start\ of\ meal}^{t=t_0+120\ min} BS(t)dt = \frac{Vol.e}{120} .AUC \quad (9)$$

The energy absorption for a CHO relative to that of glucose is then given by the following equation (utilising Equations (8) and (9)) :

$$\frac{E_{Absorb|CHO}}{E_{Absorb|Glu\ cosine}} = \frac{120.Vol.e.AUC|_{CHO}}{120.Vol.e.AUC|_{Glu\ cosine}} = \frac{f_{CHO}\eta_{CHO}m_{CHO}k_{CHO}}{f_{Glu\ cosine}\eta_{Glu\ cosine}m_{Glu\ cosine}k_{Glu\ cosine}} \quad (10)$$

Accounting for the facts that for the same person, $f_{CHO} = f_{Glu\ cosine}$, $k_{CHO} = k_{Glu\ cosine} = 4[kCal / g]$ as measured in a bomb calorimeter and $m_{CHO} = m_{Glu\ cosine}$ (eating the same amounts of CHO and glucose namely 50[g]) and assuming $\eta_{Glu\ cosine} = 1$, i.e assuming 100% metabolic conversion efficiency for ingested glucose to blood glucose (it will be slightly less), the following equation results:

$$\eta_{CHO} = \frac{AUC|_{CHO}}{AUC|_{Glu\ cosine}} \quad (11)$$

But according to the definition of GI

$$GI_{CHO} = 100 \times \frac{AUC|_{CHO}}{AUC|_{Glu\ cosine}} \quad (12)$$

By comparing Equations (11) and (12) it is proven that the conversion efficiency (η_{CHO}) of a CHO (times 100) is its GI value! The conversion efficiencies of many CHOs are therefore available through their GI values. This conclusion therefore indicates that the current thinking on GI is wrong.

3.5 Relationship between insulin response and ingested carbohydrates

In the previous sections it was shown that carbohydrate energy in food containing carbohydrates can be quantified in ets, and the total energy content in etsCal. In non-diabetic subjects, there is a relationship between increase in blood glucose absorbed into the blood and insulin secretion. After consuming a meal containing carbohydrates, insulin is secreted by the pancreas to lower the blood glucose level by storing the excess glucose as glycogen.

An experiment conducted by Lee and Wollever [14] involved measuring the insulin response of several non-diabetic test subjects ingesting different carbohydrate amounts ranging from 0 to 100 grams with different GI values ranging from 23 to 100. Botha and Mathews analysed these responses and calculated the measured insulin response as a function of (a) mass of carbohydrate (b) GI and (c) ets of the test meals ingested. The resulting insulin responses are shown in Figure 4, Figure 5 and Figure 6.

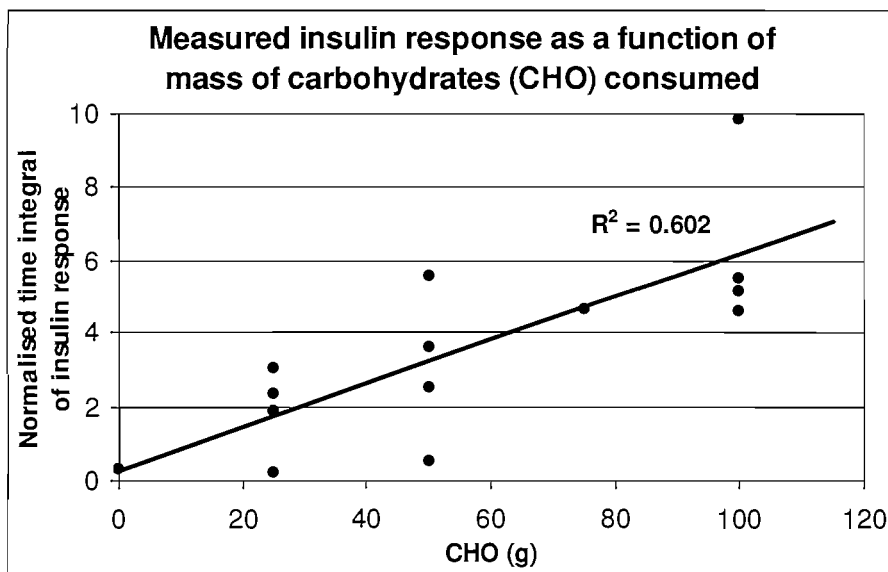


Figure 4: Measured insulin response as a function of mass of carbohydrates (CHO) consumed

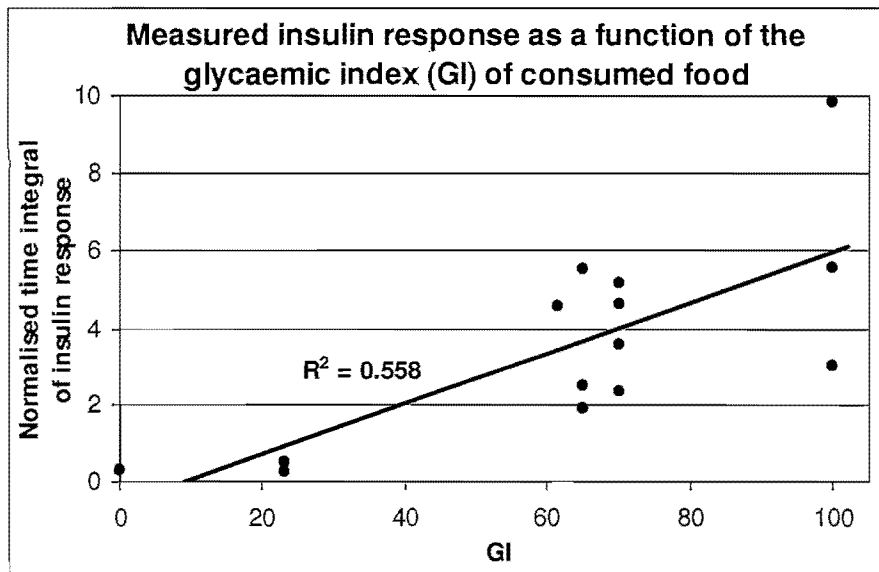


Figure 5: Measured insulin response as a function of the glycaemic index (GI) of the consumed food

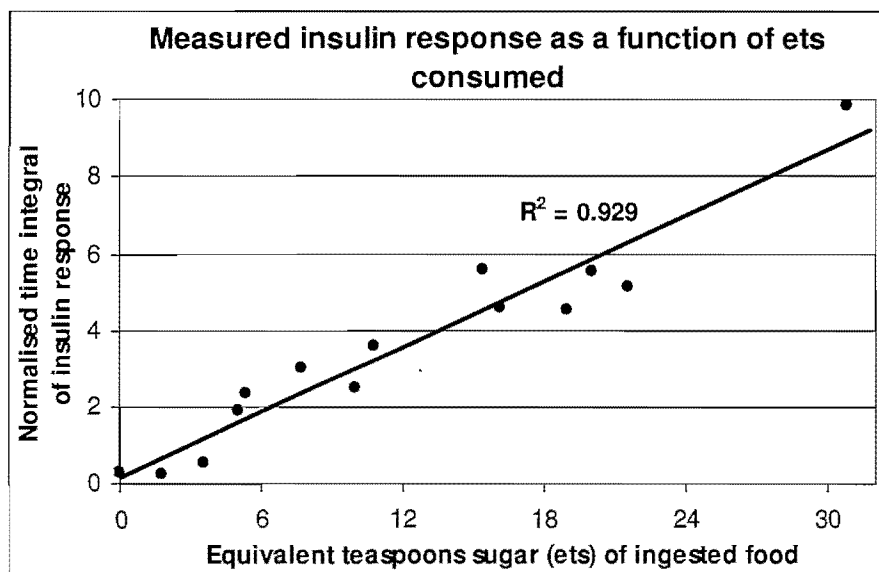


Figure 6: Measured insulin response as a function of ets consumed

The Pearson's R^2 values for the linearised trend fits were calculated and are 0.602 for mass of carbohydrates, 0.558 for GI and 0.929 for ets, which also gives the best linear trend fit. This means that ets is the most accurate predictor of insulin response for these test subjects. An analysis of data of Wollever and Bolognesi [12], taken from 15 test subjects, revealed similar results and is shown in Table 5.

	Mass of carbohydrates	Glycaemic index (GI)	Equivalent teaspoons sugar (ets)
Average R ²	0.562	0.396	0.807
% standard deviation / average R ²	32	36	10

Table 5: Pearson's R²-values for correlations between normalized insulin response integrals () and CHO, GI and ets values

Ets therefore seems to be a better predictor of insulin response in healthy test subjects. It must be remembered that Equation (6) states that the potential energy from carbohydrates different to that obtained by conventional thinking at the moment. Because ets gives a better indication of the potential energy available to the human body through digestion, it can be used to predict the increase in blood glucose more accurately than by using the mass of carbohydrates. Therefore, the insulin response when using ets is also more predictable than when using the mass of carbohydrates.

The derivation of ets is shown next. Only CHO in a meal is directly converted into blood sugar during digestion [16]. The "conversion potential" (η_{CHO}) of CHO estimates the amount of energy which is converted into blood sugar by a typical person and is discussed in section 3.5. The personalised CHO efficiency is represented by the term f_{CHO} and is also discussed in section 3.5.

As E_{Absorb} is the CHO energy converted into blood sugar for a specific person, E_{Absorb} can also be found by means of blood sugar measurements for that specific person. This calculation is discussed in section 3.4 and given by Equation (9).

The integral (Equation 9) divided by Δt gives the average concentration of blood sugar. To find the total amount of glucose (or energy) in the blood, the concentration is multiplied by the total volume of blood of the person (Vol). E_{Absorb} is then found by multiplying with k_{CHO} , the energy value of CHO (4 kcal/g).

$$E_{Absorb} = \frac{\int_{t=ingestion}^{t=basal} BS(t)dt}{\Delta t} Vol.k_{CHO} \quad (13)$$

Substitute Equation (8) into Equation (7) to find

$$\frac{\int_{t=\text{ingestion}}^{t=\text{basal}} BS(t)dt}{\Delta t} = \frac{f_{CHO}\eta_{CHO}m_{CHO}k_{CHO}}{Vol k_{CHO}} \quad (14)$$

For a typical balanced meal containing CHO there is a direct relationship between blood sugar response ($\int BS(t)dt$) and the insulin response [18] ($\int BI(t)dt$). Although the best fit to this relationship is not linear [14], a linear relationship with an R²-value of 0.963 was found through measurements by Lee and Wolever [14] using meals consisting mostly of CHO. This is deemed acceptable, especially if it is desired to keep the equations practical. Equation (15) gives this relationship:

$$\int_{t=\text{ingestion}}^{t=\text{basal}} BI(t)dt = f_{IBS} \int_{t=\text{ingestion}}^{t=\text{basal}} BS(t)dt \quad (15)$$

The insulin / blood sugar relationship varies from one person to the next and can be described by the person-specific blood insulin factor, f_{IBS} . (IBS is an abbreviation of **I**nsulin **B**lood **S**ugar relationship.)

Substituting Equation (15) into Equation (14) results in Equation (16), which describes the person-specific insulin response to ingested food. (The k_{CHO} values from Equation (14) cancelled each other out.)

$$\frac{\int_{t=\text{ingestion}}^{t=\text{basal}} BI(t)dt}{\Delta t} = \frac{f_{IBS}f_{CHO}\eta_{CHO}m_{CHO}}{Vol} \quad (16)$$

Equation (16) cannot, however, be easily used by the average person. Fortunately, this equation can be simplified. Instead of using m_{CHO} and η_{CHO} in Equation (16) for the meals, an easier measurement unit can be used. Mathews proposed that effective CHO in foods and meals be expressed in equivalent teaspoons sugar (*ets*).

A full teaspoon of sugar contains 5g of CHO. The GI of sugar 65 and therefore its η_{CHO} is approximately 65% (see Section 3.4). Sugar therefore has a η_{CHO} of 65% found from its GI_{CHO} value of 65 using the glucose reference [15]. Substituting these values into Equation (7) leads to Equation (17) for total available energy in a teaspoon sugar:

$$E_{\text{teaspoon sugar}} = GI_{\text{sugar}}m_{\text{teaspoon sugar}}k_{CHO} = (65)(5)k_{CHO} = 325k_{CHO} \quad (17)$$

The next step is to relate the effective energy for any CHO back to a teaspoon of sugar. By dividing Equation (7) for any meal (substituting η_{CHO} with GI_{CHO} for that meal) by Equation (17) ($E_{teaspoon\ sugar} = 325k_{CHO}$) for one-teaspoon sugar, the equivalent teaspoon sugar (~~$\rightarrow ets$~~) for that meal can be calculated, as shown in Equation (18)

$$ets = \frac{E_{CHO}}{E_{teaspoon\ sugar}} = \frac{\eta_{CHO}m_{CHO}k_{CHO}}{325k_{CHO}} = \frac{\eta_{CHO}m_{CHO}}{325} = \frac{GI_{CHO}m_{CHO}}{325}. \quad (18)$$

It can be shown that GI_{CHO} can be substituted with Π (Insulin Index) to arrive at a more accurate value of ets . The assumptions of linearity between insulin and blood sugar response, as well as high CHO content, are then not needed. It should also be noted that the ~~$\rightarrow ets$~~ / insulin relationship is linear to much higher ets values (approximately three times higher) than the ets / blood sugar relationship.

The equation for ets can be further simplified with Equation (16). By substituting Equation (18) into Equation (16) and substituting the term Area Under the Curve (AUC_I) for the integral, Equation (19) is found.

$$\frac{\int_{t=ingestion}^{t=basal} BI(t)dt}{\Delta t} = \frac{AUC_I}{\Delta t} = \frac{f_{IBS} f_{CHO}}{Vol} GI_{CHO} m_{CHO} = \frac{f_{IBS} f_{CHO}}{Vol} 325 \text{ ~~$\rightarrow ets$

$$\therefore \frac{AUC_I}{\Delta t} = \frac{325 f_{IBS} f_{CHO}}{Vol} \text{ ~~$\rightarrow ets$~~$$~~$$

By defining a new person specific factor, f_{AUCI} , Equation (19) can be simplified even further. f_{AUCI} accounts for the person specific factors f_{CHO} , f_{IBS} , Vol and Δt . ($AUCI$ is an abbreviation for “Area Under the Curve of Insulin response”.) f_{AUCI} , is *inter alia* a function of CHO metabolic efficiency, size, insulin resistance which depends on fitness, body mass index (BMI), age, etc. of a person. Its equation is given below, although it is easier to measure it by using Equation (21).

$$f_{AUCI} = \frac{325 f_{IBS} f_{CHO} \Delta t}{Vol} \quad (20)$$

Substituting Equations (20) into (19) yields the relationship between measured insulin response (AUC_I) and ingested food represented by ets .

$$AUC_I = f_{AUCI} \text{ ets} \quad (21)$$

where AUC_I is the integrated insulin response, f_{AUCI} is a measurable function of the individual and ets is a measurable function of the meal and is published for most foods or can be calculated using Equation (18). It was shown in the first part of this section that this simple linear equation was verified by using measurements by Lee, Wolever and Bolognesi [11,12].

Ongoing clinical trials show that the linearity of Equation (21) holds true for typical portion sizes of well-balanced meals. The application of Equation (21) by people who want to minimise insulin response is now simple. The food with the lowest ets will always lead to the smallest insulin response. As shown in Figures 4 and 5, such a simple and practical conclusion can not be drawn from either the CHO or the GI methods.

3.6 Insulin is a function of energy

It was shown in the previous section that there exists a relationship between insulin response and ingested carbohydrates expressed in ets . The increase in post-prandial insulin concentration is due to the fact that insulin is needed to store the absorbed glucose (originating from the carbohydrates in the meal) as glycogen in the body's storage cells in the liver and muscle cells.

Therefore insulin secretion is a function of not only the energy being released in the blood but also the energy being stored in the storage cells. By using ets , this function can be approximated by a simple linear relationship. Furthermore, insulin is also needed to open up cells to receive glucose in order to utilize the glucose for energy. A certain amount of insulin promotes a certain amount of glucose to be either stored in a cell or to enter the cell where the glucose can be utilized for energy.

During the day, glucose is constantly being released (glucogenesis) into the blood from the glycogen storage cells. The hormone glucagon triggers these storage cells to release the glycogen as glucose into the blood. The glucose that is gradually being released is needed by the cells in the human body for energy for metabolism.

Carbohydrates absorbed into the blood as glucose through digestion is stored by insulin (glycogenesis). Furthermore glucose is then constantly released from these stores during the day. In a balanced (optimum) scenario, the average glucose being released during the day should also be equal to the glucose being stored during the day. If more glucose is being stored than is being released, excess glucose will be stored and will eventually lead to weight gain as excess glucose will be transformed into fats.

The opposite also holds true if more glucose is being released and utilized than is being stored, there will not be enough energy available in the glucose (glycogen) stores, resulting in the body turning to other sources such as fats to transform them into glucose for energy. This will lead to weight loss.

It is therefore evident that insulin is a function of energy. The more glucose that needs to be stored, the more insulin will be required to do so. This is clearly demonstrated by Equation (21). The more energy the body requires during the day, the more insulin will be required.

3.7 Summary

In this chapter it was shown that the actual energy that is available from carbohydrates through digestion is *less* than what has previously been assumed. It was also shown that ets can be used to more accurately calculate the actual carbohydrate (or glucose) energy in food and that it is therefore a useful new energy unit that can be used to quantify energy in the human energy system. Furthermore, it was also shown that there exists a near-linear relationship between ets ingested and the resulting insulin response in healthy persons. Insulin is a function of energy in the human energy system, whether that energy is being stored or expended.

3.8 References

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CHAPTER 4

DERIVATION OF THE ETS-INSULIN-BOLUS EQUATIONS

Several important equations are derived in this chapter to help determine the type and magnitude of corrective action needed to control the blood glucose level of a Type 1 diabetic. These equations determine whether an insulin bolus is necessary, what the value of the bolus dosage should be and also whether an additional amount of carbohydrates is necessary to counter-act potential hypoglycaemia.

4 DERIVATION OF THE ETS-INSULIN-BOLUS EQUATIONS

4.1 Introduction

In this chapter equations are derived to determine the effect of food, insulin and exercise on the blood glucose level of Type 1 diabetics. The first few sections of this chapter derive the equations that help to predict the blood glucose level of the diabetic. The derived equations are then used to calculate the type and measure of corrective action needed to rectify the blood glucose level of the diabetic.

4.2 Blood glucose response of a Type 1 diabetic to ingested carbohydrates

It was shown in the previous chapter that the conventional method of measuring energy in carbohydrates is not ideal. The use of a new energy unit called ets (Equivalent Teaspoons Sugar) was proposed and initial clinical trials have shown it to be a more accurate measure of energy than grams of carbohydrates or calories.

By taking the metabolic efficiency of a specific foodstuff into account, the effective energy that is available to the human being through digestion can be found. It was shown that the metabolic efficiency of carbohydrates (η_{CHO}) is related to the glycaemic index (GI) of that foodstuff.

$$\eta_{CHO} = GI / 100 \quad (1)$$

The ets value for a specific foodstuff can be calculated using Equation (2) (see section 3.3).

$$ets_{CHO} = \frac{\eta_{CHO} m_{CHO}}{3.25} = \frac{GI_{CHO} m_{CHO}}{325} \quad (2)$$

This means that the actual glucose energy available through digestion from carbohydrates is given by Equation (2). This energy value can be converted to calories by using Equation (6) in Chapter 3. In other words, this is the potential amount of carbohydrates that is available to be

broken down into glucose through digestion and absorbed into the blood of a person. This does not mean that this full amount of ets_{CHO} will be absorbed into the blood of the person; it is merely the amount of energy that is *available* through digestion.

There are differences between individuals in how effective their digestive systems absorb nutrients from food. Some digestive systems will therefore absorb more carbohydrates that are subsequently converted into blood glucose, than others. The person-specific carbohydrate absorption efficiency factor, namely f_{CHO} , can be used to express this.

$$ets_{absorbed} = f_{CHO} \cdot ets_{eaten} \quad (3)$$

The pancreas of a Type 1 diabetic does not secrete insulin. This means that most of the blood glucose absorbed into the blood will remain there until insulin is administered. Therefore the increase in ets in the blood due to the ingestion of ets is for a Type 1 diabetic is:

$$\Delta ets_{absorbed} = f_{CHO} \cdot ets_{meal} \quad (4)$$

The increase in blood glucose level due to meal ingestion can therefore be calculated by using Equation (5).

$$\Delta BS = k_{BS/ets \text{ food}} \cdot ets_{absorbed} = k_{BS/ets \text{ food}} \cdot f_{CHO} \cdot ets_{meal} \quad (5)$$

$k_{BS/ets \text{ food}}$ is the conversion factor to convert present ets in the blood of a person to a blood glucose level. The latter is a concentration value, expressed as glucose per volume blood. $k_{BS/ets \text{ food}}$ therefore has to take into account the volume of blood of the person and also the conversion factor to convert from sucrose to glucose.

Fortunately for blood glucose prediction, it is not necessary to do this calculation. It is sufficient to know that there exists a linear relationship between an increase in blood glucose levels and ets ingestion, and that there is a person-specific factor that should be taken into account. Therefore, to predict the increase in blood glucose level due to ets ingestion, the following equation can be used at moderate levels of blood glucose.

$$\Delta BS_{meal} = f_{BS/ets \text{ food}} \cdot ets_{meal} \quad (6)$$

$f_{BS/ets\ food}$ is the person-specific factor relating to the increase in blood glucose level per ets ingested. This factor takes into account how efficiently the digestive system of the person absorbs carbohydrates, and the volume of blood of the person. It can be measured using the characterization procedure discussed in Chapter 6.

In short, this procedure entails monitoring the blood glucose level of the Type 1 diabetic after eating a test meal with a known quantity of ets without administering any insulin. The increase in blood glucose level per unit ets ingested is then calculated and represents $f_{BS/ets\ food}$.

At very high blood glucose levels, the body will slowly start to reduce blood glucose levels through the renal functioning of the kidneys. The carbohydrate absorption efficiency of the digestive system will also be reduced causing the factor $f_{BS/ets\ food}$ to decrease. This means that Equation (6) cannot be used when blood glucose levels are very high and therefore also not when meals contains a very high quantity of ets .

Further proof of the linear relationship between the increase in blood glucose level and ets ingested is shown in Section 3.5. It was shown that there exists a linear relationship between insulin secretions and ets ingested in a healthy subject. Therefore, in the absence of insulin to remove glucose from the blood (Type 1 diabetic), the blood glucose level will rise according to the amount of ets ingested.

To obtain the ets value of any meal, the ets values of all the different food and beverage items that compose the meal are added together. Different combinations of food (e.g. high fat meals, high fiber content etc.) can, however, influence these values. This is called the mixed meal effect. High-fat and high-protein meals digest slower than carbohydrate rich meals. At this stage, this effect is not being accounted for. Care should therefore be taken to select a bolus-insulin with the correct timing profile. Usually patients have to try out different insulins to see which one works best. For the purpose of this study, the total of the ets values of the different food and beverages items will be taken.

4.3 Blood glucose response of Type 1 diabetic to bolus-insulin

Bolus-insulin is used to store blood glucose in the glycogen storage cells by controlling the movement of glucose into these cells [1]. The more active insulin there is in the blood, the more cells are unlocked and therefore the more blood glucose that is stored. When blood glucose levels fall too low (hypoglycaemia) the counter regulatory system will start to release glucose from the glycogen storage cells (glucogenesis) [2].

This glucose release action is triggered by the secretion of counter regulation hormones such as glucagon (by the pancreas), adrenalin and cortisol (by the adrenal glands) and growth hormone (by the pituitary gland). Therefore by gradually increasing bolus insulin, there will be a relationship between the reduction in blood glucose level and the number of insulin units administered (in Type 1 diabetics).

There are also interpersonal differences between individuals regarding their insulin sensitivity. $f_{BS/insulin}$ is the person-specific reduction in blood glucose per unit bolus insulin factor. The reduction in blood glucose level ($\Delta BS_{insulin}$) due to bolus insulin administration (I_{bolus}) can be represented by the following equation:

$$\Delta BS_{insulin} = -f_{BS/insulin} \cdot I_{bolus} \quad (7)$$

Furthermore it should be noted that this reduction in blood glucose level takes place over a certain effective duration period. Table 4 in Chapter 2 gives the onset, peak and effective duration time for several different types of bolus insulin. These times are typical values and vary from person to person.

When the counter regulatory system starts to release glucose, the reduction per unit insulin will become considerably less. Furthermore, when the counter regulatory glycogen stores are depleted, the blood glucose level will reach a critically low level, which in severe cases may be fatal. Any bolus insulin dosage should therefore prevent blood glucose levels from falling too low, so that the blood glucose counter regulatory system can start to react.

Equation (7) can therefore only be used in the linear range, where the effect of the counter regulatory system is negligible (glucogenesis rate equals glycogenesis rate) (blood glucose levels higher than 3.8 mmol/l). Fortunately, when calculating insulin boluses, target blood glucose levels are set at values outside of the active blood glucose counter-regulation range. Therefore, for the purpose of insulin-bolus calculation, Equation (7) can be utilized.

There are several factors that influence the insulin sensitivity of a specific person. These include:

- The ambient temperature [5,6,7].
- The current activity level: as soon as a person starts to exercise, the insulin sensitivity of that person is dramatically increased by up to a factor of 4. Cells therefore need less insulin to utilize the same amount of glucose for energy [8].
- The position of the insulin administration site: the absorption efficiency of insulin is influenced by the injection site and therefore indirectly influences the insulin sensitivity of the patient [9].
- The time of the day: insulin sensitivity usually varies when measured on the same person at different times of the day. This may be partly due to the first two above-mentioned factors, since the activity level of a person as well as the ambient temperature, vary during the day.

The insulin-sensitivity of the diabetic patient should therefore, where possible, be measured at different times of the day to improve the accuracy of the insulin-bolus-calculation algorithm. This is, however, not a very practical approach. Furthermore sensitivity measurements should not take place on a particular cold or hot day.

4.4 Blood glucose response of a Type 1 diabetic to energy expenditure

Botha [10] derived the following equation for the relationship between calories expended during exercise and blood glucose etc expended.

$$E_{Expended} = f_{Expended} \text{ etc}_{removed\ exercise} \quad (8)$$

$E_{Expended}$ is the amount of energy expended during exercise and is measured in kCal. Various sources provide energy expenditure tables for different types of exercises for the average person. These values are then usually adjusted according to the weight of a specific person. If the table uses a reference weight ($m_{reference}$) and the person (used for bolus calculation)

weights ($m_{patient}$), the approximate energy expended during the exercise can be calculated using Equation (9)

$$E_{Expended} = \frac{m_{patient}}{m_{reference}} \cdot \frac{t_{period\ exercised}}{t_{period\ reference}} \cdot E_{Expended\ table} \quad (9)$$

$t_{period\ exercised}$ is the actual period of time exercised, while $t_{period\ reference}$ is the reference period of time used by the energy expenditure table.

To calculate the *ets* removed from the blood glucose for energy expenditure during exercise, Equations (8) and (9) can be rewritten as follows:

$$ets_{removed\ exercise} = \frac{E_{Expended}}{f_{Expended}} = \left(\frac{m_{patient}}{m_{reference}} \cdot \frac{t_{period\ exercised}}{t_{period\ reference}} \right) \cdot \frac{E_{Expended\ table}}{f_{Expended}} \quad (10)$$

To measure $f_{Expended}$ is a difficult and involved procedure. It was decided to use an average value for $f_{Expended}$. Botha [10] found this average value to be approximately 55. Therefore to calculate the approximate *ets* removed from the blood during exercise, the following equation can be used:

$$ets_{removed\ exercise} = \frac{E_{Expended}}{f_{Expended}} = \left(\frac{m_{patient}}{m_{reference}} \cdot \frac{t_{period\ exercised}}{t_{period\ reference}} \right) \cdot \frac{E_{Expended\ table}}{55} \quad (11)$$

If we know the approximate amount of *ets* removed from the blood, we can calculate the drop in blood glucose concentration by using the following conversion:

The volume of blood of an average person is approximately equal to 7% of the body mass [11]. Density of blood is approximately 1060kg/m³ or 1.06kg/l [12]. Therefore the volume blood (V_{blood}) of a person weighing ($m_{patient}$) can be calculated using the following equation:

$$V_{blood} = 0.07(m_{patient}) / 1.06 \quad (12)$$

The molecular formula of sucrose (table sugar) is C₁₂H₂₂O₁₁ and therefore has a molar mass of 342.3g/mol. The molecular formula of glucose is C₆H₁₂O₆ and this has a molar mass of

180.2g/mol. Therefore one ets (already absorbed or released into the blood) equals approximately 27.8 mmol glucose. (Note that one ets eaten will not result in one ets absorbed into the blood. The person specific efficiency of the digestive system lowers the amount of ets absorbed).

Therefore, for every ets removed from the blood glucose, the blood glucose level will be reduced by:

$$\Delta BS_{ets\ removed} = \frac{27.8[mmol / ets]}{0.07(m_{patient}[kg])/1.06[kg / l]} \cdot ets_{removed} \quad [mmol/l] \quad (13)$$

By substituting Equation (11) into Equation (13) the final blood glucose reduction equation for ets removal due to exercise energy expenditure can be obtained.

$$\Delta BS_{ets\ removed} = \frac{27.8}{0.07(m_{patient})/1.06} \left(\frac{m_{patient}}{m_{reference}} \cdot \frac{t_{period\ exercised}}{t_{period\ reference}} \right) \frac{E_{Expended\ table}}{55} \quad (14)$$

4.5 Blood glucose response of Type 1 diabetic to stress or illness

Emotional stress and illness causes blood glucose levels to stay elevated. The counter-regulation hormone cortisol is secreted during prolonged periods of emotional stress causing the release of glucose from glycogen stores [13]. This excess glucose in the blood therefore continues to increase the blood glucose level of the diabetic patient if no additional insulin is administered.

It should be noted that elevated blood glucose levels caused by prolonged periods of emotional stress should be rectified with basal insulin and not bolus insulin. Basal insulin has an extended activity period and is therefore able to continually counter-act the effect of cortisol on blood glucose level. A better solution, however, would be to try to reduce the stress levels of the person. This is often easier said than done.

If bolus insulin is used to rectify elevated blood glucose problems caused by prolonged periods of emotional stress, the blood glucose reduction effect will only be temporary. Short

periods of emotional stress can, however, sometimes be successfully counter-acted with bolus insulin.

4.6 Insulin-bolus calculation algorithm

In order to predict the blood glucose level of a Type 1 diabetic, several factors should be taken into account.

Pre-prandial blood glucose level

The blood glucose level prior to the meal ($BS_{pre-prandial}$) should be taken shortly before the meal and insulin bolus.

Predicted blood glucose level

The predicted blood glucose level can be calculated by taking into account the pre-prandial blood glucose level, the effect of food and exercise, insulin and the counter-regulation system on the blood glucose level of the type 1 diabetic.

$$BS_{predicted} = BS_{pre-prandial} + \Delta BS_{meal} + \Delta BS_{exercise} + \Delta BS_{insulin\ bolus} + \Delta BS_{counter\ regulation} \quad (15)$$

Controlled values

The following conditions are, however, known:

- $BS_{predicted}$ should be equal to the desired, or control blood glucose level of the diabetic patient therefore $BS_{predicted} = BS_{control}$.
- The insulin bolus dosage to be calculated should not induce hypoglycaemia and therefore not trigger the secretion of counter-regulation hormones. Therefore, the effect that the counter-regulation system has, is negligible, $\Delta BS_{counter\ regulation} = 0$.

Equation (15) can now be rewritten as follows:

$$BS_{control} = BS_{pre-prandial} + \Delta BS_{meal} + \Delta BS_{exercise} + \Delta BS_{insulin\ bolus} \quad (16)$$

Insulin-bolus

The bolus insulin dosage needs to be calculated. Equation (16) should be manipulated as follows:

$$\Delta BS_{\text{insulin bolus}} = BS_{\text{control}} - BS_{\text{pre-prandial}} - \Delta BS_{\text{meal}} - \Delta BS_{\text{exercise}} \quad (17)$$

Equations (6), (7) and (14) can now be substituted into Equation (17) to obtain Equation (18).

$$f_{BS/insulin} I_{\text{bolus}} = BS_{\text{control}} - BS_{\text{pre-prandial}} - f_{BS/ets\ food} \cdot ets_{\text{meal}} - \frac{27.8}{0.07(m_{\text{patient}})/1.06} \left(\frac{m_{\text{patient}}}{m_{\text{reference}}} \cdot \frac{t_{\text{period exercised}}}{t_{\text{period reference}}} \right) \cdot \frac{E_{\text{Expended table}}}{55} \quad (18)$$

To calculate the insulin bolus, Equation (18) should be divided by the insulin sensitivity factor to obtain Equation (19).

$$I_{\text{bolus}} = \left(BS_{\text{control}} - BS_{\text{pre-prandial}} - f_{BS/ets\ food} \cdot ets_{\text{meal}} - \frac{27.8}{0.07(m_{\text{patient}})/1.06} \left(\frac{m_{\text{patient}}}{m_{\text{reference}}} \cdot \frac{t_{\text{period exercised}}}{t_{\text{period reference}}} \right) \cdot \frac{E_{\text{Expended table}}}{55} \right) / f_{BS/insulin} \quad (19)$$

Types of insulin-bolus suggestions

Three different types of suggestions can be made from the result of Equation (19).

- Inject no insulin: If the predicted blood glucose level is close to the control blood glucose level, then the resulting insulin bolus will be zero or very small. If the bolus suggested is less than one unit, a decision should be made to take no action. In other words, no bolus insulin should then be administered.
- Administer a certain amount of insulin-bolus: If the predicted blood glucose level is significantly higher than the control blood glucose level, the calculated amount of bolus insulin would be a positive value and should be administered to lower the blood glucose level.

- Additional carbohydrates needed: If the calculated insulin bolus dosage is calculated to be a negative value, this means that the predicted blood glucose level will be below the control blood glucose level. Therefore no bolus insulin should be administered and an additional amount of ets should be ingested to counter-act the low blood glucose level.

Hypoglycaemia correction suggestion

A negative insulin-bolus value indicates possible hypoglycaemia. Therefore an additional amount of ets should be ingested to raise blood glucose levels to an acceptable level. Diabetics often ingest very high quantities of carbohydrates when they encounter hypoglycaemia. This usually raises their blood glucose levels to the other extreme, causing hyperglycaemia.

The ideal value of additional ets to ingest in such a situation can be calculated by using Equation (16). The meal can be broken down into the meal that was originally planned to be ingested and the additional meal to be ingested to counter-act hypoglycaemia.

$$BS_{control} = BS_{pre-prandial} + \Delta BS_{meal} + \Delta BS_{meal\ hypo} + \Delta BS_{exercise} \quad (20)$$

Equation (20) is then rewritten to isolate the blood glucose effect due to the additional meal to counter-act hypoglycaemia.

$$\Delta BS_{meal\ hypo} = BS_{control} - BS_{pre-prandial} - \Delta BS_{meal} - \Delta BS_{exercise} \quad (21)$$

The ideal amount of additional ets to ingest ($ets_{meal\ hypo}$) can be calculated by dividing Equation (21) by the ets sensitivity ($f_{BS/ets\ food}$).

$$ets_{meal\ hypo} = \frac{(BS_{control} - BS_{pre-prandial} - \Delta BS_{meal} - \Delta BS_{exercise})}{f_{BS/ets\ food}} \quad (22)$$

The blood glucose control level is usually chosen with a safety buffer. This will help to make the hypoglycaemic correction suggestion a conservative and thus safer suggestion.

4.7 Blood glucose characterization of Type 1 diabetics

Equations (19) and (22) derived in the previous section to calculate insulin-boluses, use two person-specific factors (sensitivity values) namely $f_{BS/insulin}$ (insulin sensitivity) and $f_{BS/ets\ food}$ (food ets sensitivity). For the bolus calculation equations to provide accurate results, it is crucial that these two factors be measured for the specific diabetic patient. This allows the bolus calculation system that utilize these equations to be customized for the specific diabetic patient.

The blood glucose characterization procedure to determine the insulin and food ets sensitivity of an individual is discussed in Chapter 6. These sensitivity values vary tremendously between individuals and for this reason the use of average values is unacceptable. Most of the insulin regimes established by medical professionals are unfortunately based on initial ball park values, which are adjusted through trial-and-error. This approach wastes a lot of time and causes unnecessary inconvenience and risks to the diabetic patient.

A third sensitivity value for determining the *exercise* sensitivity $f_{BS/exercise}$ value of a diabetic patient is much more involved and difficult to measure. A generalized value was used to describe the reduction in blood glucose level per unit ets energy expended during exercise. It is better to use an estimated value than to disregard the effect of exercise completely. Unfortunately, most people do not exercise sufficiently, and therefore this part of the bolus calculation is most often negligible.

4.8 Conclusion

This chapter has shown how ets can be used to quantify the effects that food consumption, exercise and insulin administration have on the blood glucose levels of Type 1 diabetics. ets is used to predict blood glucose levels following the ingestion of a meal. In order to do this, the pre-prandial blood glucose level, food consumption and exercises to be performed within the next few hours, are taken into account.

An appropriate type and measure of corrective action is then suggested for the user to control his/her blood glucose level within the desired range. This suggestion can either be an amount

of insulin to administer, a suggestion to take no action or a suggestion to ingest an additional amount of ets to prevent hypoglycaemia.

The equations derived in this chapter are practical, and the information necessary to perform these calculations is quantifiable. The equations are, however, too difficult to be calculated without the help of a calculation device. The next chapter addresses this concern and utilizes the derived equations to develop several insulin-bolus calculation products.

4.9 References

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CHAPTER 5

DEVELOPMENT OF THE ETS-INSULIN-BOLUS CALCULATOR

This chapter shows how the equations derived in Chapters 3 and 4 were utilized to design and develop practical end-user products that are able to calculate insulin dosages for Type 1 diabetics. Three products were developed for this purpose.

5 DEVELOPMENT OF THE ETS-INSULIN-BOLUS CALCULATOR

5.1 Introduction

The equations to calculate insulin boluses were derived in Chapter 4. These equations were then utilized as the basis for three end-user products. Bolus calculators were designed for implementation on a PDA (personal digital assistant), a cellular phone and a slide rule. Although quite different to each other, these products all share the same objective, namely insulin bolus calculation.

This chapter looks at the two software implementations; namely the PDA and Cellphone based bolus calculators. The PDA based calculator was developed first. Feedback from patients who participated in an initial clinical trial at the University of the Free State helped to identify certain barriers to user acceptance. These concerns were then addressed and after a few iterations, a cellular phone based bolus calculator was developed. The protection of intellectual property of the ets insulin bolus calculation products is also discussed.

5.2 Objectives and advantages of the system

The main objective of the system (ets insulin bolus calculation system) is to calculate accurate insulin boluses for Type 1 diabetics. This is done by taking into account food intake, exercise, person-specific factors relating to blood glucose and insulin response. Furthermore, various other user specific parameters have to be taken into account in order to improve the blood glucose control of a Type 1 diabetic.

The main advantages of such a system include the following:

- a reduced risk of hypoglycaemia and the associated complications;
- a reduced risk of hyperglycaemia and the associated long-term complications;
- an improved effort from the diabetic's side to tighten blood glucose control – if the system is easy-to-use and not complicated, the patient will be more likely to use it;
- great educational value of the system will help the diabetic to quickly gain valuable experience in controlling blood glucose levels and

- an accurate system will reduce the time needed to establish good glycaemic control by cutting out a lot of trial-and-error adjustments (done by the medical doctor) to the insulin regime.

The need for tight glycaemic control is discussed in detail in Chapter 3 . An accurate insulin bolus calculation device will help achieve this tight control.

5.3 User requirement statement

The system requirements were listed by taking into account information from several sources which include:

- Discussions with numerous diabetics during initial clinical trials conducted at the University of the Free State and diabetics who evaluated some of the prototype products at Human-Sim's offices.
- Discussions with dieticians who gave some valuable insight into the meal planning behavior of diabetic patients.
- Discussions with medical professionals, diabetes researchers and corporate delegates at several international diabetes conferences including the 64th Scientific Sessions (2004) of the American Diabetes Association (ADA), Orlando, Florida, USA; 31st Annual Meeting (2004) of the American Association for Diabetic Educators (AADE), Indianapolis, Indiana, USA; 40th Annual Meeting (2004) of the European Association for the Study of Diabetes (EASD), Munich, Germany and the 65th Scientific Sessions (2005) of the American Diabetes Association (ADA), San Diego, California, USA⁴.
- Information gathered from a study of similar blood glucose control devices on the market.
- A study of similar blood glucose control devices that are patented.⁵
- An extensive literature survey regarding insulin bolus calculation.

The system requirements for the ets-insulin-bolus calculator system are as follows:

⁴ Including: Dr. J. Mastrototaro, Dr. B. Keenan (MedTronic); Dr. H. Wolpert (Joslin Clinic, Harvard University); Dr. S. De Loach (Educator en Diabetes Certificado); Dr. P.J. Galley, W. Ragg, (Roche), E. Otto, Dr. N. Pellegrini, Dr. C. Davis (Lifescan); D. Dundov, S.Shwartz (Nipro Diabetes Systems); Dr. R.E. Pope (Smiths Medical); Prof S. Bong, J.S. Song (Sooil – Dana Diabecare); Dr. D.C. Klonoff (Diabetes Technology & Therapeutics); Dr S. Sterba (Disetronic); Dr. K.D. Crothall (Animas); M. Blomquist (Deltec); S. Syme (Inverness medical); R. Trzybinski (Bayer Healthcare); Dr. D. Deutsch & P.L. Inman.

⁵ See Chapter 1

- **Calculation of insulin boluses:** The system is intended to calculate insulin boluses and therefore the primary function of the system should be to calculate acceptable insulin boluses for Type 1 diabetics following a basal-bolus regime.
- **Accuracy:** The system has to calculate and provide accurate insulin bolus suggestions. These suggestions should ensure that the blood glucose levels of the diabetic patients stays within the defined acceptable blood glucose ranges. The system should also be able to recognize when an insulin bolus is out of range and warn the user.
- **Recovery from hypoglycaemia:** Although the primary function of the system is to calculate insulin-boluses, diabetics often encounter hypoglycaemia (low blood glucose) and do not know how much food they should ingest to rectify the problem. Often diabetics then overcompensate by ingesting too much carbohydrates, causing the other extreme, hyperglycaemia. The system should therefore be able to advise diabetics on the corrective action necessary.
- **Trust:** The diabetic user should be able to trust the suggestions made by the system. The suggestions should therefore be based on sound research. No evident programming bugs are allowed. These would immediately cause the user to stop trusting, and using, the device.
- **Acceptance by medical professionals:** The acceptance of the system by medical professionals is very important. They should be able to confidently recommend the system to diabetic users.
- **Ease-of-use:** This is probably the most important requirement to gain user acceptance for any technological product. If the system is too complicated to use, the user will soon lose interest, regardless of the many advantages that the product might have. It is also important that the product should be precise and not be ambiguous. If instructions are not clear, the user might use the product incorrectly, and this might lead to an incorrect insulin-bolus being calculated and administered.
- **Quick results:** In a hectic and stressful lifestyle, time is precious and cannot be wasted. The operation should not take up a lot of time. The user should be able to

quickly select food items to be consumed, exercise activities to be performed and enter a pre-prandial blood glucose level, to get an immediate insulin-bolus suggestion.

- **Cost:** Cost is always an important aspect. Some medical funds might possibly pay for the device if it does improve glycaemic control of patients. For those diabetics whose medical funds will not contribute to such a system, or those diabetics without any form of medical fund or state contributed healthcare fund, the device should be affordable. Improvement of glycaemic control lowers the diabetic user's risk to the various diabetic complications. This means that the device might save money that would have been spent on treating these medical complications.
- **Visibility:** Many diabetics suffer from bad eyesight. This is often due to the long-term complications caused by hyperglycaemia. Some of the patients complained that the contrast on the initial PDA device used was too low. They struggled to read the display of the device and therefore could not use it effectively.
- **Practicality:** It should not be a hassle to use the device. Diabetics complained that they already have to carry around their blood glucose measuring equipment and their insulin administration devices. The PDA bolus calculator was seen as an extra device to carry around so it was often left at home. The cellphone software application on the other hand does not require an additional device.
- **Food database:** The basis of the calculation of an insulin bolus is the meal that the bolus is compensating for. The food database provided to the user should therefore be complete and cater for all the different cultural groups and their foods. Items in the food database should also be easy to find. Furthermore, the portion sizes used in the food database should be practical to use and easy to visualize.
- **Exercise database:** The exercise database should cater for the most common sports activities, especially those applicable to the country in which the system will be used. Different exercise intensities should be accounted for (e.g. running at 10km/h or running at 20km/h).

- **Informative:** The system should be informative. In other words, the diabetic user should learn something from using the device. Diabetics often wonder whether they are following the correct diet or not.
- **Customizable:** Diabetic users try to control their blood glucose levels within different ranges. Some diabetics with good glycaemic control are more confident regarding their control and tend to control their glucose levels closely to the healthy normal glucose level. Other diabetics, however, are scared of inducing hypoglycaemia through over-dosage of insulin and therefore aim for a higher blood glucose level to play it safe. This difference between diabetics should be accounted for in the system. It should therefore be customizable to enable adjustment of these type of parameters for a specific patient.
- **Predefined meals:** Diabetic users often eat the same meals and find it tedious to enter the same food items over and over again. Some users requested that the device should be customizable in order to allow them to create predefined meals which will eliminate the need to re-enter the constituents of these meals every time these meals are to be consumed. This will save a lot of time.
- **Similarity to known practices:** The device should not confront the user with unknown practices nor require inputs that they do not understand or know how to deal with. The technological barrier should therefore be low in order to allow the majority of users to use the system without too much difficulty. The operation of the device should fit into the normal daily routine of the diabetic.

The major challenge of this study was to develop a system with acceptable accuracy but also acceptable to end-users in terms of ease-of-use. This aspect has consistently been improved throughout the study.

5.4 Software application

The PDA and cellphone implementations of the ets-insulin-bolus calculation device are software programs written for these devices. Only the more advanced (and latest) cellphone

implementation will be discussed in detail. Like any software application, there are different navigable windows (interfaces).

5.4.1 Main menu

The first interface that the user sees when the ets-insulin-bolus software application is loaded, is the main menu. This is the central control interface from where the application is managed.

It is shown in

Figure 7 below.

The main menu presents the user with the following options:

- *Logbook*: to display all activities and their associated times
- *Food*: to enter food and/or beverage items into the logbook
- *Exercise*: to enter exercise activities into the logbook
- *Glucose*: to enter a measured blood glucose value into the logbook
- *Insulin*: to initiate the insulin-bolus calculation algorithm
- *Totals*: to display a breakdown of the daily food intake
- *Favorites*: to create or select predefined meals
- *Setup*: to enter user specific parameters
- *Quit*: to close the software application in order to return to normal phone operation

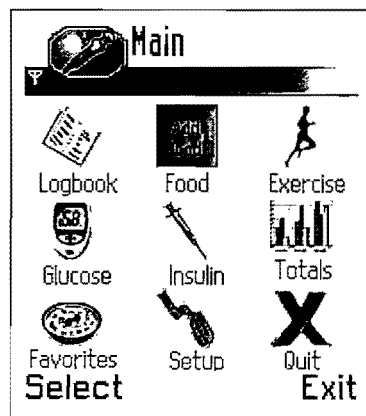


Figure 7: Main menu interface of ets-insulin-bolus calculator

The initial software application used only text in its user interface. It was decided to rather make use of a GUI (Graphical User Interface) with large icons (pictures). These icons are

similar to those used in the GUI of Microsoft Windows and therefore make the GUI more user friendly for the end-user.

5.4.2 Databases

The software application utilizes five different databases to store and retrieve information.

There are three read-only databases:

- the *food-and-beverage*-database,
- the *exercise* database and
- the *search keyword* database.

There are also two read-write databases namely

- the *logbook* database and
- the *user parameter* database.

Food and beverage database

A food and beverage database was developed by Human-Sim (Pty) Ltd. It contains more than 1200 food and beverage items. The database is categorized into several main categories and sub-categories to make navigation through the database easy.

Every item in the food database contains the following information:

- Description of the main category that item belongs to;
- Description of the sub-category that the item belongs to;
- Description of the food or beverage item;
- Description of the typical portion (e.g. a cup or slice);
- Weight of the typical portion (m_{portion});
- Grams of carbohydrates (m_{cho}) per 100g;
- Grams of proteins (m_{pro}) per 100g;
- Grams of fats (m_{fat}) per 100g;
- Grams of alcohol ($m_{\text{alc}/100\text{g}}$) per 100 grams; and
- ets per 100g.

The food and beverage database used for the purpose of the study includes the food and beverages of several of the most popular fast food restaurants in South Africa. It is important

- age [years],
- activity level (low, medium, high),
- total daily dose basal insulin [U],
- total daily dose bolus insulin [U],
- blood glucose scale used [mmol/l] or [mg/dl],
- ets sensitivity value for morning, afternoon and evening [mmol/l.ets],
- insulin sensitivity value for morning, afternoon and evening [mmol/l.U],
- target blood glucose level [mmol/l] or [mg/dl],
- maximum allowable meal ets [ets],
- maximum allowable insulin bolus [U],
- carbohydrate to insulin ratio [g_{CHO}/U],
- protein to insulin ratio [g_{PRO}/U],
- RDA (Recommended Daily Allowance) ets,
- RDA etsCal,
- energy scale used (either kJ or kCal) and
- RDA kJ or RDA kCal.

5.4.3 Logbook

The logbook option displays the contents of the logbook database for the present day. An example of a typical logbook display is shown in

Figure 8. The logbook interface displays the following information:

- present date,
- current time (very important for bolus calculation algorithm) and
- list of entries of which each entry contains a time, description of the type of entry (e.g. food, exercise, blood glucose measurement or insulin) and a magnitude of each entry (e.g. ets value for food item, ets value for exercise activity, blood glucose level in mmol/l or mg/dl or insulin units).

to note that different databases should be developed for different countries, regions or cultures. For example, the South African database will not be very useful in the United States.

The size of the electronic file, that is used to store the database information, was an important consideration in the choice of the cellular phone on which to implement the application. Fortunately, most of the newer generation phones have adequate memory. The food and beverage database is a read-only database file.

Exercise Database

An exercise database was developed with some of the most common exercise activities. Every item in this database contains a description of the exercise and the energy value being expended per minute per kilogram bodyweight ($ets_{exercise/min/kg}$). The exercise database is also a read-only file.

Search keyword database

The search keyword database is a look-up table that contains a list of all possible keywords in the food and beverage database, with reference to their location in the food and beverage database. This database is utilized by a search function to help the user quickly find a specific food or beverage item, without having to navigate through the large database.

Logbook Database

The logbook is used to store all the entries of the user together with their associated times. These entries include all food and/or beverage items, exercise activities, blood glucose measurements and insulin administrations. The contents of the logbook database can be displayed to the user on request and can also be downloaded for analysis onto a personal computer. The logbook database is a read-write database file.

User parameter database

The user parameter database is used to store the parameters of the specific user. These parameters are used to customize the bolus-calculation algorithm for the user.

The following parameters are stored in the user parameter database:

- Gender (male or female),
- weight [kg],
- height [m],

Logbook		
25 Apr 2005		9:20
Time	Description	Value
09:18	Food	8.6ets
09:18	Blood glucose	8mmol/l
09:19	Insulin	4U
10:30	Exercise	-3.7ets

Back		Options

Figure 8: Logbook interface of ets-insulin-bolus calculator

The logbook interface also presents the user with the option to remove either a single entry or to delete all the listed entries in the logbook database. (The latter option will only remove the present day's entries from the database.)

The logbook was included in the design because diabetics are used to writing information into logbooks. This helps them to identify certain trends in their blood glucose levels and this reduces the likelihood of them making similar mistakes later on. The information in a diabetic logbook is also of great value to the medical doctor, who can use the information to make adjustments to the insulin regime of the diabetic patient.

5.4.4 Entering meals

To calculate the ets in a food item the following equation can be used:

$$ets_{\text{food item}} = \frac{(\text{number of portions}) \cdot (m_{\text{portion}} / 100g) \cdot (m_{\text{cho}} / 100g) \cdot GI}{325} \quad (1)$$

To calculate the ets contents of a meal composed of n different food and/or beverage items, the sum of all the food items' ets values can be taken.

$$ets_{\text{meal}} = \sum_{x=1}^{x=n} ets_{\text{food item } x} \quad (2)$$

The user therefore needs to select the “All the food and beverage items” from the database and specify the number of portions of each food item. The initial software system implemented on a PDA system allowed the user to browse through the food database.

Figure 9 shows the algorithm to allow the user to browse through the database and select items.

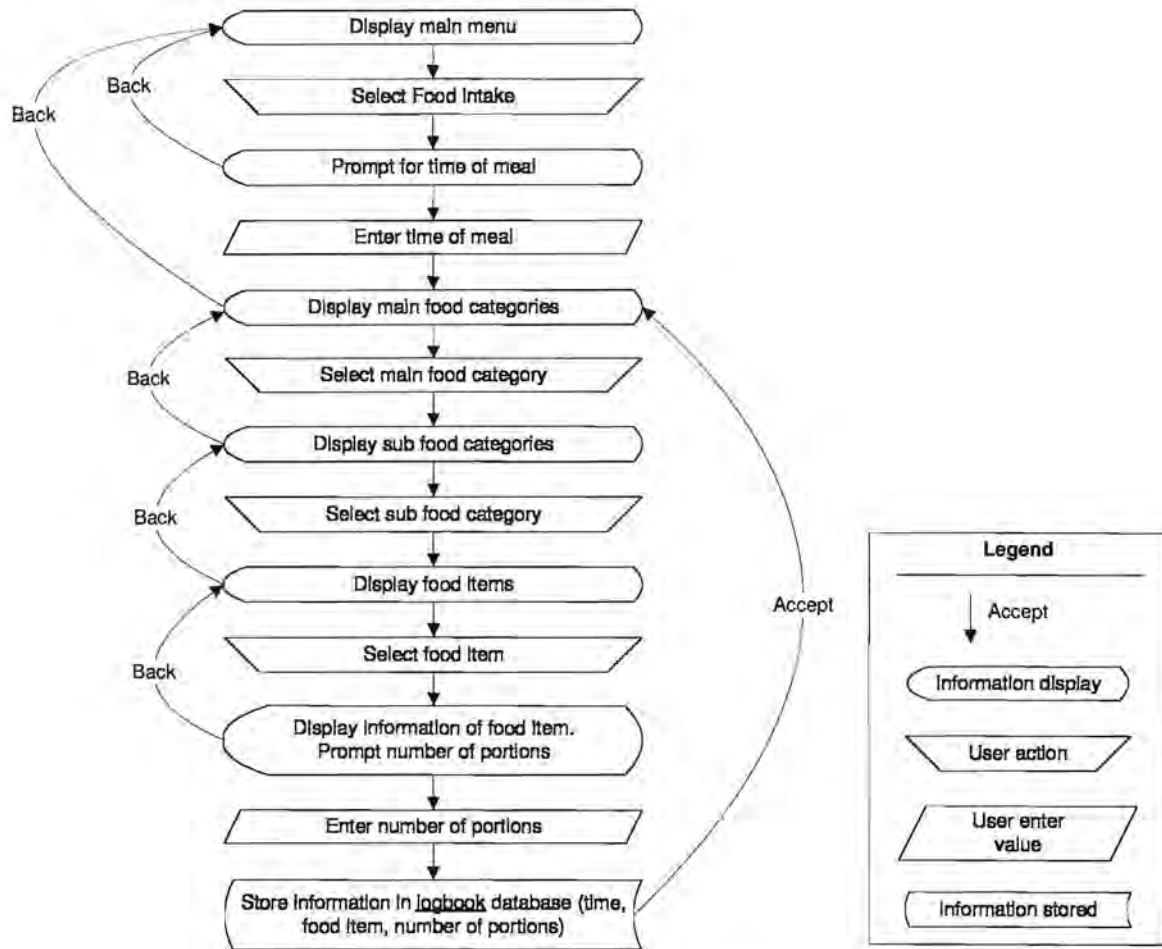


Figure 9: Flow diagram for algorithm to navigate through food database

The user is first prompted to enter the time of the meal (Figure 10). This is a very important consideration. The bolus calculation should only take into account the meal that is taken at roughly the same time as the insulin-bolus administration.

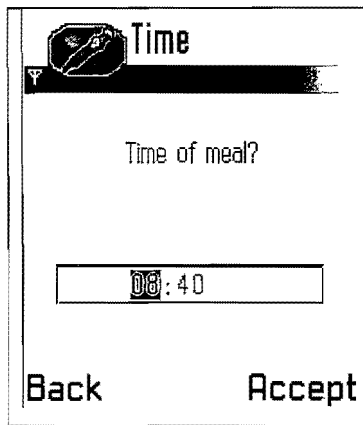


Figure 10: Interface for entering the time of a meal

The system first displays the main food categories. After selecting one of the main food categories, the relating sub-categories are listed. The user then selects a sub-category and all the food or beverage items relating to that sub-category are then listed. After selecting a specific food item, the user is shown the relevant ets value per portion of that food item. The user is then prompted to enter the number of portions to include in the meal.

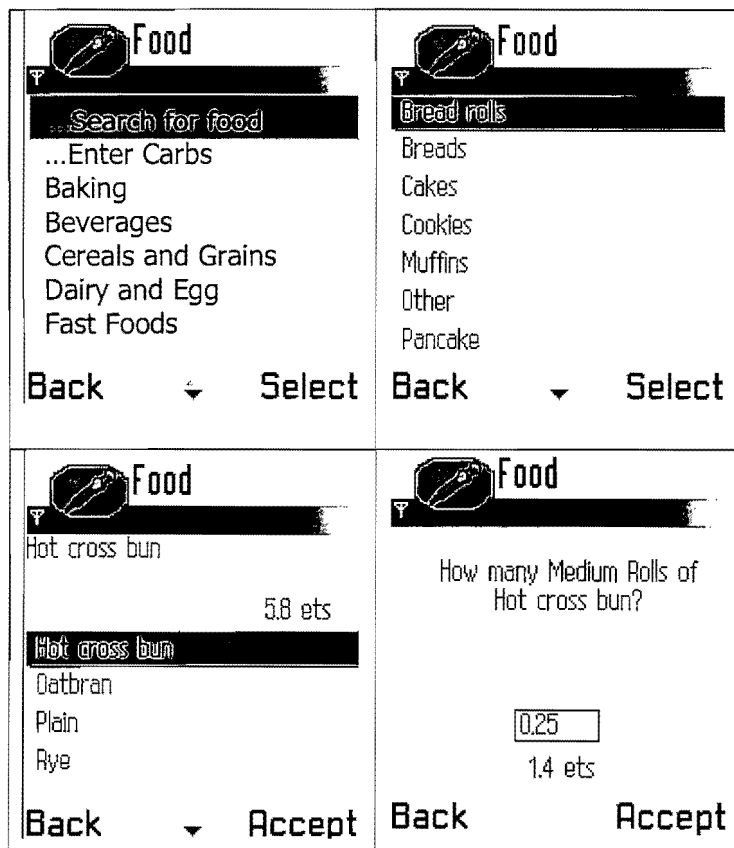


Figure 11: Interfaces for navigating through the food and beverage database

Because the database includes three levels of food data, it is important to be able to browse both forward and backward. The algorithm therefore allows the user to browse backwards at any stage. After selecting a food item and entering the number of portions, the data is stored in a logbook database. The user is then allowed to either select more items from the food database, or to return to the main menu of the software program.

Users of the PDA based bolus calculator often struggled to find all the food items in the database. Either the specific food item was not included in the database, or the user did not browse to the correct main and/or sub-category. The algorithm used by the cellphone based bolus calculator was therefore redesigned to address these two problems.

A search function was implemented in the cellphone based bolus calculation. The user is given the option to search for specific food items by entering keywords. This keyword can be either the full description of the food (e.g. milktart) or only a part of the description (e.g. tart). All the matching food items are then listed, and the user can then select the specific food or beverage item. The algorithm for selecting food items using the search function is shown in Figure 13.

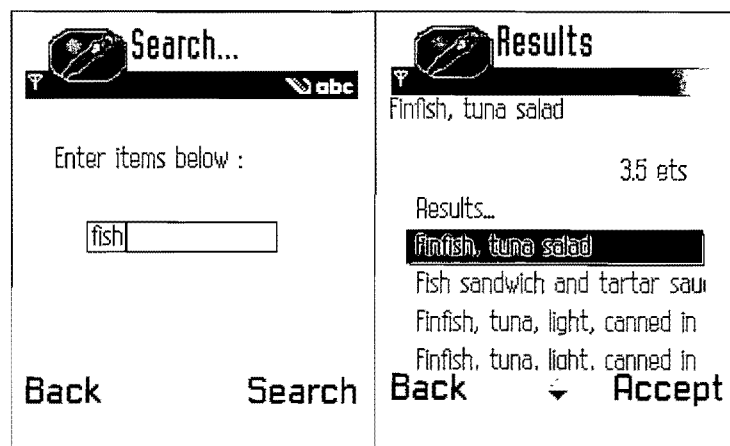


Figure 12: Interfaces for food and beverage database search function

The first implementation of the search procedure was very slow. The limited processing power and speed of the cellphone was a problem. An additional keyword database was used to speed up the search procedure. Search results can therefore be provided immediately with this improved implementation.

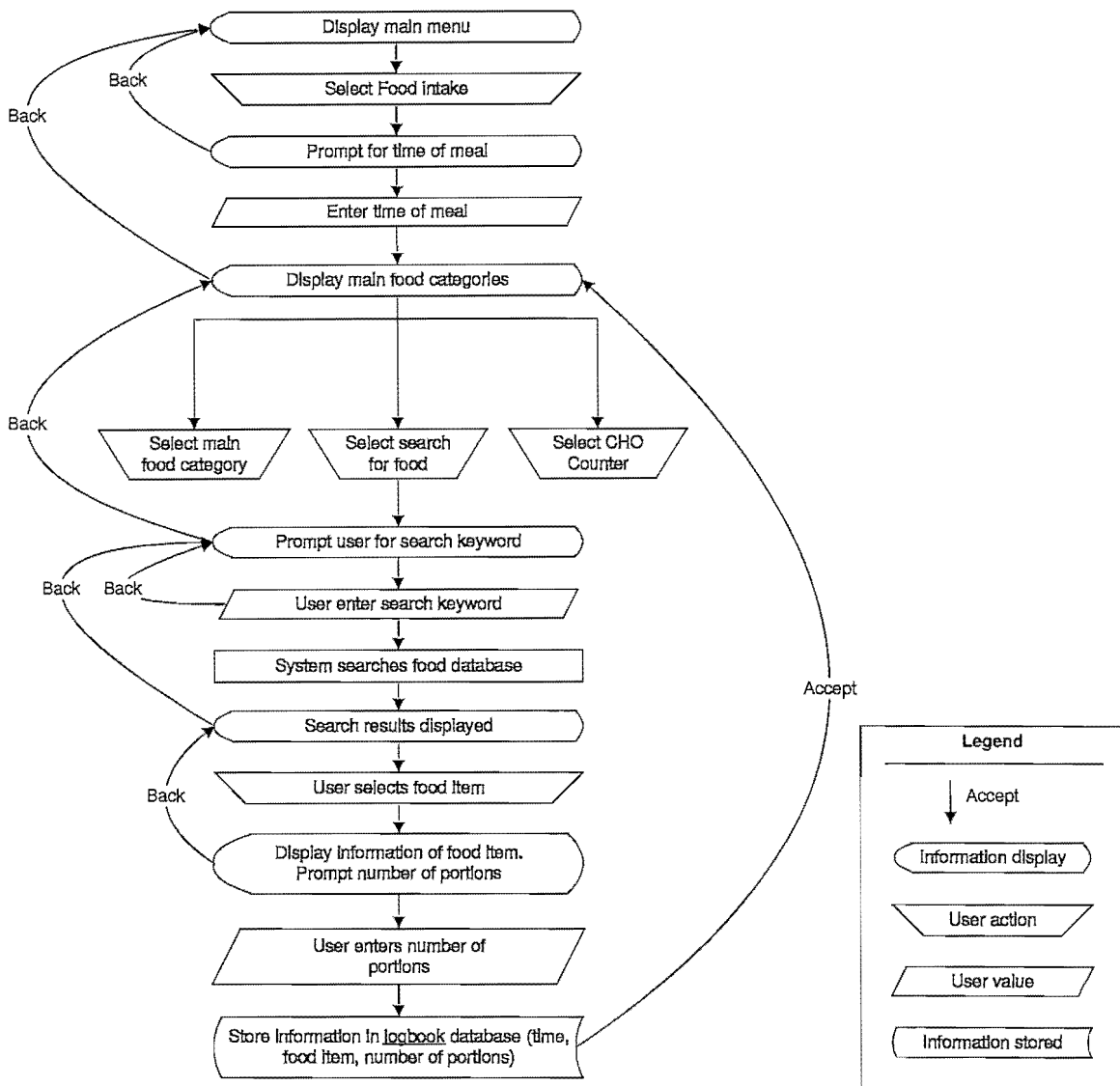


Figure 13: Flow diagram for algorithm to search for a specific food or beverage item

The second problem, namely that some food items are not included in the database, was also addressed. It is not possible to include every single food item commercially available. Different food chains stock different brands of products, and there are always new products introduced and some withdrawn from the market. The database provides a good selection of typical foods and even includes food items from various fast food chains.

If the user cannot find a specific food item in the food database, there is the option to enter the amount of carbohydrates in that food item. Most food items list this value on the nutritional information label on the packaging of the product. The user enters the number of grams of carbohydrates for the portion to be ingested into the system. This value is then stored in the logbook database. This algorithm is shown in Figure 15.

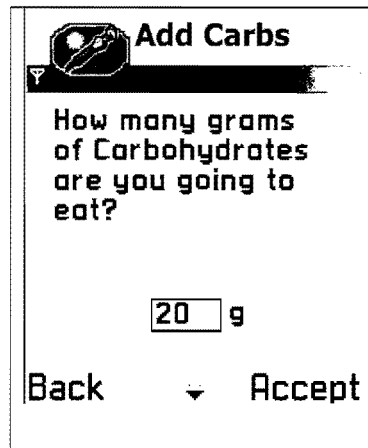


Figure 14: Interface for entering CHO content of a food or beverage item

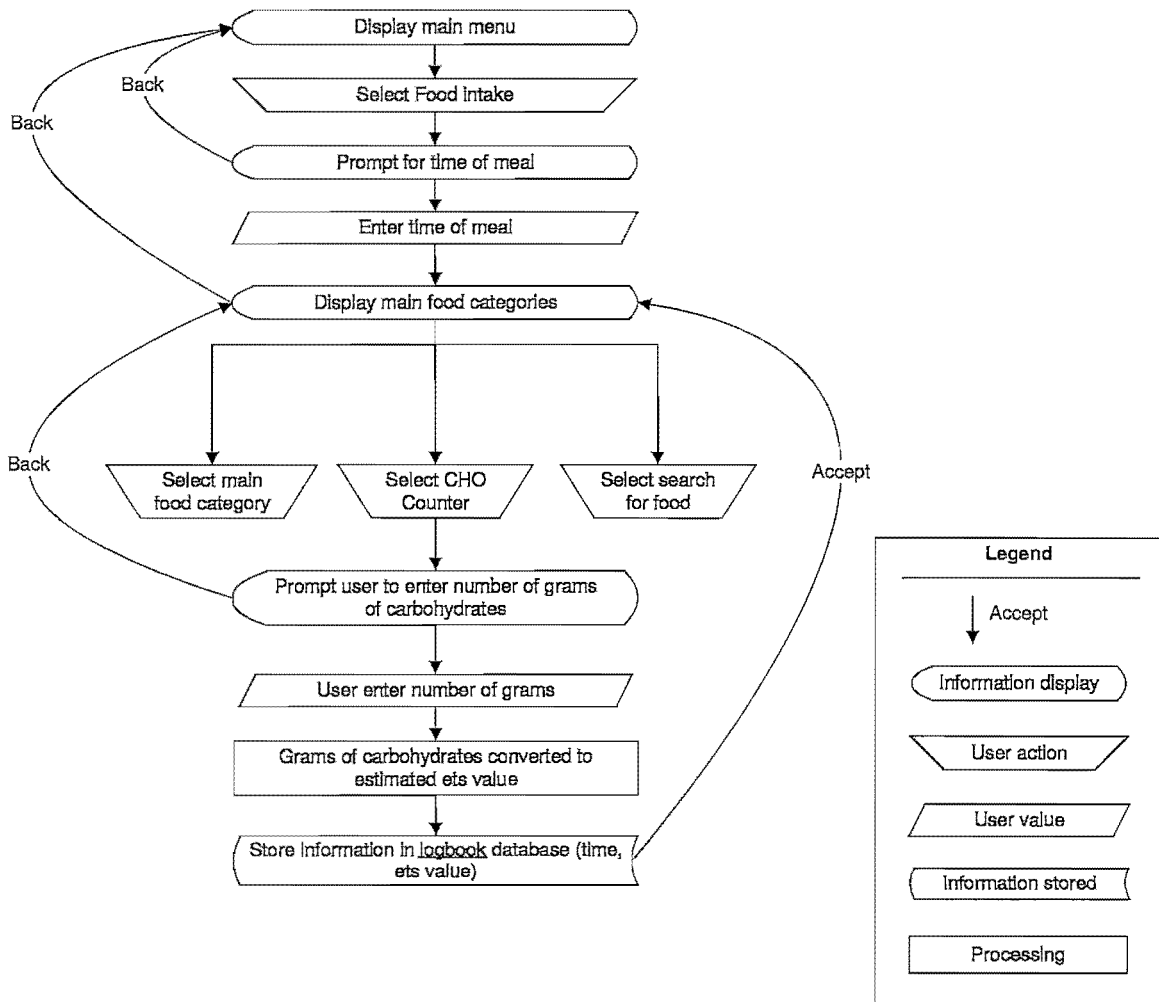


Figure 15: Flow diagram for algorithm to add a food or beverage item not present in the food and beverage database

To make the software application easier to use a “*Favorites*” function was implemented. This option allows users to create predefined meals by selecting different items from the food and beverage database. Certain meals are often repeatedly eaten. By creating these predefined meals on the device, a lot of time and effort can be saved later on. By selecting a predefined meal, all the meal items therein will be added to the logbook database.

5.4.5 Entering exercise activities

The estimation of energy being expended during exercise is a difficult task. This energy value is dependant not only on the type, duration ($t_{duration}$) and intensity of the exercise, but also on several person specific factors. These factors include weight (m_{person}) and fitness level. For example, the more a person weighs, the more energy is needed for exercise. More weight is being carried around and this uses a lot of extra energy. Some people utilize energy more efficiently than others and will therefore expend less energy during exercise.

In order to estimate the amount of ets energy being expended during exercise, an exercise database was derived by Human-Sim. This database contains some of the most common exercises. Average energy values (for average fitness level) were used for the activities.

Every item in the exercise database contains:

- A description of the type of exercise and
- Energy value being expended per minute per kilogram bodyweight ($ets_{exercise\ per\ minute\ per\ kilogram}$) (Also see section 4.4).

To calculate the ets energy being expended during exercise the following equation can be used:

$$ets_{exercise} = t_{duration} \cdot m_{person} \cdot ets_{exercise / min / kg} \quad (3)$$

The algorithm to enter exercise activities is shown in Figure 17. The user is again prompted to enter the time of the exercise activity. Exercise activities should be entered in advance. In other words, if the user is going to exercise within six hours from the current bolus to be calculated, the details regarding the exercise should be entered.

The user is then required to select the specific activity to be performed as well as the duration of the exercise. Any exercises selected by the user are stored in the logbook database.

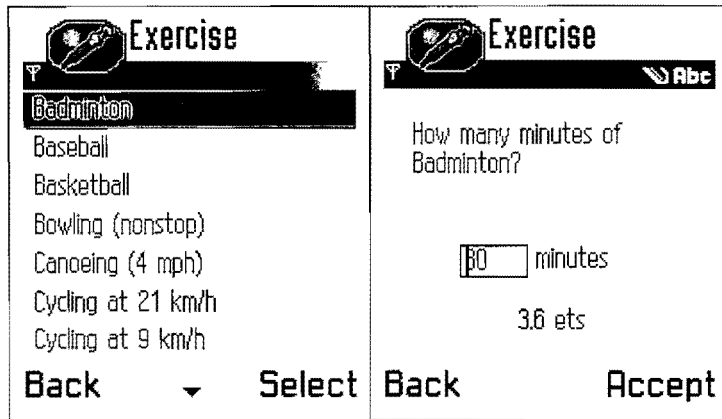


Figure 16: Interfaces for selecting the type and duration of exercise activity

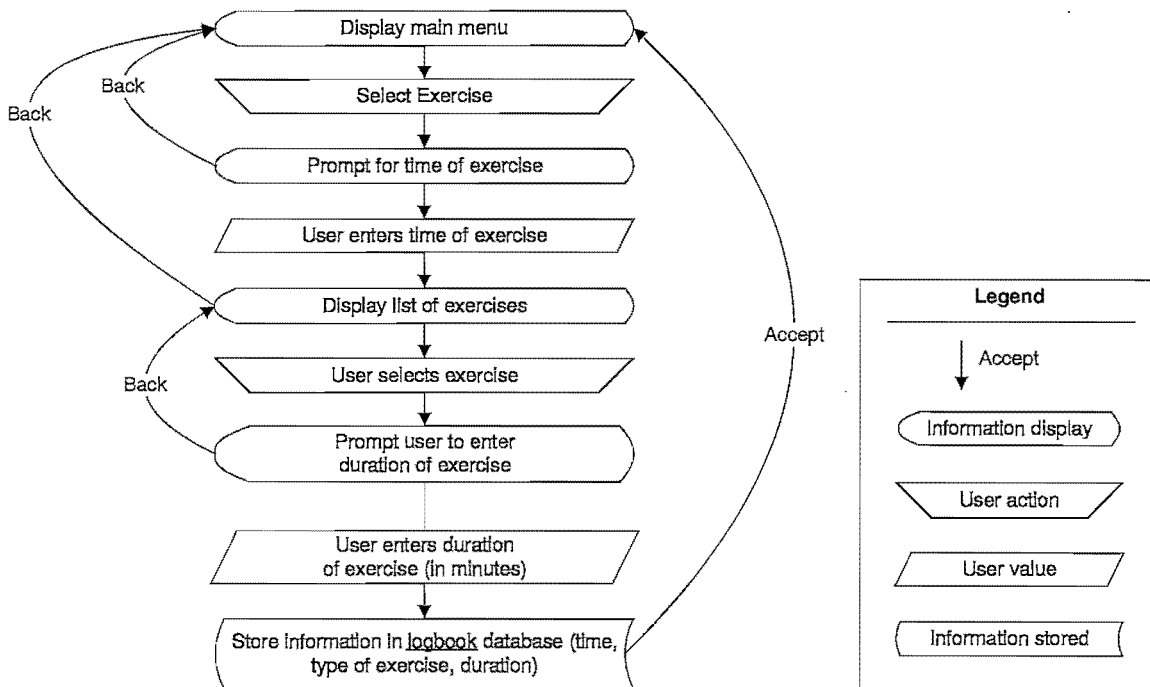


Figure 17: Flow diagram for algorithm to add exercise activities to the logbook database

5.4.6 Entering blood glucose measurements

The current blood glucose ($BG_{current}$) level should be measured shortly prior to the insulin-bolus and meal. This value is also called the pre-prandial blood glucose level. It is necessary to determine whether the bolus should be adjusted for a high or low blood glucose level prior

to the meal, and also to determine whether the meal contains enough ets, in case of an extremely low blood glucose level.

The diabetic user can also use this function to store any other blood glucose levels measured during the day. Currently blood glucose levels are measured with a blood glucose monitor requiring the diabetic to place a drop of blood on a glucose test strip which is inserted into a blood glucose monitor. The new Medtronic insulin pump with integrated CGMS systems allows the user to see blood glucose levels in real time and therefore makes this measurement task easier.

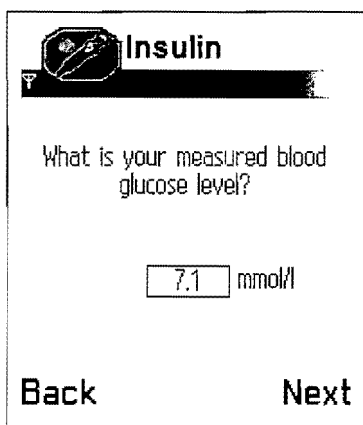


Figure 18: Interface for entering a blood glucose value

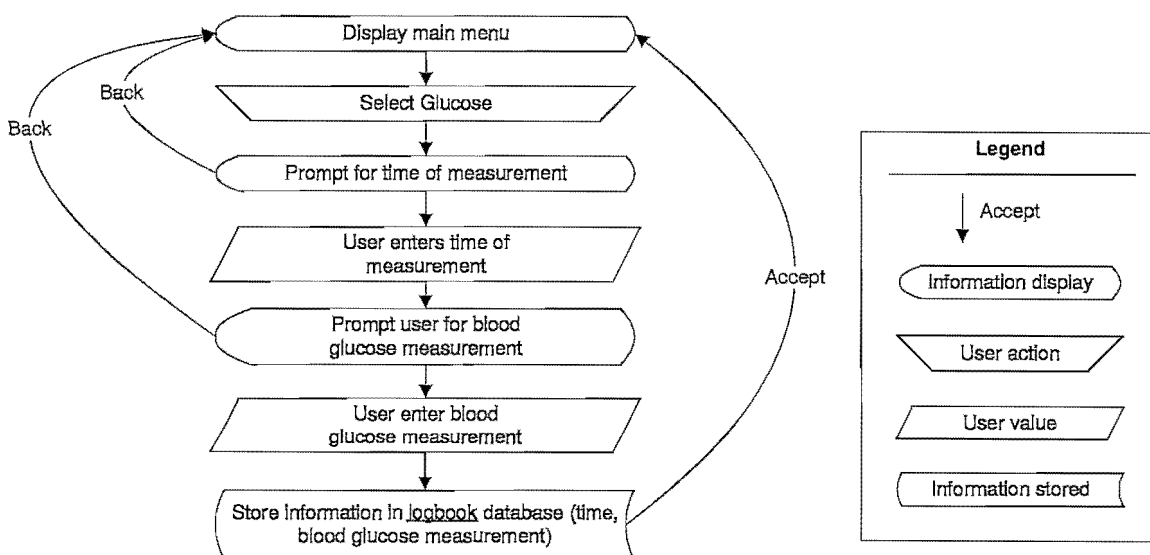


Figure 19: Flow diagram for algorithm to enter a blood glucose level.

5.4.7 User parameters

The ets-insulin-bolus calculation algorithm should be customized for the specific user before it can be used. To do this, the patient should first be characterized to see how his/her blood glucose responds to food intake and insulin. This characterization procedure is discussed in the next Chapter of this study.

RDA

The following parameters are used to determine the RDA (Recommended Daily Allowance) of ets and etsCal for the diabetic patient:

- gender,
- height [m],
- weight [kg],
- activity level (low, medium, high or very high) and
- age [years].

The following equation developed by the USDA/ARS Nutrition Research Center at Baylor College of Medicine [1] is used to determine the calorie RDA:

$$RDA_{Calories} = fa_{gender} + fa_{age} + fa_{activity} (fa_{weight} + fa_{height})$$

The factors for this equation can be calculated using Table 6.

Factor	Male	Female
fa_{gender}	662	354
fa_{age}	-9.53*age [years]	-6.91*age [years]
$fa_{activity}$	1.0 (low activity level) 1.11 (moderate activity level) 1.25 (high activity level) 1.48 (very high activity level)	1.0 (low activity level) 1.12 (moderate activity level) 1.27 (high activity level) 1.45 (very high activity level)
fa_{weight}	15.91 * weight [kg]	9.36 * weight [kg]
fa_{height}	539.68 * height [m]	726 * height [m]

Table 6: Factors for calculating RDA energy requirement in Calories (kCal)

If 40% of the energy requirements should come from carbohydrates and there is 20kCal in one teaspoon of sugar (ets) the the RDA ets can be calculate with Equation (4)

$$RDA_{ets} = 0.4 RDA_{calories}/20kCal \quad (4)$$

The RDA etsCal can be calculated with Equation (5)

$$RDA_{etsCal} = RDA_{calories} \quad (5)$$

These RDA parameters are suggested to the user. The user is, however, able to change these values should he/she feel the need to do so.

ets sensitivity

ets Sensitivity ($f_{BS/ets\ food}$) is defined as the increase in blood glucose level per ets ingested. This is a person-specific factor and varies between people. It is measured using the characterization procedure discussed in the next chapter. Different ets sensitivity values can be used for the different times of the day.

Three distinct ets sensitivity values can be entered for the user:

- $f_{BS/ets\ food\ morning}$ [mmol/l.ets]: used for bolus calculations between 0h00 and 11h00.
- $f_{BS/ets\ food\ afternoon}$ [mmol/l.ets]: used for bolus calculations between 11h00 and 17h00.
- $f_{BS/ets\ food\ evening}$ [mmol/l.ets]: used for bolus calculations between 17h00 and 0h00.

Insulin sensitivity

Insulin sensitivity ($f_{BS/ins}$) is defined as the decrease in blood glucose level per unit bolus insulin administered. This is also a person-specific factor and varies between people. It is measured using the characterization procedure discussed in the next chapter. Different insulin sensitivity values can be used for the different times of the day.

Three distinct insulin sensitivity values can be entered for the user:

- $f_{BS/ins}$ [mmol/l.U]: used for bolus calculations between 0h00 and 11h00.
- $f_{BS/ins}$ [mmol/l.U]: used for bolus calculations between 11h00 and 17h00.
- $f_{BS/ins}$ [mmol/l.U]: used for bolus calculations between 17h00 and 0h00.

Target blood glucose level

The target blood glucose level is the control set point for the bolus calculation algorithm. This value should be carefully selected by the diabetic user in consultation with a medical doctor. A value should be selected that allows the user to achieve an acceptable Hemoglobin (A_{1c}) level according to the guidelines that associations such as the ADA [2] and AACE [3] have developed (see chapter 2).

This target blood glucose level should include a safety margin to reduce the risk of hypoglycaemia. It should not be selected too low, e.g. 4mmol/l. Although this value is an ideal blood glucose level, a slight overdose of bolus insulin may induce hypoglycaemia. A slightly more conservative value of 5 – 6 mmol/l should rather be used, until good glycaemic control is established.

Maximum values

A few of the user parameters are maximum values. The purpose of these parameters is to identify situations where a bolus calculation may be incorrect. The two maximum value parameters are the maximum meal ets limit and the maximum insulin bolus limit.

The maximum limit for meal ets is relevant whenever a meal contains very high amounts of ets that will cause blood glucose levels to surge very high. At these high levels of ets ingestion, the linearity of the ets-blood glucose response is influenced. At high blood glucose levels, additional ets ingestion will cause the ets sensitivity to decrease.

It therefore becomes difficult and risky to calculate an insulin bolus suggestion. Whenever the ets content of a meal exceeds this maximum value, a warning message will be displayed to the user that the meal ets exceeded the limit and that no bolus suggestion can be calculated.

The maximum insulin bolus limit is relevant when the pre-prandial glucose level is high and the meal to be ingested contains a moderate-to-high amount of ets. This scenario might cause the resulting insulin bolus suggestion to be very high. It is dangerous to administer very high amounts of insulin at once.

Therefore, whenever the insulin bolus value calculated exceeds the maximum insulin bolus limit, a warning message will be displayed to the user that a bolus suggestion cannot be calculated. It is recommended that when this situation occurs, the diabetic user should

administer a moderate amount of bolus insulin and monitor blood glucose levels a few hours after the administration. If blood glucose levels stay elevated, then a second insulin dosage can be administrated.

Total daily dose of bolus insulin

This is an average value entered and is the sum of all the insulin bolus units administered during a typical day. Whenever the total bolus calculations for a day exceed this value by far, a warning message is displayed to the user. If this situation frequently occurs, the diabetic should consider consulting his/her medical doctor. This might be an indication that the diet of the diabetic has changed considerably, the insulin requirements of the diabetic has changed or that the sensitivity values are not correct.

5.4.8 Calculating insulin boluses

According to Equation (19) in Chapter 4, the following information is necessary to calculate an insulin bolus: pre-prandial blood glucose level, ets value of meal, ets value of exercises to be performed and the user specific sensitivity values. In order to calculate these values from the logbook database, more information is necessary; such as the specific times of entries in the logbook and the time of the bolus administration.

Time of bolus administration

The user is prompted to enter the time of the bolus administration. This time is very important. It is used to determine which entries in the logbook should be used for the bolus calculation. Furthermore, this time is also used to detect whether the previous insulin bolus was administered a short while ago, meaning that there might still be some active bolus insulin in the blood that should be accounted for.

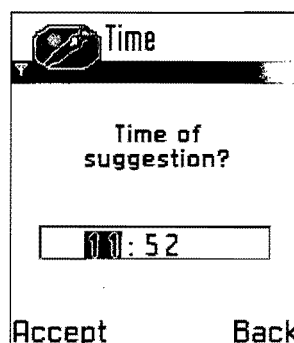


Figure 20: Interface for entering time of insulin-bolus calculation

Pre-prandial blood glucose level

After entering the time of the bolus administration, the user is prompted to measure and enter his/her blood glucose level. This level is called the pre-prandial (pre-meal) blood glucose level. If a blood glucose level was measured and entered during the previous 10 minutes, this value will be displayed allowing the user to use this value.

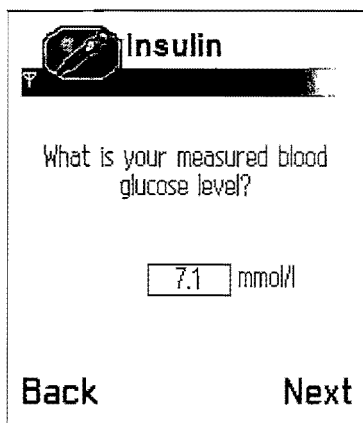


Figure 21: Interface for entering pre-prandial blood glucose level

Confirmation of values

Figure 22 shows the confirmation interface shown before an insulin-bolus suggestion is made. This information is displayed to the user to make sure that no obvious error in entering information has occurred.

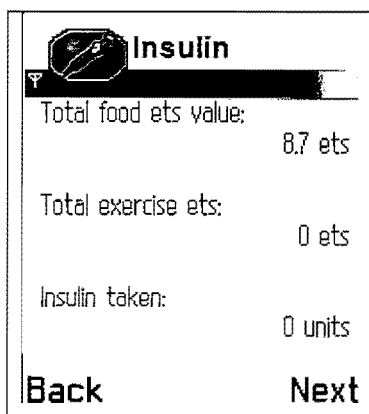


Figure 22: Interface for confirming values used for insulin-bolus calculation

The values displayed are calculated as follows: The meal (food) ets value is obtained by scanning through the logbook database and adding up all the ets values of the meal and beverage items within a time range of 10 minutes prior to the suggestion time entered up to 10 minutes after the suggestion time. The exercise ets is calculated by adding all the ets values for exercises to be performed within the next six hours. The insulin value will reflect the previous insulin bolus dosage if that dosage was administered less than three hours ago. If the previous insulin administration was more than three hours ago, this value will be displayed as zero.

Bolus-suggestion

The input information is processed and used together with the user parameters to make a suggestion. The suggestion is either one of three corrective measures:

- **A suggestion to take no action:** If the predicted blood glucose level is close to the control blood glucose level, then a suggestion will be made neither to administer any insulin nor to ingest any further carbohydrates.
- **A suggestion to administer insulin:** If the predicted blood glucose level is higher than the control blood glucose level, an appropriate dosage of short acting insulin will be suggested. This bolus aims to lower the blood glucose level back to the control level. This is the most common suggestion.
- **A suggestion to ingest additional carbohydrates:** If the predicted blood glucose level is lower than the control blood glucose level, a suggestion will be made to ingest an appropriate amount of additional carbohydrates. This bolus aims to raise the blood level back to the control level.

There is also the possibility that one of the maximum limits may have been exceeded. A message containing the reason why the bolus cannot be calculated will then be displayed. This can happen when:

- the meal ets exceeds the acceptable maximum limit set in the user parameters,
- the insulin bolus dosage exceeds the acceptable maximum limit set in the user parameters or

- the previous insulin bolus was administered less than three hours ago (this indicates that there is still a lot of active bolus insulin in the blood which should be accounted for).

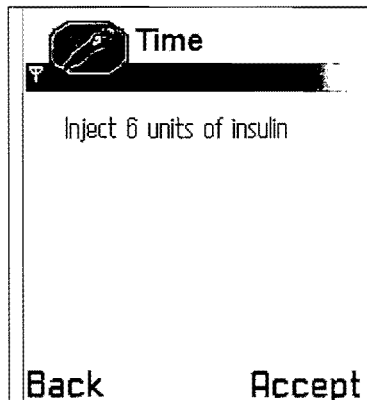


Figure 23: Interface for displaying insulin bolus suggestion

By accepting the suggestion, the action together with its associated time will be stored in the logbook database. It should be noted that this value is always only a suggestion. The diabetic user should therefore still use his/her own discretion. Errors in the software algorithm, human operation of the device and incorrect user parameters might lead to inaccurate suggestions being made. It is important to bring this under the attention of the user. This is explained in the user manual (Appendix F).

Algorithm for insulin bolus calculation

The first part of the insulin-bolus calculation algorithm initiates the variables for the total food ets, grams of CHO entered, exercise ets, last insulin dosage and also a counter. Next, the algorithm scans through the logbook database and adds all the food and exercise ets values. It also detects whether a recent blood glucose level was measured. Furthermore, the algorithm scans to see if the previous insulin bolus administration was administered less than three hours ago.

After the algorithm has calculated all the totals, it firstly determines whether the maximum ets meal limit was exceeded or whether the previous insulin bolus was administered less than three hours ago. If any of these conditions are true, the software application will not calculate an insulin bolus suggestion and will display an error message to state the problem. This part of the algorithm is shown in

Figure 24.

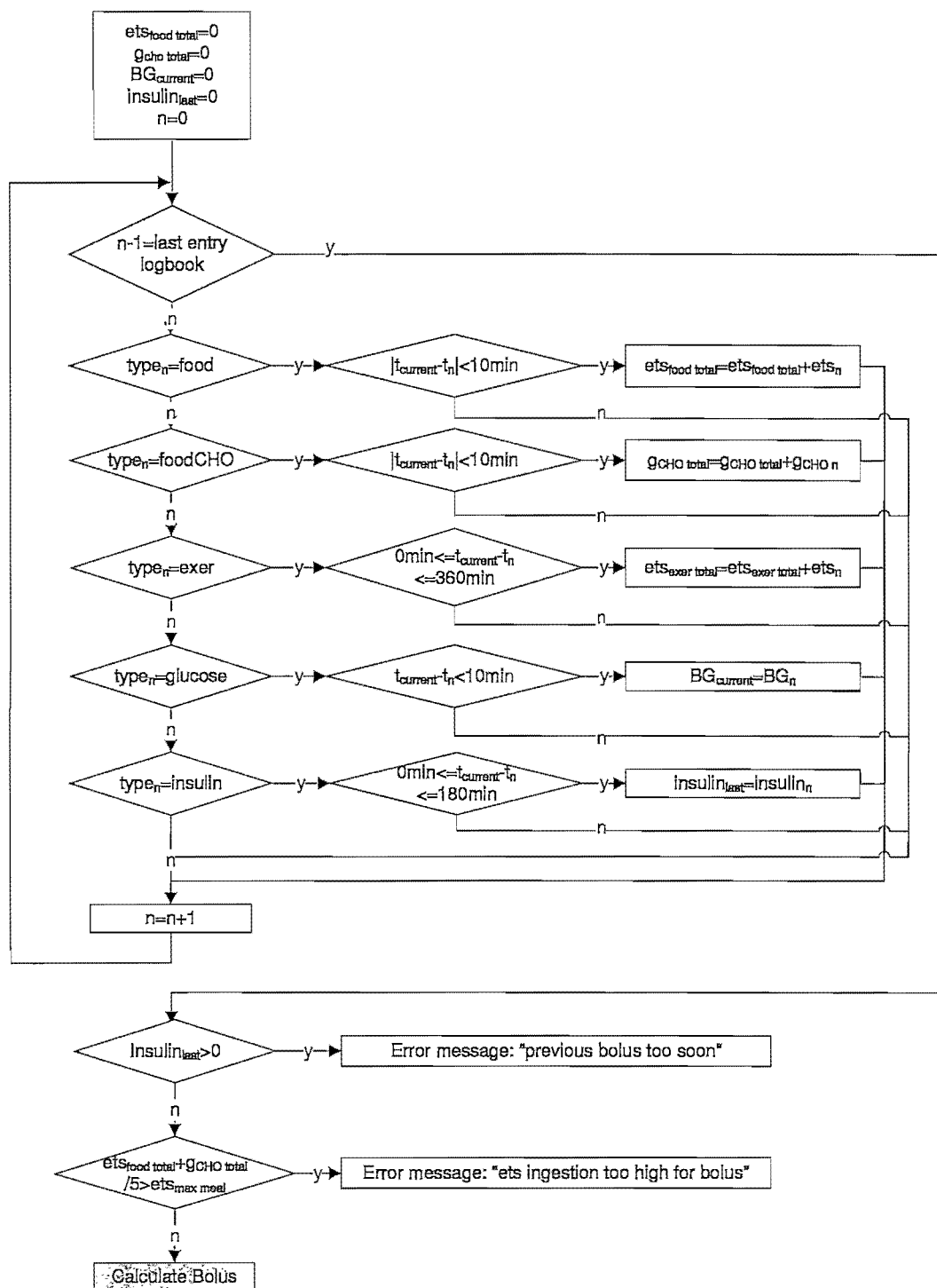


Figure 24: Flow diagram for calculating totals from the logbook database and initial safety check.

The bolus is then calculated by using the equations derived in Chapter 5. The resulting suggestion will then be displayed to the user. The accuracy of this suggestion is dependant on

the data entered by the user and also the accuracy of the results obtained from the characterization procedure to customize the product for the specific diabetic patient.

5.5 PDA vs. Cellphone based bolus calculator

The initial ets-insulin-bolus calculation software was developed for a PDA (Personal Digital Assistant) such as the Palm device. A small clinical trial was conducted at the University of the Free State with the help of Prof. W. Mollentze. Although patients found the device to be useful, some concerns were identified. Most of these concerns were addressed by implementing the software application on a cellphone instead.

The disadvantages of the PDA based bolus calculator are as follows:

- Additional bulky device needed to be carried around.
- Most people do not own a PDA, and these are expensive.
- New user interface takes some getting used to.
- Low cost PDA's often have displays with poor contrast levels which cause legibility problems for some diabetics.

The main advantages of a cellphone implementation (addressing these concerns of the PDA) are as follows:

- No need for an additional device. The phone and bolus calculation technology is on a single device
- No need to buy a new device, the software application can merely be downloaded onto the cellphone⁶.
- Users are familiar with the user interface of the cellphone, they do not perceive this as new technology.
- Newer generation cellphones have bright, high contrast screens.
- The various connectivity options available to cellphones make the download of software, such as the bolus calculation software, very easy.

The last clinical trial was therefore conducted by using the cellphone-based bolus calculator.

⁶ With the introduction of many newer generation phones to the market, more and more phones will be compatible for use with the software application.

5.6 Slide rule based bolus calculator

A need was identified to develop a simple bolus calculator that is easy-to-use, inexpensive but also accurate. This need led to the idea of a slide rule device shown in Figure 25.

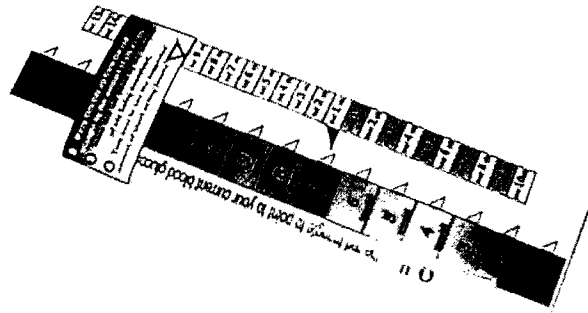


Figure 25: ets slide rule device for insulin-bolus calculation

The slide rule device is used in conjunction with a database booklet containing the ets values for some common foodstuffs and exercises. Unfortunately, this device requires more time to operate because the ets value for foods, beverages and exercises have to be looked up in a database booklet. This is the most significant drawback to this implementation.

The ets-insulin-bolus slide rule consists of a center rule, large sleeve and a small sleeve. Figure 25 shows the main parts of the slide rule device. The large sleeve slides over the center rule, while the small sleeve slides over the large sleeve. The surface of the large sleeve is mostly transparent except for the area where the scale is printed.

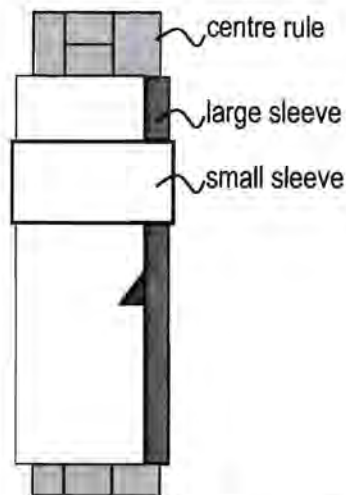


Figure 26: Main parts of the ets-insulin-bolus slide rule

The center rule has printed on the front a blood glucose scale and on its back an insulin dosage scale. This scale is calibrated so that the actual distance between two consecutive calibration marks on the blood glucose scale, divided by the actual distance between two consecutive marks on the insulin dosage scale, equals the insulin sensitivity of the user.

The large sleeve is mostly transparent and slides over the center rule. Printed on its front is an ets scale for food and exercise. The calibration of this scale is similar to the insulin scale. The ets scale is calibrated so that the actual distance between two consecutive calibration marks on the blood glucose scale, divided by the actual distance between two consecutive marks on the ets scale, equals the ets sensitivity of the user.

The calibration technique therefore allows the different scales to be customized for the specific end user. Several different sleeves with different calibration values can be printed and mixed-and-matched to customize the device according to the ets and insulin sensitivity of the specific patient.

Operation of the device is fairly simple and instructions are printed on the device. The first step is to set the pointer on the large sleeve to point to the pre-prandial blood glucose level of the diabetic. Next, the diabetic uses the database booklet to determine how much ets there is in the meal that is to be ingested. The small sleeve is then move up from the pointer on the large sleeve by the number of markings equivalent to the ets value of the meal.

If the person is going to perform any exercises during the following six hours from insulin administration, the small sleeve should be moved down by the number of markings on the

large sleeve, equivalent to the ets value of the exercise that is going to be performed. The device is then turned over and the small sleeve will point to either an appropriate dosage of bolus insulin, a suggestion to take no action (not to administer any insulin) or a suggestion to eat an additional amount of ets to counter-act hypoglycaemia.

The slide rule device is not the focus of this study. It is, however, a very useful device. More information on this device regarding the design and operation can be found in the patent, Appendix A. This device makes an ideal low-cost promotional item for a pharmaceutical company that wants to promote their brand of insulin. The device can be branded with the logo of a pharmaceutical company and be distributed free of charge to their patients.

5.7 Intellectual property

The ets-bolus system that is described in this chapter, is novel. This is due to the fact that ets-counting is used, as opposed to the carbohydrate counting that is used by several other products and patents. Although this chapter only describes a few of the implementations of the ets-insulin bolus calculation system, there are many other possible implementations.

A preliminary patent was written and registered with the help of patent attorneys DM Kisch. The patent is titled: “Apparatus and method for predicting the effect of ingested foodstuff or exercise on the blood sugar level of a patient and suggesting a corrective action”. The patent is included in Appendix A.

The patent includes descriptions of the following implementations of the ets-insulin-bolus system:

- patient characterization method and system implemented as a slide rule device,
- ets-insulin-bolus calculator implemented as a slide rule device,
- ets-insulin-bolus calculator implemented as a PDA based software application,
- ets-insulin-bolus calculator implemented as a mobile phone based software application and
- ets blood glucose simulation software program for educational purposes.

Several PCT registrations were also done in February 2005. These include:

- PCT/ZA2005/000038: “Interactive diabetes educational system” claiming priority from preliminary South-African patent 2004/1349 [4];
- PCT/ZA2005/000039: “Characterization device for carbohydrate and insulin sensitivity” claiming priority from preliminary South-African patent 2004/1352 [5];
- PCT/ZA2005/000040: “Insulin bolus calculator for mobile communication device” claiming priority from preliminary South-African patent 2004/1345 [6] and
- PCT/ZA2005/000044: “Diabetes slide rule for blood glucose control” claiming priority from preliminary South-African patent 2004/1353.

All the specifications for the abovementioned preliminary patents and PCT registrations were written by the author of this study.

Patents are essential for protecting the IP (intellectual property) of any R&D company. The investment in these R&D projects can be substantial and therefore it is crucial to protect IP to ensure that the initial investing companies gain the maximum financial benefit from their investments.

5.8 Summary

This chapter discussed the design and development of three different insulin bolus calculation products using ets-counting as a basis for these calculations. The PDA based software application was initially developed and tested. Although patients found the device to be useful, some concerns were raised. Most of these concerns related to the ease-of-use and practicality of the solution.

An improved algorithm was then designed and developed for a cellular phone. This implementation is a lot simpler to use and also more practical. This software application includes an extensive food-and-beverage as well as an exercise database. Throughout the design and development of this device, the end-user was kept in mind to provide a practical and easy-to-use solution.

Finally a more cost-effective version of the insulin-bolus calculator was implemented on a slide rule. This device is inexpensive and easy to use and is accompanied by a booklet with food and exercise ets values. This device is ideal for marketing and corporate branding by a

pharmaceutical company who may want to sponsor the distribution of this device to their clients.

5.9 References

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5. WO 2005/081172 A1, PCT/ZA2005/00039, 1 Sep 2005, Characterization device for carbohydrate and insulin sensitivity, WIPO, 34 Chenin des Colobettes, 1211 Geneva 20, Switzerland (2005)
6. WO 2005/081173 A1, PCT/ZA2005/00044, 1 Sep 2005, Diabetes slide rule for blood glucose control, WIPO, 34 Chenin des Colobettes, 1211 Geneva 20, Switzerland (2005)

CHAPTER 6

IMPROVED BLOOD GLUCOSE CHARACTERIZATION

The ets-insulin-bolus calculation products discussed in Chapter 5 need to be customized for the specific patient. This chapter deals with the patient-characterization procedure to measure the insulin and ets food sensitivity values of Type 1 diabetics. These values are used to customize the bolus calculation algorithms to provide accurate bolus results for the diabetics.

6 IMPROVED BLOOD GLUCOSE CHARACTERIZATION

6.1 Introduction

The success of any medical treatment is dependant on the customization thereof for the specific patient. The correct choice, timing and dosage of medication are crucial for the management of diseases. Type 1 diabetes is even more complicated to manage than most other chronic diseases. Special care has to be taken to establish an insulin regime for the diabetic patient.

The bolus-calculation products developed and discussed in Chapter 5, rely on certain user parameters as inputs to the calculations. These include the ets food sensitivity and insulin sensitivity of the diabetic patient. They are used to predict the blood glucose response to food and insulin of the specific diabetic. The characterization procedure to measure these values is discussed in this chapter.

6.2 Equipment

Two different measuring devices can be used to carry out the blood glucose characterization of the Type 1 diabetic patient. Both systems involve monitoring the blood glucose level of the diabetic patient for a few hours.

The first option is the standard blood glucose monitor utilizing a sample of blood put onto a blood glucose test strip to measure the blood glucose level. This measurement gives only a discrete (single) value. If blood glucose should be monitored for a period of three hours for example, this would mean that the patient has to prick his/her finger every few minutes to measure the blood glucose level. This is therefore not a very convenient option.

The second option is the use of a CGMS (Continuous Glucose Monitoring System). This system uses a glucose sensor connected by means of a wire to an electronic measuring device. The glucose sensor is inserted into the subcutaneous tissue of the patient and then calibrated. When correctly inserted and calibrated, the CGMS system will monitor blood glucose levels for up to three days.

The CGMS measures the blood glucose level of the patient every five minutes and stores these values together with their associated times. This data can then be downloaded onto a personal computer for further analysis. This continuous set of blood glucose data is very useful to the medical professional designing the treatment of the patient. This system has proved to be a very important part of diabetes diagnosis and treatment [1,2,3,4]



Figure 27: Medtronic CGMS

Unfortunately, the CGMS system and its sensors are very expensive at this stage. Hopefully the cost of this technology will decrease with time, since Medtronic's competitors are working on similar products. Fortunately, the characterization procedure only has to be performed once and therefore the costs involved are justified.

6.3 Measurement of ets (food) sensitivity

Ets food sensitivity ($f_{BS/food\ ets}$) is defined as the rise in blood glucose level per ets ingested. This sensitivity value should be measured when there is no residual effect of bolus insulin on the blood glucose level. This is to separate the effects of the two blood glucose altering factors, namely food ingestion and insulin administration. For convenience, Table 4 is repeated below.

	Onset (h)	Peak (h)	Effective Duration (h)
Rapid acting			
Insulin lispro	< 0.3 - 0.5	0.5 - 2.5	3 - 4
Insulin aspart	< 0.25	0.5 - 1.0	1 - 3
Short acting			
Regular	0.5 - 1	2 - 3	3 - 6

Table 7: Rapid and short acting insulin suitable for bolus insulin administration

To ensure that the effect of the previous insulin bolus administration is negligible, a period of time equal to the sum of the insulin onset and the effective duration period should be allowed to pass before performing the ets sensitivity measurement. Table 7 can be used as a guide of how long this period should be.

The diabetic patient should therefore fast for a period of up to four to six hours (depending on the specific insulin used) before the ets food sensitivity measurement is performed. The blood glucose level should then be measured prior to the test meal that is to be ingested. The diabetic patient should then ingest a test meal of which the ets contents are known. This test meal should contain at least 50% carbohydrates and be less than 8 ets.

The blood glucose should then be monitored for a period of three hours. This can be done by either taking finger prick blood glucose measurements every 15 minutes or by using the CGMS to measure blood glucose levels every 5 minutes as described above.

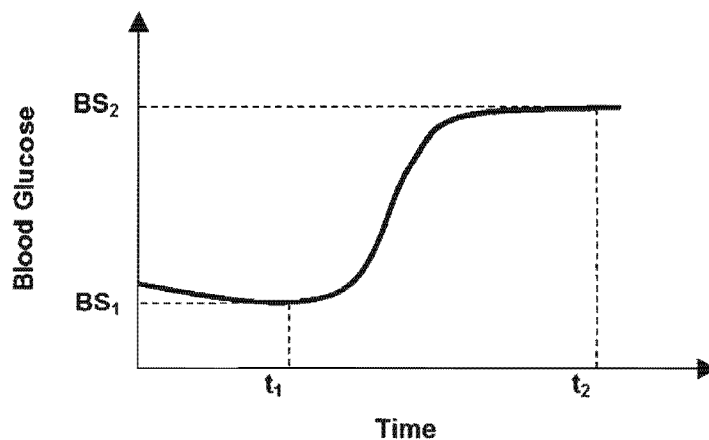


Figure 28: Blood glucose response for ets food sensitivity measurement

Figure 28 illustrates a typical blood glucose response of a Type 1 diabetic during the ets food sensitivity measurement procedure. The time prior to t_1 is the fasting period. The test meal containing $ets_{test\ meal}$ is taken at t_1 . The blood glucose level (BS_1) taken at time t_1 should be measured. The blood glucose level should then be monitored for at least two to three hours. The blood glucose level (BS_2) is then measured again at time t_2 (usually after two hours).

The ets food sensitivity can then be calculated by using the following equation:

$$f_{BS/ets\ food} = \frac{BS_2 - BS_1}{ets_{test\ meal}} \quad (1)$$

Typical ranges for $f_{BS/ets\ food}$ is between 0.4 and 1 mmol/l.ets for Type 1 diabetics (from clinical results). If this value falls outside of this range, the value should be measured again to make sure that the measurements are correct. This test procedure should not be performed when the person is under emotional stress or ill, since this will influence the accuracy of the measurement.

It should also be noted that the blood glucose level prior to the test meal should not be very high, and preferably below 10mmol/l. If this is not the case, the linear response of blood glucose elevation to ets ingestion is influenced and therefore the sensitivity value cannot be accurately measured. The CGMS system can also not be calibrated at high blood glucose levels.

6.4 Measurement of insulin sensitivity

Insulin sensitivity ($f_{BS/insulin\ bolus}$) is defined as the change in blood glucose level per Unit bolus insulin administered. This sensitivity value should be measured when there is no residual effect of the previous meal on the blood glucose level. It is usually convenient to perform this test procedure immediately after the ets food sensitivity test procedure.

To make sure that there is no residual effect from the previous meal, there should be a period of at least two to three hours of fasting prior to the insulin sensitivity test procedure. There

should also not be any active bolus insulin left in the blood (see Table 2 for timing of different types of bolus insulin).

The blood glucose level should be high, preferably between 10mmol/l and 15mmol/l before the insulin sensitivity test procedure is performed. The blood glucose level should be measured immediately before the insulin is administered. An appropriate number of bolus insulin units should then be administered to lower the blood glucose level.

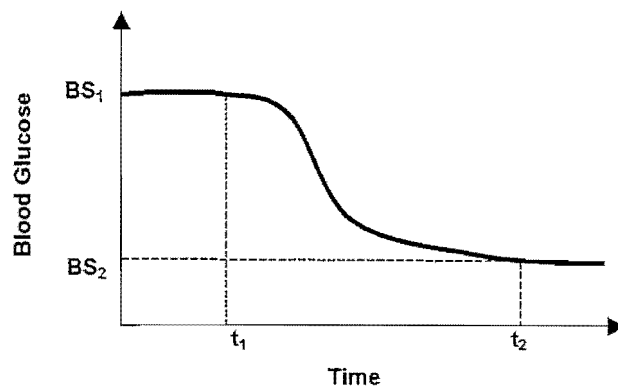


Figure 29: Blood glucose response for insulin sensitivity measurement

Figure 28 illustrates a typical blood glucose response of a Type 1 diabetic during the insulin sensitivity measurement procedure. The time of the insulin administration (I_{bolus}) is t_1 . The blood glucose level immediately before the insulin administration is BS_1 . The blood glucose level should then be monitored for a period equal to the sum of the onset and effective duration period of the specific bolus insulin used. The blood glucose level is then again measured (BS_2) at time t_2 .

The insulin sensitivity can then be calculated by using the following equation:

$$f_{BS/insulin} = \frac{BS_2 - BS_1}{ets_{test\ meal}} \quad (2)$$

Typical ranges for $f_{BS/insulin}$ is between -0.3 and -3.5 mmol/l.ets for Type 1 diabetics. If this value falls out of this range, the value should be measured again to make sure that measurements are correct. This test procedure should also not be performed when the person is under emotional stress or ill, since this will influence the accuracy of the measurement.

The blood glucose level prior to the insulin administration should also be high, preferably between 10 and 15 mmol/l. If the blood glucose level is too low, the linear response of blood glucose reduction to insulin administration is influenced and therefore the sensitivity value cannot be accurately measured.

6.5 Characterization procedure and verification

The following characterization procedure is proposed. For the most accurate results, the use of a CGMS system is recommended. The patient should be connected to the CGMS system for a period of three days. The resulting blood glucose levels measured over this period is then downloaded onto a personal computer for analysis.

During this period the patient is required to keep track of any food intake, exercise and insulin administration. This is done by logging the following information against time in a log sheet provided to the patient:

- description of food or beverage item, as well as portion size and number of portions ingested;
- type of exercise, intensity and duration of exercise;
- any blood glucose measurements (measured with finger prick monitor) and
- type (brand) of insulin and number of units administered.

The CGMS data can then be analyzed together with the log sheets. The patient is requested to continue with his/her normal daily schedule. This means that the patients should continue to eat, drink, exercise and administer insulin as normal. On the third day, the patient is required to first eat meals, but only administer insulin two to three hours after the meal. Usually Type 1 diabetics administer insulin immediately prior to their meals. Furthermore, patients are requested not to take any snacks between the three main meals.

The delay in insulin administration between meals makes it possible to isolate the effects of the food and insulin on blood glucose levels. Equations (1) and (2) can therefore be used to calculate the ets food and insulin sensitivity of the patient. The ets content of meals can be

calculated from the log sheet data. The CGMS data makes it possible to easily calculate these values.

It is important to verify these sensitivity values. This can be done in the following manner: The total daily ets (ets_{2days}) ingested over the first two days on the CGMS system should be calculated from the log sheet data. The total bolus insulin ($I_{2days\ bolus}$) administered over the first two days should also be calculated.

Two new ets per insulin ratios can be defined as follows:

$$R_{ets / insulin\ 2days} = \frac{ets_{2days}}{I_{2days\ bolus}} \quad (3)$$

and by using Equations (1) and (2):

$$R_{ets / insulin\ calculated} = \frac{f_{BS / insulin}}{f_{BS / ets}} \quad (4)$$

The two ratios defined by Equations (3) and (4) should now be compared with each other.

Condition	Experienced hypoglycaemia	Good Control	Experienced hyperglycaemia
$R_{ets / insulin\ 2days} \approx R_{ets / insulin\ calculated}$	Possible error	Possibly correct	Possible error
$R_{ets / insulin\ 2days} < R_{ets / insulin\ calculated}$	Possibly correct	Possible error	Possible error
$R_{ets / insulin\ 2days} > R_{ets / insulin\ calculated}$	Possible error	Possible error	Possibly correct

Table 8: Possible outcomes of verification of patient characterization values

If these two ratios are roughly the same, the values are probably correct. Table 8 can be used to verify whether the characterization values are correct or not. If the values appear to be incorrect, it is suggested that the characterization procedure be repeated. The condition refers to the general state of glycaemic control during the test period.

6.6 Conclusion

The CGMS system developed by Medtronic is a very useful tool. Without proper blood glucose characterization of the blood glucose response of the diabetic patient, the bolus calculation products discussed in Chapter 5 will not provide accurate results.

An easy to use system should be developed to automatically analyze CGMS data and patient log sheets to make the patient characterization procedure even easier and less time consuming. This will help to win the acceptance of medical professionals who will eventually carry out the patient characterization. The procedure discussed in this chapter was used during the clinical trial that will be discussed in Chapter 7.

6.7 References

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CHAPTER 7

ETS-INSULIN-BOLUS CALCULATOR CLINICAL TRIAL

The ets-insulin bolus calculation device had to be tested to determine whether accurate insulin boluses can be calculated. The clinical trial also helped to demonstrate that the device tested was a practical solution.

7 ETS-INSULIN-BOLUS CALCULATOR CLINICAL TRIAL

7.1 Introduction

The ets-insulin-bolus calculator was designed and developed in order to help Type 1 diabetics improve their blood glucose control. However, before this device can be made commercially available, it has to be thoroughly tested. Prototypes of the bolus calculator products were frequently evaluated by diabetics during the different stages of development. This feedback helped to shape the current implementation of the system.

A clinical trial of small magnitude (pilot study) was designed and conducted at Montana Hospital using several Type 1 diabetics. Each used the device over a period of three months. This chapter discusses the various aspects of this clinical trial and also the results obtained. The purpose of this clinical trial was to establish whether the ets-insulin-bolus calculator does in fact improve glycaemic control of Type 1 diabetics and at the same time to ascertain whether diabetics find the device useful and easy-to-use.

7.2 Problem and Hypothesis

The main **problem** addressed by this study in this clinical trial was the following:

Type 1 diabetics struggle to control their blood glucose levels. One of the main reasons for this is inaccurate bolus calculation. Hyperglycaemia can be caused by injecting too little bolus insulin, whilst injecting too much bolus insulin can cause hypoglycaemia. Conventional methods for bolus calculation, such as CHO counting, are not very accurate. Therefore, most diabetics do not easily achieve good glycaemic control. Furthermore, the literature survey shows that ets is a better predictor for insulin requirements than CHO counting.

The **hypothesis** is therefore:

By using the ets concept for three months on a test group of Type 1 diabetics familiar with CHO counting, HbA1C levels can be lowered by at least 1% (HbA1C is measured as a percentage value, with the ADA target set at 7%).

A secondary objective was to determine whether fewer occurrences of hypo- and hyperglycaemia were being encountered. This information was obtained from questionnaires.

7.3 Protocol, Questionnaires and PIC's

Conducting research on human-beings (and even animals) requires a great deal of caution and care. There are several issues that need to be addressed. All research conducted on human-beings is subjected to certain ethical guidelines [1,2]. The potential advantages of the intervention being tested should outweigh the possible discomfort and risks to the diabetic patients.

In order to conduct a clinical trial on human subjects, approval should be obtained from an ethical committee in the country where the clinical trial is to be conducted. It was decided to make use of a commercial ethical committee, namely Pharma-Ethics. The following documentation was submitted to the ethical committee for review:

- Clinical Trial Protocol (Appendix B),
- Patient Informed Consent (PIC) forms (Appendix C),
- Pre-trial questionnaire (Appendix D) and
- Post-trial questionnaire (Appendix E).

The PIC forms and questionnaires were made available in both English and Afrikaans as prescribed by the guidelines of the ethical committee.

Clinical trial protocol

The following sections make out the clinical trial protocol:

- a literature review on insulin-bolus calculation,
- problem statement and hypothesis,
- possible benefits arising from the study,
- objectives of the study,
- a materials and methods section including:
 - the experimental model to be used,
 - experimental design criteria,

- observations and analytical procedures,
- data analysis and
- project management;
- reporting of information,
- reporting of deviations,
- ethical considerations,
- trial budget and the
- duration and time schedule of the clinical trial.

Patient informed consent (PIC) form

The patient informed consent form is to inform the patient of the purpose of the study, how the study is going to be conducted, possible benefits and risks arising from the study and information regarding the termination of the clinical trial. This is an agreement between the trial coordinator and the trial subject. It sets out the terms and conditions of participation in the clinical trial.

Trial subjects may at any time decide to withdraw from the clinical trial. Furthermore, when certain adverse events happen, the trial coordinator and/or trial doctor may use his/her discretion to terminate a trial subject's participation in the clinical trial. If a trial subject fails to comply with these terms and conditions, the trial subject is taken out of the study group (e.g. when a trial subject becomes pregnant).

Pre-trial questionnaire

The pre-trial questionnaire was used to obtain the following information:

- age,
- gender,
- weight at onset of trial,
- height,
- number of years diagnosed as a Type 1 diabetic,
- typical daily routine during week and weekend,
- frequency and intensity of any exercises,
- frequency of occurrences of hypo- and hyperglycaemia,
- skill level of cellphone usage,
- knowledge of CHO counting and insulin-to-carbohydrate-ratio,
- total daily long-acting insulin and total daily short-acting insulin dosage,

- breakdown of insulin regime (including type and brands) of insulins,
- type of insulin therapy (pump, pen, syringe, other),
- brand and model of blood glucose monitor being used,
- frequency of blood glucose measurements on a typical day,
- medical history relating to diabetes or other chronic diseases,
- other diabetic and non-diabetic medication used,
- ~~ets~~ sensitivity value as measured,
- insulin sensitivity value as measured and also
- HbA1C as measured.

Because this trial primarily focuses on the causality between blood glucose control and ets-Bolus calculations, the baseline examination will consist of the pre-trial questionnaire completed by the trial subject and reviewed by the trial doctor and also the HbA1C level measured on the day that the clinical trial commences.

Post-trial questionnaire

The post-trial questionnaire is completed at completion of the clinical trial (after three months) and was used to gather the following additional information:

- Weight at completion of trial,
- typical daily routine during weeks and weekends of clinical trial,
- frequency and intensity of any exercises,
- frequency of occurrences of hypo- and hyperglycaemia,
- total daily long-acting insulin and total daily short-acting insulin dosage,
- HbA1C as measured (measured by Ampath).

It also included an evaluation of the use of the bolus calculation device, with questions like:

- Is it easy to use?
- Is it user-friendly?
- Are the food and exercise databases easy to use?
- Is it difficult to find a specific food?
- Is it easy to calculate the insulin bolus?
- Are the subjects able to trust the suggested values?
- Are the calculations reliable?
- Is it difficult to operate the cellular phone?

7.4 Execution of the clinical trial

The clinical trial was conducted with the help of Dr. L. Johnson who acted as the trial doctor. Dr L. Johnson has a diabetic practice at Montana Hospital in Pretoria. All the trial subjects were randomly selected from her practice's patients and sent a letter informing them of the study. The patients who responded and were characterized were included in the clinical trial.

Participation for the trial subjects included the following activities:

- Trial subject receives a request to take part in the clinical trial and is requested to reply if he/she is willing to participate in the clinical trial;
- Trial subject signs PIC form;
- Trial subject completes the pre-trial questionnaire (see Appendix D);
- The characterization procedure described in Chapter 6 is performed on the trial subject to determine ets and insulin sensitivity values;
- The hemoglobin (HbA_{1c}) level of the trial subject is measured (Ampath);
- Trial subject receives an instruction manual describing the operation of the ets-insulin-bolus calculation software installed on the cellphone;
- Trial coordinator enters the user-specific parameters (that were measured using the characterization procedure described in Chapter 6) into the ets-insulin-bolus calculation software application on the cellphone;
- Trial subject receives the customized cellular phone with the ets-insulin-bolus calculation software;
- Trial subject uses the software application for a period of three months to calculate insulin boluses;
- After three months, the trial subject returns the cellular phone, completes the post trial questionnaire (see Appendix E) and the hemoglobin level is measured again (HbA_{1c}).

7.5 Clinical results

The initial test group consisted of 12 Type 1 diabetics following a basal-bolus insulin regime. These patients all signed the Patient Informed Consent form and completed the clinical trial. One patient had to be removed from the test group after becoming pregnant, since the ethical

committee stipulated that pregnant women may not participate. Another had to be removed from the test group because she was still in the honey-moon phase of her diabetes. Her insulin treatment was temporarily halted at the onset of the trial and therefore she could not continue with the clinical trial.

A further two patients decided on their own accord to end their participation in the trial. According to the Patient Informed Consent form, test subjects may decide to end participation at any time. Complete data results are thus only available for 8 test subjects who completed the full 3 month clinical trial.

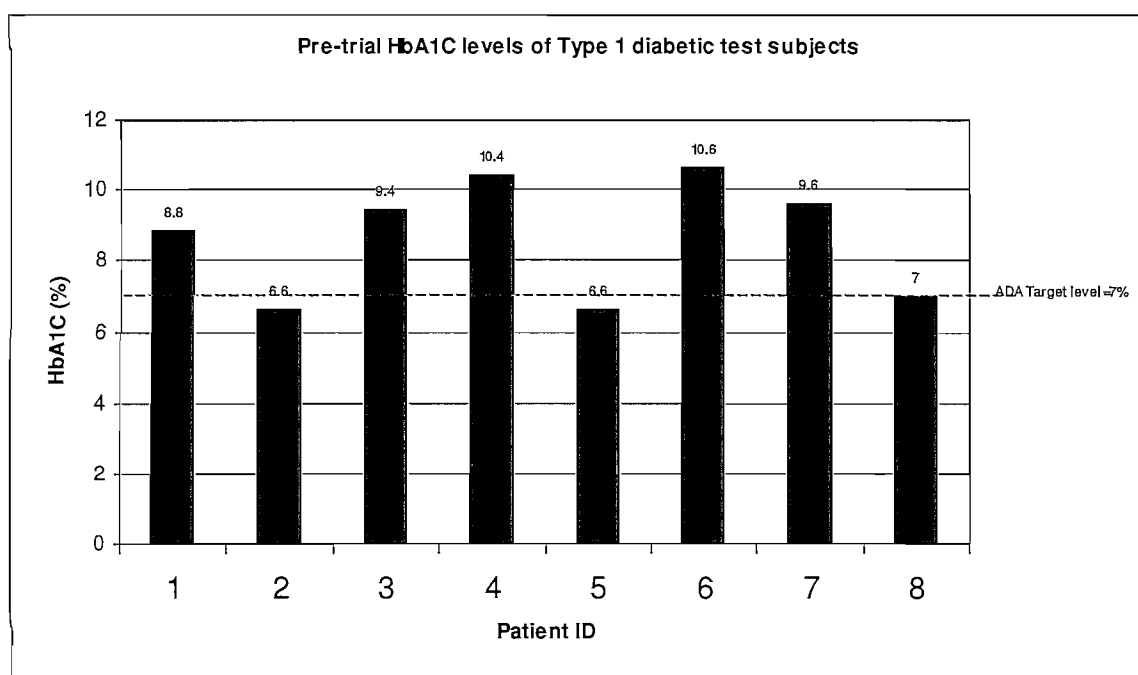


Figure 30: Pre-trial HbA1c levels of Type 1 diabetic test subjects

Figure 30 shows the pre-trial HbA1c levels of these eight test subjects. HbA1c levels are measured as percentage values. The average pretrial HbA1c level was 8.6% with a standard deviation of 1.7%. The ADA target HbA1c guideline level is 7%. Therefore only two patients (patients 2 & 5) had HbA1c levels below the target level and one (patient 8) bordering the target level. The other five test subjects' HbA1c levels (and therefore their glycaemic control) was above the target level.

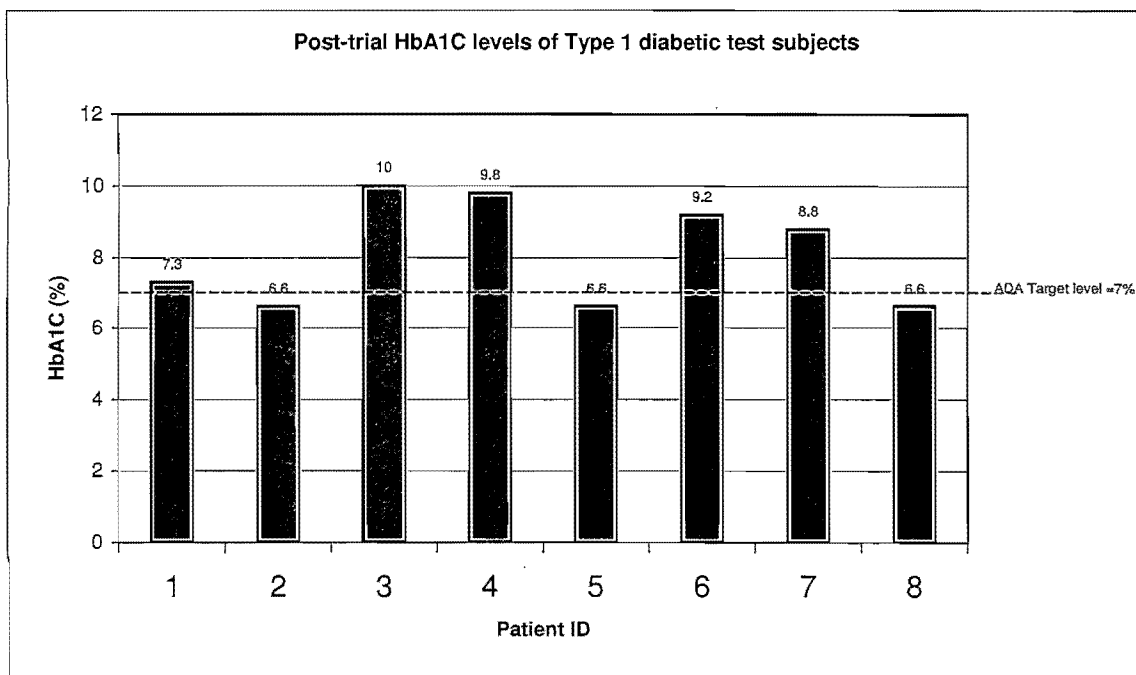


Figure 31: Post-trial HbA1c levels of Type 1 diabetic test subjects

Figure 31 shows the post-trial HbA1c levels measured on the last day of the clinical trial. The average post-trial HbA1c level was 8.1% with a standard deviation of 1.5%. Three patients (2,5 & 8) had HbA1c levels below the ADA target of 7%. The other 5 patients had HbA1c levels above the target level.

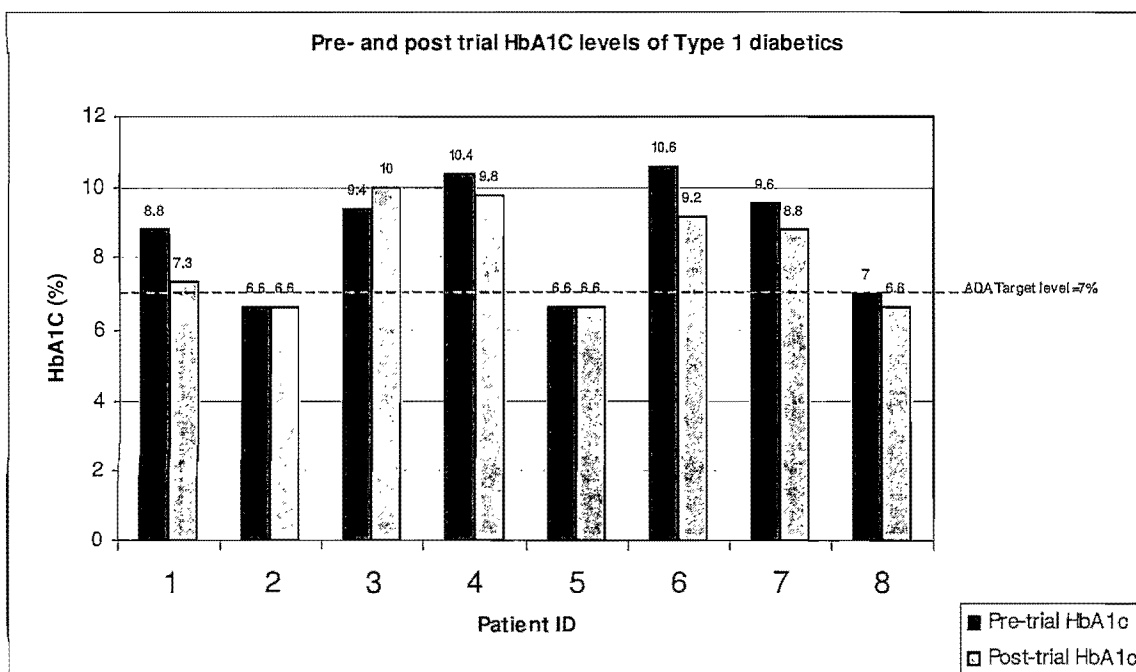


Figure 32: Pre- and post-trial HbA1c levels of Type 1 diabetic test subjects

Figure 32 shows the pre- and post-trial HbA1c levels of the test subjects, whilst Figure 33 shows the reduction in HbA1c levels. From Figure 33 it can be seen that 5 subjects had a reduction in their HbA1c levels, two subjects' HbA1c levels remained unchanged whilst one test subject's HbA1c level increased.

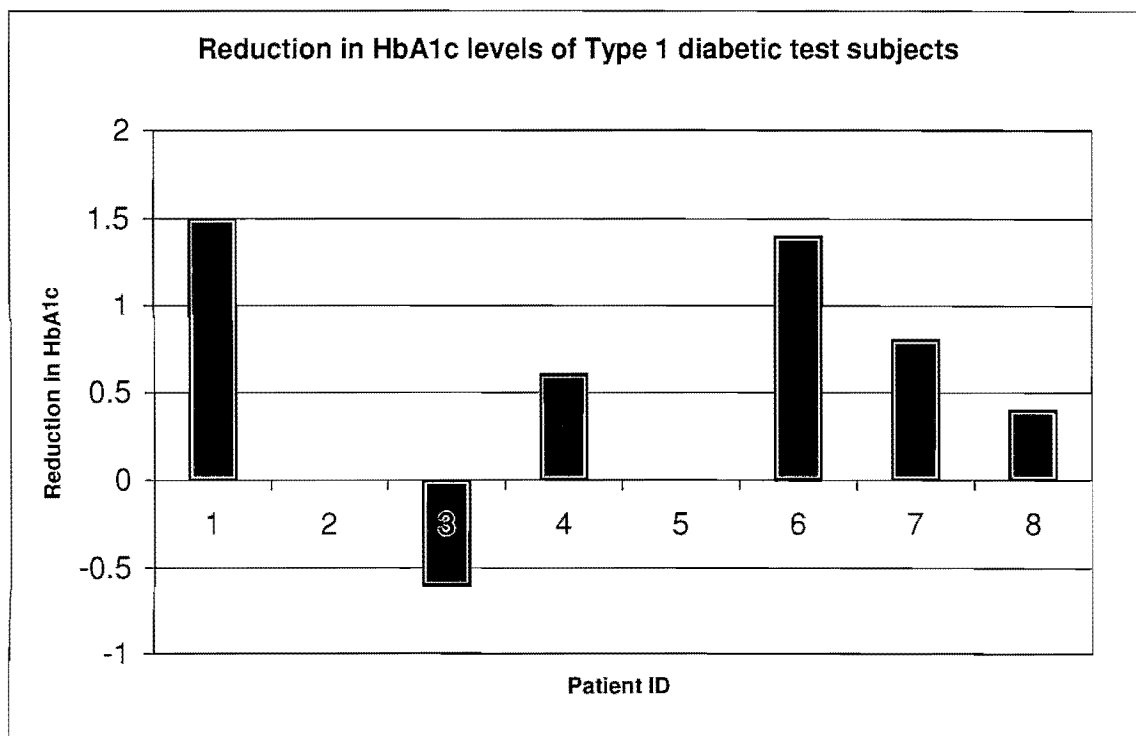


Figure 33: Reduction in HbA1c levels of Type 1 diabetic test subjects

Discussion of HbA1c results

Please note that HbA1c is measured as a percentage value.

Reduction in HbA1c: Patients 1,4,6,7 & 8

These five patients had an average reduction in their blood glucose levels of 0.94% (standard deviation of 0.43%). All five experienced considerable reductions (especially patients 1 and 7 with a reduction of 1.5% and 1.4% respectively) which were achieved over a relative short period of time (3 months). Patient 8 had a significant reduction when keeping in mind that the patient's HbA1c level was already equal to the ADA target level of 7% at the onset of the trial and this was reduced further to 6.6 at the end of the trial.

Unchanged HbA1c: Patients 2 & 5

The HbA1c levels of Patients 2 and 5 remained unchanged. Their HbA1c levels (6.6 and 6.6 % respectively) at the onset of the clinical trial were already well below the target level of 7% and therefore already had acceptable glycaemic control. Their glycaemic control therefore did not deteriorate, nor did it improve. It therefore seems that for patients with good glycaemic control, the ets-insulin bolus calculation is equal in performance to carbohydrate counting.

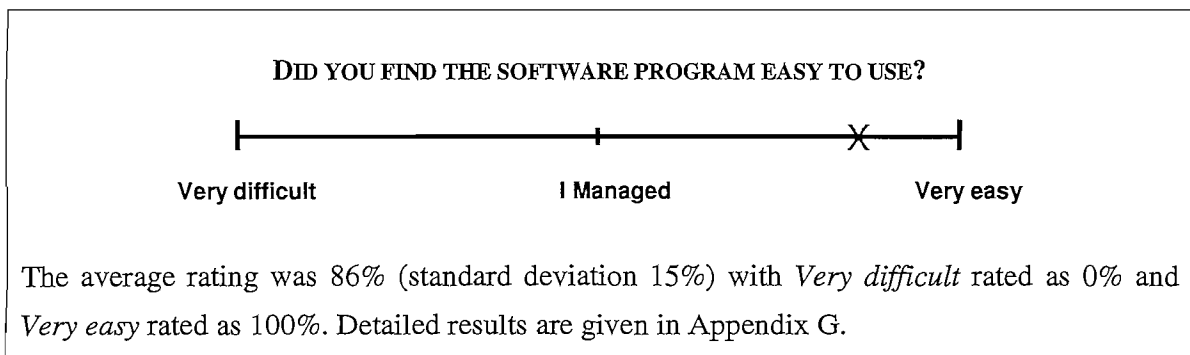
Elevated HbA1c: Patient 3

The HbA1c level of Patient 3 increased with 0.6%. Unfortunately, patient 3 underwent two shoulder operations and had severe dental infections during the duration of the clinical trial. Infections cause elevated blood glucose levels in diabetics. These elevations should rather be accounted for with basal (long-acting) insulin and not with bolus insulin (see Chapter 4.5).

The initially hypothesized average HbA1c reduction of 1% was not achieved. The average reduction of 0.53% is however considerable. It is difficult to judge the performance of a treatment with an intervention nature if similar studies have not been conducted. It is therefore especially difficult to formulate an initial hypothesis for a clinical study. According to the DCCT *any* sustained lowering of blood glucose helps, even if the person has a history of poor control [7].

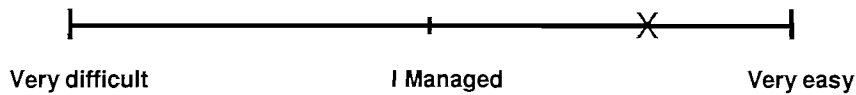
Assessment of Questionnaires and feedback

Software application



In general, all the patients found the software application easy to use. No patient reported that they did not manage to operate the software application or found the device difficult to operate.

DID YOU EASILY FIND FOOD AND EXERCISES IN THE DATABASES?



The average rating was 80% (standard deviation 12%) with *Very difficult* rated as 0% and *Very easy* rated as 100%.

All the patients found it easy to locate food and exercise items in the databases. This is important, because it is probably the most difficult and time-consuming task of operating the software application. No patients reported that they did not cope or found it difficult to do this task.

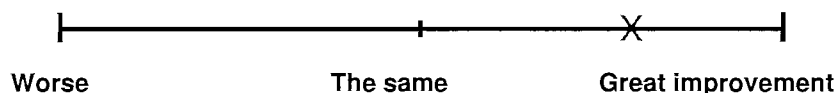
DID YOU FIND IT EASY TO CALCULATE YOUR INSULIN BOLUSSES?



The average rating was 85% (standard deviation 18%) with *Very difficult* rated as 0% and *Very easy* rated as 100%.

Six patients reported that they found it easy to calculate their insulin boluses with the device. One patient did not answer the question while one patient reported that he/she just managed, but did not find it easy nor difficult to do this task.

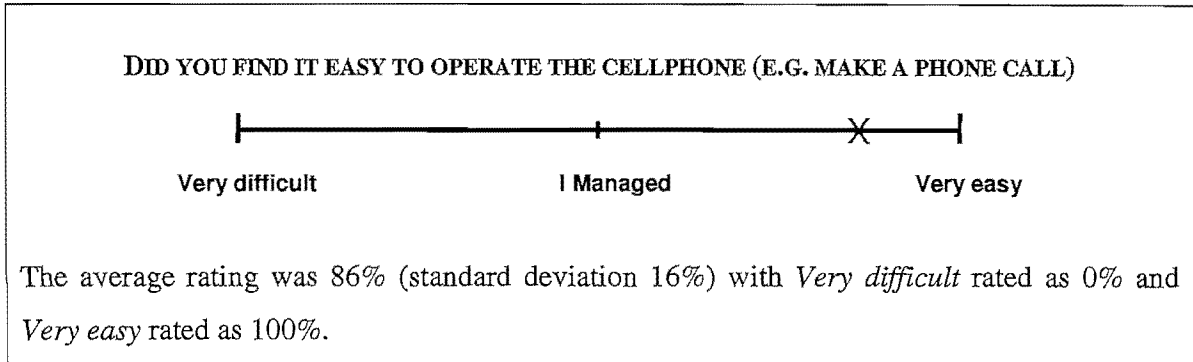
IF YOU HAVE MADE USE OF A SIMILAR DEVICE IN THE PAST, PLEASE RATE THE BOLUS CALCULATOR ACCORDINGLY



The average rating was 79% (standard deviation 6%) with *Worse* rated as 0% and *Great improvement* as 100%.

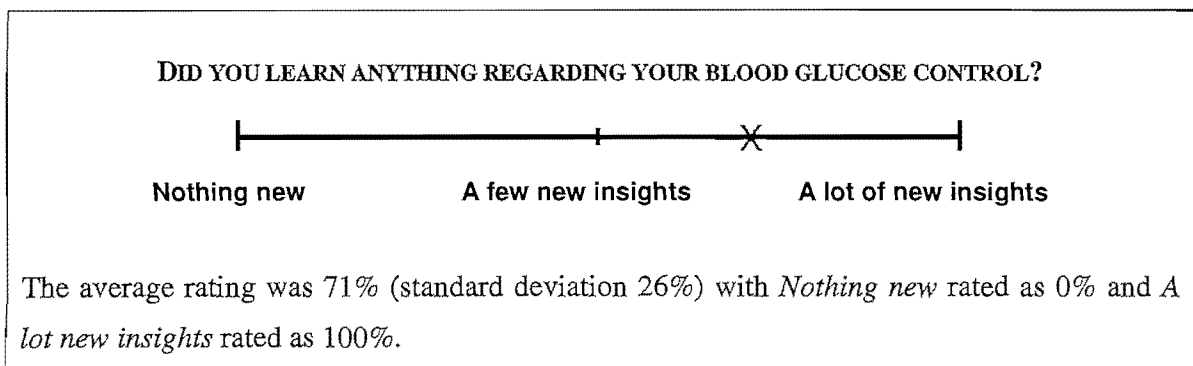
Only 2 patients have previously made use of similar devices. They both reported that the ets-insulin bolus calculator was an improvement on what they have used before.

Nokia Cellular Phone



It was important to establish whether patients experienced difficulties in operating the cellular phone. If they did, they would obviously also have difficulties operating the software program on the cellular phone. Seven patients reported that they found the Nokia cellular phone to be easy to use while one patient reported that he/she just managed but did not find it easy nor difficult to operate the phone. (It was the same patient that reported that she just managed but did not find it easy nor difficult to calculate insulin boluses.)

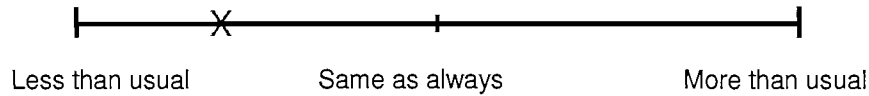
Educational value



Seven patients reported that they did learn some new insights regarding their blood glucose control while participating in the clinical trial. One patient, however, reported that she did not learn anything new from the clinical trial. Patient education is an important goal of this clinical trial.

Blood glucose control

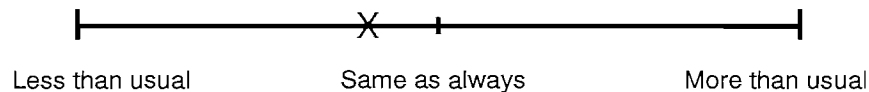
HOW OFTEN DID HYPO'S (LOW BLOOD SUGARS) OCCUR?



The average rating was 20% (standard deviation 16%) with *Less than usual* rated as 0% and *More than usual* rated as 100%.

Seven patients reported that they experienced less hypoglycaemic events during the clinical trial than before the trial. One patient experienced the frequency of hypoglycaemic events to have stayed the same. A lower frequency in hypoglycaemic events is one of the major goals of this clinical trial.

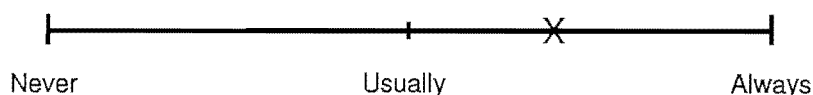
HOW OFTEN DID YOU MEASURE HIGH BLOOD SUGAR LEVELS?



The average rating was 40% (standard deviation 23%) with *Less than usual* rated as 0% and *More than usual* rated as 100%.

Four patients experienced less hyperglycaemic events during the clinical trial than before. Two patients reported that this frequency has stayed the same while two patients experienced an increase in hyperglycaemic frequency. It should, however, be remembered that an overall reduction in HbA1c level was achieved, and therefore, on average, their blood glucose levels were lower during the clinical trial than before.

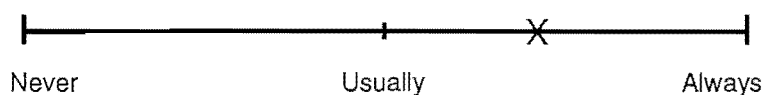
DID YOU TRUST THE BOLUS SUGGESTIONS MADE?



The average rating was 70% (standard deviation 18%) with *Never* rated as 0% and *Always* rated as 100%.

Six patients reported that they trusted the suggestions made by the device most of the time. Two patients reported that they usually trusted the suggestions made. No patients reported that they did not trust the suggestions calculated.

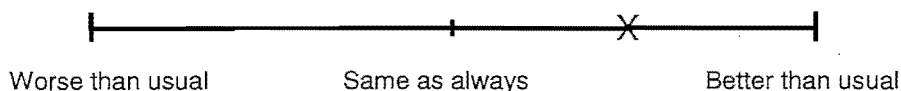
DID YOU FIND THE SUGGESTIONS THAT WERE MADE TO BE RELIABLE?



The average rating was 72% (standard deviation 19%) with *Never* rated as 0% and *Always* rated as 100%.

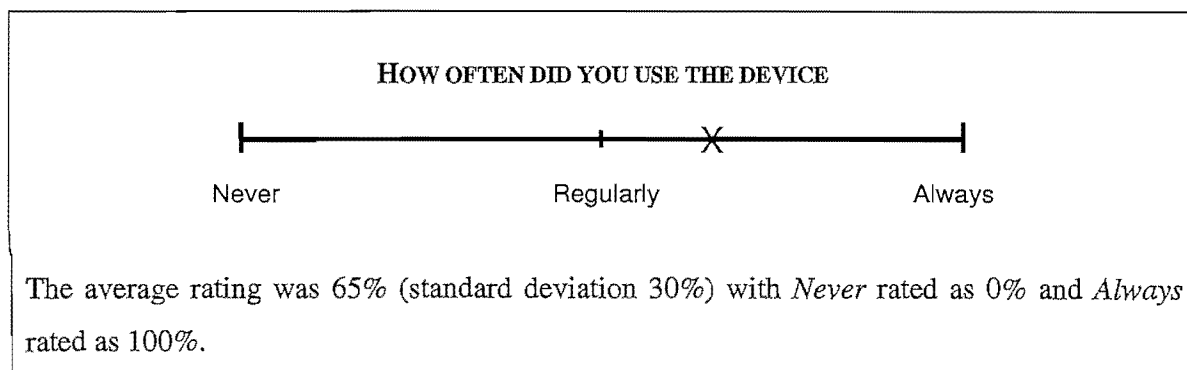
Six patients reported that they found the suggestions made by the device to be reliable most of the time. Two patients reported that they usually found the suggestions made to be reliable. No patients reported that they found the suggestions calculated to be unreliable.

HOW DID YOU FIND YOUR BLOOD GLUCOSE CONTROL TO BE DURING THE CLINICAL TRIAL?



The average rating was 74% (standard deviation 13%) with *Worse than usual* rated as 0% and *Better than usual* rated as 100%.

All the patients reported that an improvement in their blood glucose control was experienced during the clinical trial. An improvement in glycaemic control can be viewed as a combination of fewer hypo- and hyperglycaemic events, a lower HbA1c level and, in general, less diabetes-related complications (e.g. infections).



Four patients reported that they used the device almost always, three reported the frequency of use to be less than regular, while one patient did not answer the question.

7.6 Conclusion

A significant average reduction of 0.53% (standard deviation 0.72%) was achieved. [Note that HbA1c levels are measured as percentage values]. The average pre-trial HbA1c level was 8.63% (standard deviation 1.7%) whilst the average post-trial HbA1c level was 8.10% (standard deviation 1.5%). The HbA1c levels of two patients (who already had acceptable blood glucose control) remained unchanged. One patient had an increase in HbA1c level (her medical records were discussed above).

The reduction in HbA1c levels indicated that the patients' HbA1c levels were brought 32% closer to the ADA guideline for acceptable glycaemic control. This was achieved over a relative short period of three months. It is therefore predicted that these levels can be lowered even further over an extended period of time. This can be done by introducing a reduction in the safety margin of the target blood glucose control level of the bolus calculation parameters. Patients with acceptable blood glucose control stayed the same and, in one case, even improved.

Overall it can be stated that the patients did find the device to be easy to use, calculation of insulin boluses was simple, they trusted the suggestions made, found these suggestions to be reliable and perceived an improvement in their blood glucose control.

7.7 References

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CHAPTER 8

CLOSURE

This chapter concludes this study. The potential of both the ets-concept and the ets-insulin-bolus calculator is discussed. Recommendations for further work are also made.

8 CLOSURE

8.1 Introduction

During this study, a new concept was developed to calculate insulin boluses for Type 1 diabetics. The cornerstone of good glycaemic control is a healthy lifestyle, proper self-monitoring and an appropriate insulin regime. The ets-bolus calculator promotes all three of these requirements. This chapter lists the contributions made by this study and makes recommendations for further work.

8.2 Summary of contributions

The ets-insulin-bolus calculation concept, and the implementation thereof on a cellphone, is a success. This study has shown that the device developed meets the specifications set out in the user requirement statement. This study makes a contribution in several different ways.

Patient characterization: Establishing good insulin regimes for diabetics is a time consuming task, usually requiring a lot of trial-and-error. The proposed characterization procedure is a new *practical, accurate, timesaving and cost effective* procedure to determine how the individual patient's blood glucose responds to food and insulin. Even if the patient is not going to use the ets-bolus calculation tools, these measured values will help both the diabetic, as well as the medical practitioner, to quickly achieve better glycaemic control. This method is therefore a *viable alternative to the current practice of merely estimating values*.

Patient education: All the products developed help to educate patients and they can therefore be seen as diabetic educators that are available at any time. When meals or beverages are selected, the devices show the relevant ets values. *The patient is immediately informed of bad dietary choices*. Many diabetics are unaware that some of the foodstuffs they consume daily is loaded with sugar. For instance, by selecting a slice of brown bread rather than a slice of white bread, one teaspoon of sugar less is absorbed into the blood.

The analysis of daily food intake is used to make suggestions to the diabetic. If the diabetic exceeds the daily RDA ets or energy values, the device will inform the diabetic. Furthermore, if meals contain a high percentage of fat, the device will also warn the diabetic patient. Since diabetics in general have a higher risk for cardio vascular disease (CVD), these types of *suggestions are therefore important in the fight to combat CVD and obesity*. The food database can further be expanded to include more dietary information. This will result in more accurate dietary advice (e.g. to increase intake of Omega 3 fats to lower CVD risk).

The basic steps of *glycaemic control can quickly be learned* by using the ets-bolus calculator. Later on, the diabetic may even be able to calculate bolus values without a calculation device. This will happen when the diabetic becomes aware of how many units of insulin are needed for a fixed number of ets, and also how much blood glucose levels are lowered by a certain insulin dosage. The diabetic will soon start to remember the ets values for different meals and beverages.

It can clearly be seen that the ets-insulin-bolus calculator is much more than just a dosage calculator. It will continually give the diabetic *the best advice for maintaining a healthy balanced diet*, avoiding risky decisions regarding insulin administration and, lastly, teaching the diabetic the logical steps of how to control blood glucose levels.

Improved glycaemic control: This study has shown that the glycaemic control of Type 1 diabetics with currently poor control can be improved. Furthermore, the reduction of incidents of hypo- and hyperglycaemia can be achieved, thereby reducing the risk of complications. Although this study was relatively small, it does lay a *solid foundation on which further studies can be based*. Insulin regimes are a nightmare for many diabetics, and this study effectively addresses this problem.

Utilization of the latest technology: This study clearly demonstrates how *new technology can be utilized in the medical field*. Firstly, the integration of an insulin dosage calculation device with a cellphone is novel and revolutionary. No additional expensive equipment is required. Patients are familiar with the operation of cellphones so that the additional software does not intimidate patients. Secondly, a new use for the CGMS system is proposed, namely patient characterization.

Derivation of practical insulin-bolus-calculation equations: The *equations derived in chapter 4 are practical*. These equations were derived with individual patient characterization in mind. The linearity of these equations can be attributed to the ets-concept. The relationship of insulin response to ets is superior to the carbohydrate relationship. This is why bolus calculation using ets as the unit provides better results than carbohydrate counting, which is currently the most common method of calculation. The ets-concept is also easier to understand and visualize than grams of carbohydrates.

Clinical study: The clinical study *highlighted the potential of the ets-concept*. Several new issues have been identified which will help to improve future designs. The protocol developed for the clinical trial, and feedback received from diabetic test subjects, will greatly aid future development and testing of improved products.

8.3 Recommendations for further work

The following future work is recommended:

- More comprehensive clinical trials on the bolus calculator.
- Clinical studies monitoring the long-term performance of the bolus calculator.
- Clinical studies monitoring the performance of the bolus calculator on newly diagnosed patients.
- Designing bolus algorithms for patients using insulin mixes (i.e. not on basal-bolus regimes).
- Finding partners for full-scale commercialization and large clinical trials.
- Increasing ets awareness amongst diabetics.

8.4 Novelty of this study

The work done in this study is novel. This can be stated for the following reasons:

- The bolus-calculation equations derived in this study are based on the novel ets-concept.

- Bolus equations use ets and not carbohydrate counting. Ets measures the effective energy available from carbohydrates for different types of food. For the first time, bolus suggestions can be based on accurate blood glucose predictions.
- The cellphone bolus application is unique and therefore several provisional patents and PCT registrations were done. This demonstrates the uniqueness and novelty of this work.

8.5 Closure

This study has demonstrated how merging the medical sciences with engineering can solve complicated medical problems. By integrating a novel concept, standard engineering control principles and new advanced technology, a practical solution was developed. This enables Type 1 diabetics to improve their blood glucose control. It is predicted that in the future, an increasing amount of advanced engineering technology will be used to solve difficult medical problems.

APPENDIX A: PRELIMINARY PATENT

Preliminary South African Patent 2005/0663 filed 24 January 2005: *“Apparatus and method for predicting the effect of ingested foodstuff or exercise on the blood sugar level of a patient and suggesting a corrective action”*

**APPARATUS AND METHOD FOR PREDICTING THE EFFECT OF INGESTED
FOODSTUFF OR EXERCISE ON THE BLOOD SUGAR LEVEL OF A PATIENT
AND SUGGESTING A CORRECTIVE ACTION**

Field of the Invention

This invention relates to an apparatus and method for calculating corrective action required by a patient to normalise blood sugar level in response to changes effected by ingesting foodstuff or exercising. More particularly, but not exclusively, to an apparatus and method for calculating the required insulin bolus or quantity of carbohydrates required by a diabetic patient to normalise blood sugar level in response to ingestion of foodstuff or exercise, the foodstuff and exercise being characterised in linear units such that blood sugar response is linearly proportional to the amount of linear units gained or lost, through ingestion or exercise, respectively. It will be appreciated that blood sugar levels may be too high or too low for reasons other than exercise or food.

Background to the Invention

In the treatment of diabetes, characterising blood glucose or blood sugar (“glucose” and “sugar” are used interchangeably throughout this specification) response in an individual in order to estimate the amount of insulin required to normalise the blood sugar level, is critical to maintaining health.

Presently foodstuffs are characterised, inter alia, in terms of the CHO content or the Glycaemic Index (GI) thereof. An estimate of the bolus of insulin required, which is based on the carbohydrate content or GI of the food ingested, is often inaccurate because there is a poor linear relationship between grams of carbohydrates ingested and/or the GI of the foodstuff and

the consequential elevation in blood sugar. The effect of this is that suggested insulin boluses calculated from the anticipated effect on blood sugar level will often be incorrect leading to hypoglycaemia or hyperglycaemia in a diabetic patient.

Further, there are a number of other physiological factors which differ from patient to patient, that influence the resultant change in blood sugar after eating or injecting insulin. For example, some patients are more sensitive to insulin while others are insulin resistant. Many prior art techniques for estimating the insulin bolus required to neutralise the effect of ingested food on blood sugar do not take these physiological factors into account.

Object of the Invention

It is an object of the present invention to provide an apparatus and method for calculating corrective action required by a patient to normalise blood sugar level in response to changes effected by ingesting foodstuff or exercising, which, at least partially, alleviate some of the abovementioned difficulties.

Summary of the Invention

A first aspect of the invention comprises characterising foodstuffs and/or exercise in terms of a unit of energy (hereinafter referred to as a “linear unit”), in which the quantity of energy in linear units that is associated with an ingested foodstuff is directly proportional to the resultant elevation in blood sugar. The invention also extends to characterising exercise in terms of linear units, such that the quantity of energy in linear units that is expended by a person during exercise, is directly proportional to the resultant decrease in their blood sugar level.

For the purposes of exemplification, Equivalent Teaspoons of Sugar (ETS) are used as the linear unit throughout the specification and the reasons for using this particular linear unit are set out more fully below. Any linear unit which characterises foodstuff or exercise such that the number of linear units gained by eating or lost through exercise, correspond proportionally and linearly to the resultant effect on blood sugar level, could be used.

According to a second aspect of the invention an apparatus is provided for predicting the effect of ingested foodstuff or exercise on blood sugar level and suggesting a corrective action, comprising receiving means for receiving original blood sugar information relating to the original blood sugar level of a patient and energy information relating to the linear units of energy gained by ingesting foodstuff or lost through exercise; and outputting means for outputting the suggested corrective action required to normalise the effect of the gain or loss of energy on the blood sugar level of the patient.

The outputting means may output a suggested insulin bolus required to normalise the effect of the ingested foodstuff on the patient's blood sugar level. Alternatively, the outputting means may output a suggested quantity of linear units of energy to ingest to raise the patient's blood sugar to an accepted normal level. Further alternatively, the outputting means may output a suggestion to take no action.

The suggested corrective action may automatically be implemented, such as when the apparatus is used in conjunction with an automatic blood sugar regulating device.

The system may include a processor for calculating the corrective action required to normalise the effect of the gain/loss of energy on the patient's blood sugar level, given the patient's

original blood sugar level and the linear units gained by ingesting the foodstuff or lost through exercise, as inputs.

Further, the receiving means may receive patient specific information, such as any one or more of the patient's : ETS sensitivity (f_{ets}); insulin sensitivity ($f_{insulin}$); exercise sensitivity ($f_{exercise}$); age; gender; height; normal activity level (E.g. low, medium, high); typical daily routine (E.g. office, house etc.); total daily dose of short- and long-acting insulin; and target blood glucose level and acceptable blood glucose range;

The receiving means may be in the form of a body member displaying a series of original blood sugar levels thereon and a first marker, movable relative to the body member. It is envisaged that a user would align the first marker with the original blood sugar level of a patient displayed on the body member.

The body member may also include a graduated scale of linear units, the scale of linear units being fixed relative to the first marker; and a second marker which is movable relative both to the series of original blood sugar levels and the scale of linear units. It is envisaged that a user will move the second marker to correspond with the number of linear units to be gained when ingesting a particular foodstuff or the number of linear units lost when exercising.

The output means may include a first bolus indicator in the form of a graduated scale provided on the body member and a third marker fixed relative to the second marker, the scale being disposed such that when the second marker is moved to indicate the energy in linear units associated with the ingested foodstuff or exercise, the third marker indicates the suggested insulin bolus required to normalise the effect of ingested foodstuff on blood sugar level.

The output means may include a second bolus indicator in the form of a further graduated scale on the body member, the scale being disposed such that when the second marker is moved to indicate the quantity of energy in linear units associated with the foodstuff the third marker indicates the suggested insulin bolus required to normalise the effect of the energy gain/loss, when physiological characteristics of the patient, such as insulin resistance or sensitivity, are taken into account.

The output means may include a carbohydrate indicator in the form of a graduated scale on the body member and a fourth marker fixed relative to the first marker, the scale being disposed such that when the first marker is located to indicate the original blood sugar level and the second marker is located to indicate the quantity of linear units lost by exercising, the fourth marker indicates the suggested carbohydrates (quantified in ETS) required to be ingested to normalise the blood sugar level of the patient, should this action be required.

The apparatus may be provided in the form of a software application used in conjunction with a Portable Electronic Device (PED). The software application includes receiving means for receiving the original blood sugar level of a patient and foodstuff/exercise information relating to the linear units gained by ingesting a foodstuff or lost through exercise, input by a user; and outputting means for outputting the suggested corrective action to normalise the effect of the ingested foodstuff or exercise on the blood sugar level of the patient.

The receiving means may co-operate with input means provided on the PED. The input means may be provided in the form of a keypad, keyboard, sensor, touch screen, communication port or the like.

The outputting means may co-operate with an electronic display for displaying the corrective action. The corrective action may be provided in the form of a suggested quantity of linear units to ingest, suggested mass of a particular foodstuff to ingest or suggested insulin bolus to receive, for example.

The software application may include accessing means for accessing an electronic storage medium. The electronic storage medium may store a library of foodstuffs and the corresponding linear units associated with a particular mass of that foodstuff. The receiving means may receive information relating to the mass of a particular foodstuff from a user, the accessing means may access the library stored on the electronic storage medium to lookup the energy in linear units associated with that foodstuff and the processor may calculate the quantity of linear units associated with that quantity of foodstuff, by referencing the foodstuff library.

The PED may be provided in the form of a cellular telephone, laptop computer, palm pilot, hand-held electronic diary or the like.

The software application may be provided for use as part of an integrated insulin pump and glucose administration device.

According to a third aspect of the invention, there is provided a method for predicting the effect of ingested foodstuff or exercise on blood sugar level and suggesting corrective action, the method comprising the steps of:

- receiving original blood sugar information relating to the original blood sugar of a patient;

- receiving energy information relating to the quantity of linear units gained by ingesting foodstuff or lost through exercise; and
- outputting the corrective action to normalise the effect of the ingested foodstuff or exercise on the blood sugar level of the patient.

These and other features of the invention are described in more detail below.

Brief Description of the Drawings

Numerous embodiments of the invention are described below, by way of example only, and with reference to the accompanying drawings in which:

- Figure 1a shows measured insulin response as a function of mass of carbohydrates (CHO) consumed.
- Figure 1b shows measured insulin response as a function of the glycaemic index (GI) of consumed food.
- Figure 2 shows the measured insulin response as a function of equivalent teaspoons sugar (ETS) consumed.
- Figure 3a shows the distribution of short-acting insulin dose required by Type 1 diabetic vs. ETS ingested.
- Figure 3b shows the distribution of the normalized time integral insulin response for healthy patients vs. ETS ingested.
- Figure 4 shows blood glucose response of typical Type 1 diabetic during the ETS and insulin sensitivity test procedure.

- Figure 5 shows Illustrative blood glucose and insulin concentration curves of a non-diabetic person after ingesting a meal containing carbohydrates.
- Figure 6 shows the Illustrative blood glucose and insulin concentration curves of a Type 1 diabetic after ingesting a meal containing carbohydrates (not using short-acting insulin).
- Figure 7 shows the linear relationship between ETS ingested and increase in blood glucose level.
- Figure 8 shows the information block diagram for a typical bolus calculation device.
- Figure 9 shows the bolus calculation scales and use thereof of the bolus calculation slide rule.
- Figure 10a shows the front view of the bolus calculation slide rule.
- Figure 10 b shows the rear view of the bolus calculation slide rule.
- Figure 11 shows the front view of the centre sleeve of the bolus calculation slide rule.
- Figure 12a shows the rear view of the main ruler of the bolus calculation slide rule.
- Figure 12b shows the front view of the main ruler of the bolus calculation slide rule.
- Figure 13 shows the front and rear view small outer sleeve of the bolus calculation slide rule.
- Figure 14a-n shows possible interfaces for the bolus calculation software application.
- Figure 15a-u shows possible interfaces for the bolus calculation software application implemented on a mobile communication device (E.g. cellular phone).

- Figure 16a shows the front view of the characterization slide rule for ETS sensitivity.
- Figure 16b shows the top wheel of the characterization slide rule for ETS sensitivity.
- Figure 16c shows the centre wheel of the characterization slide rule for ETS sensitivity.
- Figure 16d shows the bottom wheel of the characterization slide rule for ETS sensitivity.
- Figure 17a shows the front view of the characterization slide rule for insulin sensitivity.
- Figure 17b shows the top wheel of the characterization slide rule for insulin sensitivity.
- Figure 17c shows the centre wheel of the characterization slide rule for insulin sensitivity.
- Figure 17d shows the bottom wheel of the characterization slide rule for insulin sensitivity.
- Figure 18 shows the software flow diagram for patient characterization device determining insulin and ETS sensitivity.
- Figure 19a-1 shows the different interfaces for the blood glucose simulation software application.
- Figure 20 shows the block diagram for the blood glucose-regulating device using the ETS concept.

Detailed Description of the Drawings

A first aspect of the invention comprises characterising the energy gained by ingesting foodstuffs or lost by exercise in terms of linear units of energy, in which the quantity of linear units associated with an ingested foodstuff or duration of a particular exercise is directly proportional to the resultant increase/decrease in blood sugar.

In the present embodiment, foodstuffs and exercise are characterised in terms of Equivalent Teaspoons Sugar (ETS). In this example, ETS are the linear unit used to quantify energy. It is used to quantify the glucose or glucose energy in foodstuff, the sugar energy that is expended during exercising or any other energy quantity relating to energy from glucose or carbohydrates.

Examples of energies that can be quantified in ETS include: glucose energy in the blood, glycogen stored in the liver and energy expended during exercise.

The quality of insulin predictions is examined in more detail for the CHO and the GI methods using measurements by Lee and Wolever⁵. These measurements give insulin response curves for different healthy test subjects ingesting different amounts of CHO (0 to 100 grams) with varying GI values (23 to 100).

The time integrals ($\int BI(t)dt$) of the Lee and Wolever blood insulin (BI) response curves for one subject are normalised and plotted against the amount of CHO consumed (Figure 1a) and against the GI (Figure 1b) of the ingested foods. Pearson's R^2 -values⁶ were calculated for linearised trend fits through the plotted data. The R^2 -values for the CHO and the GI methods

were 0.603 and 0.558 respectively. For the CHO method the worst spread is at 50g CHO, namely a factor 12, while for GI at 65 the factor is close to three.

The characterisation of foodstuff and exercise according to the invention is theoretically derived using energy balance techniques⁷, namely the ingested CHO / blood glucose energy balance. The simple linear link between insulin response and ETS is given by Equation (11) and is derived below.

The quality of insulin predictions by the ETS method are substantially better than the predictions using the prior art methods. The Lee and Wolever⁵ measurements for the same test subject as in Figures 1a and 1b are used again. The results are given in Figure 2. The linear trend line for the ETS method (Equation (11)) yields an R²-value of 0.929, which is significantly better than those of the other methods.

The same procedure as for the single subject can now be used to investigate more test subjects. The full dataset of Lee and Wolever⁵ as well as another dataset from Wolever and Bolognesi³ are used. Correlation coefficients for data of the 15 test subjects are presented in Table 1. The average R²-values for the different methods show the inventive method to be the preferred insulin predictor.

Table 1 Pearson's R²-values for correlations between normalised insulin response integrals ($\int BI(t)dt$) and CHO, GI and ETS values. The integrals were calculated from insulin response measurements by Wolever & Bolognesi³ and Lee & Wolever⁵.

Test subject	Mass carbohydrates (CHO)	of Glycaemic index (GI)	Equivalent teaspoons sugar (ETS)
1	0.345	0.451	0.734
2	0.380	0.395	0.803
3	0.408	0.506	0.805
4	0.456	0.521	0.882
5	0.430	0.398	0.710
6	0.226	0.718	0.631
7	0.628	0.237	0.745
8	0.624	0.355	0.877
9	0.792	0.378	0.874
10	0.603	0.558	0.929

11	0.718	0.377	0.915
12	0.834	0.228	0.848
13	0.745	0.186	0.736
14	0.622	0.403	0.826
15	0.614	0.226	0.784
Average R²	0.562	0.396	0.807
% standard deviation average R²	32	36	10

It should be noted that had the equations been derived in a different fashion using the Insulin Index (II) instead of the GI, even better accuracies are expected. This is especially true for mixed meals containing a high percentage of protein and/or fat. The GI was used due to better availability of published values¹⁵. This will enhance the initial usefulness of the ETS concept.

ETS is used a linear unit because it is an easy concept to comprehend and to use. Firstly, *Equation (11) shows that less ETS in a meal always leads to less insulin, making food and meal choices very easy.* Secondly, ETS values for typical foods and serving sizes are usually less than 10 e.g. tomato = 0.5 ETS, can of soda = 7 ETS, apple = 2.5 ETS. Numbers less than 10 are easy to grasp. Thirdly, in a mixed meal of high CHO content the ETS values of the individual constituents can simply be added to arrive at the total ETS value for the full meal. Fourthly, it is easy to visualise a teaspoon full of sugar, which makes it a practical reference. Fifthly, for Type 1 diabetics the numerical ETS value of an ingested meal corresponds remarkable well with the numerical amount of insulin dosage required.

The exact relationship between ETS and insulin is dependant on the physiological characteristics of a person (f_{AUCI} in Equation (11)). If AUC is converted to insulin units we find that for many diabetics the relevant factor is close to one, which results in an easy-to-remember one unit of short-acting insulin needed for one ETS ingested. This makes diabetic glycaemic management easier than before. Better accuracy, as previously described, and easier application will have an important impact on diabetics.

Figure 3b depicts the spread in f_{AUCI} between the healthy individuals measured in the Wolever, Lee and Bolognesi^{3,5} trials.

The f_{AUCI} sensitivity is also important for weight watchers, those having CVD and certain cancers as high insulin concentrations and insulin resistance are prevalent in them^{5,6,7}. By accounting for f_{AUCI} (and similar factors for the protein and fat cycles) more correct diets could be designed for a specific patient. It is hypothesised that through “self preservation” f_{AUCI} will increase when a person is on a “fasting” diet to ensure maximum storage. This can make weight loss a little more difficult than expected.

f_{AUCI} could help explain why people from poor developing nations are prone to Type 2 diabetes when they change over to high caloric western diets with high ETS (high CHO and high GI). With an evolutionary high f_{AUCI} to ensure maximum storing efficiency they “over react” to the high ETS, resulting in hyperinsulinemia, weight gain, insulin resistance and eventually Type II diabetes.

The impact of such a predictor on diabetics, endurance sportspeople, weight watchers and those with CVD and certain cancers or those who want to live a healthy life is obvious. In general all these interest groups strive to minimise insulin response. *Equation (11) shows that the CHO containing food with the smallest ETS will always lead to the smallest insulin response making food choices easy from now on.*

Wolever & Bolognesi³ and Lee & Wolever⁵ trials. Fifteen healthy patients ingested eight different foods with varying amounts of CHO (0, 25, 50, 75 and 100 grams). The ingested foods and their published GI values¹⁶ were the following: fructose = 23, barley = 25, spaghetti = 41, glucose / fructose mix = 61.5, sucrose = 65, bread = 70, potato = 83 and glucose = 100.

The full methods are described in references 3 and 5. Our time integrals ($\int BI(t)dt$) for plasma insulin values (minus the baseline insulin) are similar to the “Area Under the Curve (AUC)” described in reference 3 and 5.

Derivation of equations. Only CHO in a meal is directly converted into blood glucose during digestion¹⁷. The “conversion potential” (η_{CHO}) of CHO estimates the amount of energy, which is converted into blood glucose by a typical person. All losses, including energy needed for digestion, incomplete digestion, etc. are accounted for in η_{CHO} . This value can be measured (as discussed later) and is a property of the meal. It depends on many factors including the content of dietary fibre, fat and protein in the meal.

Energy from CHO which can be utilised by a person (E_{CHO}) in the form of blood glucose is then a function of the mass of CHO in the meal (m_{CHO}), the full energy content per mass of the CHO (k_{CHO}) measured outside the body by means of a bomb calorimeter¹⁸ and η_{CHO} of the meal which accounts for how efficient the energy can be extracted inside the body.

Note that historically it was incorrectly assumed in diet planning that the energy content (k_{CHO}) of CHO measured outside the body by a different process (bomb calorimeter) was fully utilised inside the body through another process, namely digestion and absorption. (The same mistake is also made with protein and fat.) The correct equation for CHO energy in a meal which can be utilised inside the body (E_{CHO}) is shown by:

$$E_{CHO} = \eta_{CHO} m_{CHO} k_{CHO}. \quad (1)$$

Efficiency towards converting the effective CHO from a meal (Equation (1)) into blood glucose varies between different people. This personalised CHO efficiency can be represented by the term f_{CHO} . (f_{CHO} is a function of a specific person while η_{CHO} is a function of a meal.)

The total energy absorbed in the blood for a specific person is then given by

$$E_{Absorb} = f_{CHO} E_{CHO} = f_{CHO} \eta_{CHO} m_{CHO} k_{CHO}. \quad (2)$$

As E_{Absorb} is the CHO energy converted into blood glucose for a specific person, E_{Absorb} can also be found by means of blood glucose measurements for that specific person. The response

curve for blood glucose concentration has to be integrated ($\int BS(t)dt$) above basal level from time of consumption back to basal level. This time elapsed is described by Δt . The elapsed time is specific to a person's blood glucose response and is *inter alia* dependant on a person's insulin secretion rate and sensitivity, etc.

The integral divided by Δt now gives the average concentration of blood glucose. To find the total amount of glucose (or energy) in the blood the concentration is multiplied by the total volume of blood of the person (Vol). Finally, E_{Absorb} is then found by multiplying with k_{CHO} , the energy value of CHO.

$$E_{Absorb} = \frac{\int_{t=ingestion}^{t=basal} BS(t)dt}{\Delta t} Vol.k_{CHO} \quad (3)$$

Equation (3) is substituted into Equation (2) to find

$$\frac{\int_{t=ingestion}^{t=basal} BS(t)dt}{\Delta t} = \frac{f_{CHO}\eta_{CHO}m_{CHO}k_{CHO}}{Vol.k_{CHO}} \quad (4)$$

For a typical balanced meal containing CHO there is a direct relationship between blood glucose response ($\int BS(t)dt$) and the insulin response¹⁹ ($\int BI(t)dt$). Although the best fit to this relationship is not linear⁵, a linear relationship with an R²-value of 0.963 was found through measurements by Lee and Wolever⁵ using meals consisting of mostly CHO. This is deemed acceptable, especially if the equations are to be kept practical. To write this fact in equation form we obtain:

$$\int_{t=ingestion}^{t=basal} BI(t)dt = f_{IBS} \int_{t=ingestion}^{t=basal} BS(t)dt \quad (5)$$

The insulin / blood glucose relationship varies from one person to the next and describes this person specific characteristic with the blood insulin factor, f_{IBS} . (*IBS* is an abbreviation for **I**nsulin **B**lood **G**lucose relationship.)

Equation (5) is substituted into Equation (4) to find Equation (6), which describes the person specific insulin response to ingested food. (The k_{CHO} values from Equation (4) cancelled each other out.)

$$\frac{\int_{t=\text{ingestion}}^{t=\text{basal}} BI(t)dt}{\Delta t} = \frac{f_{IBS} f_{CHO} \eta_{CHO} m_{CHO}}{Vol} \quad (6)$$

Equation (6) cannot easily be used by the average diabetic therefore it is simplified. Instead of using m_{CHO} and η_{CHO} in Equation (6) for the meals, an easier measurement unit can be used. It is proposed that effective CHO in foods and meals be expressed in equivalent teaspoons sugar (ETS).

An investigation into the properties of a teaspoon full of sugar containing 5g of CHO is in order. What is the η_{CHO} of sugar? It is hypothesised that the glycaemic index of a specific CHO (GI_{CHO}) approximates this value. Although the official definition¹⁶ of GI_{CHO} is “rate of CHO digestion”, GI_{CHO} has more value when expressed in this way.

GI_{CHO} represents the total amount of blood glucose which can be converted from a meal containing 50g CHO divided by the amount of blood glucose converted from 50g glucose by a specific person. As blood glucose is glucose it can safely be assumed that glucose have a η_{CHO} of close to 100%. This means that the GI_{CHO} of any meal, referenced to glucose, could be a useful predictor of η_{CHO} of that meal.

Sugar therefore has a η_{CHO} of 65% found from its GI_{CHO} value of 65 using the glucose reference¹⁶. Substituting these values into Equation (1) leads to Equation (7) for total available energy in a teaspoon sugar:

$$E_{\text{teaspoon sugar}} = GI_{\text{sugar}} m_{\text{teaspoon sugar}} k_{CHO} = (65)(5)k_{CHO} = 325k_{CHO} \quad (7)$$

The effective energy for any CHO can now be related back to a teaspoon of sugar. Equation (1) for any meal (substituting η_{CHO} with GI_{CHO} for that meal) can be divided by Equation (7) ($E_{\text{teaspoon sugar}} = 325k_{CHO}$) for one teaspoon sugar to find the equivalent teaspoon sugar (ETS) for that meal, as shown in Equation (8)

$$\text{ETS} = \frac{E_{CHO}}{E_{\text{teaspoon sugar}}} = \frac{\eta_{CHO} m_{CHO} k_{CHO}}{325k_{CHO}} = \frac{\eta_{CHO} m_{CHO}}{325} = \frac{GI_{CHO} m_{CHO}}{325} \quad (8)$$

It can be shown that GI_{CHO} can be substituted with Π to arrive at a more accurate value of ETS. The assumptions of linearity between insulin and blood glucose response as well as high

CHO content are then not needed. It should also be noted that the ETS / insulin relationship is linear to much higher ETS values (approximately three time higher) than the ETS / blood glucose relationship.

Now that the equation for ETS has been established Equation (6) can be further simplified. By substituting Equation (8) into Equation (6) and substituting the term Area Under the Curve (AUC_I) for the integral, the following is obtained:

$$\frac{\int_{t=ingestion}^{t=basal} BI(t)dt}{\Delta t} = \frac{AUC_I}{\Delta t} = \frac{f_{IBS} f_{CHO}}{Vol} GI_{CHO} m_{CHO} = \frac{f_{IBS} f_{CHO}}{Vol} 325_{ETS}$$

$$\therefore \frac{AUC_I}{\Delta t} = \frac{325 f_{IBS} f_{CHO}}{Vol} ETS \quad (9)$$

By defining a new person specific factor, f_{AUCI} , Equation (9) can be simplified further. f_{AUCI} accounts for the person specific factors f_{CHO} , f_{IBS} , Vol and Δt . ($AUCI$ is an abbreviation for “Area Under the Curve of Insulin response”.) f_{AUCI} , is *inter alia* a function of CHO metabolic efficiency, size, insulin resistance which depends on fitness, body mass index (BMI), age, etc. of a person. Its equation is given below, although it is easier to measure it by using Equation (11).

$$f_{AUCI} = \frac{325 f_{IBS} f_{CHO} \Delta t}{Vol} \quad (10)$$

Substituting Equations (10) into (9) yields the relationship between measured insulin response (AUC_I) and ingested food represented by ETS

$$\boxed{AUC_I = f_{AUCI} ETS} \quad (11)$$

where AUC_I is the integrated insulin response, f_{AUCI} is a measurable function of the individual and ETS is a measurable function of the meal and is published for most foods²⁰ or can be calculated using Equation (8). In this study the simple linear Equation (11), is verified and derived from first order principals, using measurements by Lee, Wolever and Bolognesi^{3,11}.

Ongoing clinical trials show that the linearity of Equation (11) holds true for typical portion sizes of well-balanced meals. *The application of Equation (11) by our target audience who want to minimise insulin response is now simple. The food with the lowest ETS will always lead to the smallest insulin response. As shown in Figure 1, such a simple and practical conclusion could not be drawn from either the CHO or the GI methods.*

Equation (11) can be converted to Insulin Units by using a proportionality constant, f_{aucI_U} .

$$I_{bolus} = f_{aucI_U} AUC_I = f_{aucI_U} \cdot f_{AUCI} ETS \quad (12)$$

f_{AUCI} is the person specific factor for relating insulin response to ETS ingestion for a specific healthy person. f_{aucI_U} is also a person specific factor to relate the insulin response to the equivalent insulin units I_{bolus} (U). The two proportionality constants, f_{AUCI} and f_{aucI_U} can be combined into a single constant, f_{BS_I} .

$$I_{bolus} = f_{BS_I} ETS \quad (13)$$

Equation (13) can be used to calculate the number of Insulin Units being secreted by the pancreas of a healthy person, with f_{BS_I} being the person specific proportionality constant.

The pancreas of a Type 1 diabetic does not secrete insulin. This means that after ingesting a meal, the carbohydrates being absorbed into the blood is not stored. The diabetic then has to administer some short acting insulin (bolus) to store the glucose in the blood and thereby lowering the blood glucose level. The ideal would be to mimic the insulin response of the pancreas of a healthy person. f_{BS_I} is a person specific factor and if it can be measured for a specific diabetic, the bolus for a specific meal can also be calculated. It is also known that there is a direct relationship between insulin response (in the case of the Type 1 diabetic – bolus insulin to be administered) and number of ETS ingested. f_{BS_I} is the insulin units per ETS being ingested factor for a specific person. The following method is therefore proposed to determine f_{BS_I} for a Type 1 diabetic. f_{BS_I} can be written as two relational factors, namely $f_{BS/I}$ and $f_{BS/ets}$.

$$f_{BS_I} = f_{BS/ets} / f_{BS/I} \quad (14)$$

$f_{BS/I}$ is the decrease in blood glucose level after administering bolus insulin. It can be measured by performing a simple procedure. Blood glucose levels are monitored after a meal until it has become stable, $BS_{prior\ insulin}$. An appropriate bolus $I_{units\ test}$ is then administered. The blood glucose level is then monitored for a minimum period equalling the total of the onset and duration time of the specific bolus insulin being used. The final stabilized blood glucose level, $BS_{post\ insulin}$, is then measured. $f_{BS/I}$ for the Type 1 diabetic can now be calculated as follows:

$$f_{BS/I} = \frac{\Delta BS_{test}}{I_{units\ test}} = \frac{BS_{prior\ insulin} - BS_{post\ insulin}}{I_{units\ test}} \quad (15)$$

With:

$f_{BS/I}$ = Insulin sensitivity of the individual; (mmol / l.U) or (mg / dl.U)

ΔBS_{test} = Difference (decrease) in blood glucose levels before and after insulin

$I_{units\ test}$ = Units of bolus insulin injected during test procedure (U)

$BS_{prior\ insulin}$ = Stabilized blood glucose level before insulin administration

$BS_{post\ insulin}$ = Stabilized blood glucose level a while after the insulin injection

See Figure 4.

$f_{BS/I}$ is also called the insulin sensitivity and can be used to calculate the bolus (number of short acting insulin units, I_{units}) needed to lower the blood glucose level. For convenience, the insulin sensitivity $f_{BS/I}$ will be denoted by the symbol $f_{insulin}$.

$$\Delta BS_{predicted} = -f_{insulin} \cdot I_{units\ injected} \quad (16)$$

$f_{BS/ets}$ is the increase in blood glucose level after ingesting a meal containing a certain amount of ETS. It can be measured by performing a simple procedure. Blood glucose levels are monitored before a meal until it has become stable, $BS_{prior\ meal}$. A meal with a known ETS quantity is then ingested. The blood glucose level is then monitored for a minimum period of

about one hour. The final stabilized blood glucose level, $BS_{post\ meal}$, is then measured. $f_{BS/ets}$ for the Type 1 diabetic can now be calculated as follows:

$$f_{BS/ets} = \frac{\Delta BS_{test}}{ets_{meal}} = \frac{BS_{post\ meal} - BS_{prior\ meal}}{ets_{meal}} \quad (17)$$

With:

$f_{BS/ets}$ = ETS sensitivity of the individual; (mmol / l.ets) or (mg / dl.ets)

ΔBS_{test} = Difference (increase) in blood glucose levels before and after meal

ets_{meal} = Quantity of ETS being ingested

$BS_{prior\ meal}$ = Stabilized blood glucose level before test meal

$BS_{post\ meal}$ = Stabilized blood glucose level after the test meal

$f_{BS/ets}$ is called the ETS sensitivity and can be used to calculate the rise in blood glucose level after ingesting a certain quantity of ETS. For convenience the insulin sensitivity will be denoted by the following symbol: f_{ets} .

$$\Delta BS_{predicted} = f_{BS/ets} \cdot ets_{meal} = f_{ets} \cdot ets_{meal} \quad (18)$$

Equation (14) can now be used to calculate f_{BS_I} for the specific diabetic. Now a practical blood glucose prediction model for a Type 1 diabetic can be developed.

The blood glucose level of a person is influenced by several factors. These factors include but are not limited to the following:

Diabetic status: Does the person have diabetes? If so, does the person have Type 1 or Type 2 diabetes? The duration of the illness is also important here.

Food intake: Ingested carbohydrates (CHO) are absorbed into the blood and cause the blood glucose level to rise. Certain beverages (e.g. alcoholic beverages can cause blood glucose levels to fall under certain conditions)

Long acting insulin (basal): Basal insulin is used for energy utilization. Without this insulin cells cannot use glucose for their metabolism energy.

Short acting insulin (bolus): Ingested carbohydrates from food are converted to glucose and absorbed into the blood. Bolus insulin is used to store glucose in the liver and other storage cells.

Stress: Stress tends to cause elevated blood glucose levels. The magnitude of the elevation in blood glucose levels is proportional to the intensity of the stress.

Illness: Various illnesses (e.g. bacterial infections) cause elevated blood glucose levels.

Activity level and exercise: The energy used during a day depends on the activity level of a specific person. The utilization of glucose from the blood for energy plays an important role on blood glucose regulation.

Blood glucose counter regulation hormones: When the blood glucose level is too low, various counter regulation hormones will act to restore the blood glucose concentration.

Blood glucose and food ingestion

Blood glucose level or blood glucose level refers to the blood glucose concentration of a person at a given time and is expressed in either mmol/l or mg/dl.

$$[mmol/l] = [mg/dl] / 17.857 [mg.l / mmol.dl] \quad (19)$$

Type 1 diabetics have to control their blood glucose level and therefore measure their blood glucose levels frequently. A variable can be defined to represent the blood glucose level namely, BS . There will be distinguished between the following three blood glucose variables.

$BS_{current}$: The current blood glucose level measured with a blood glucose monitor.

$BS_{predicted}$: The predicted blood glucose level calculated from food intake, exercise and other related information.

$BS_{control}$: The desired blood glucose level (control set point). This value should also include a safety margin to reduce the risk of hypoglycaemia. $BS_{control}$ will therefore be a bit higher than the normal blood glucose level of non-diabetics.

When food is ingested it is decomposed into its three main components (macronutrients) namely carbohydrates, fats and proteins. Carbohydrates are broken down in the digestive track into basic sugars called glucose. Glucose is absorbed into the blood from the digestive track. This absorption of glucose causes the blood glucose level to rise.

In a non-diabetic person the pancreas of the person will sense the increase in blood glucose concentration and start to secrete insulin. The secreted insulin is used to store the excess glucose present in the blood thereby causing a decrease in blood glucose concentration.

The pancreas of Type 1 diabetics cannot secrete insulin and therefore the excess glucose cannot be stored efficiently. When diabetics consume meals it cause their blood glucose levels to stay elevated. This condition is called hyperglycaemia and can cause severe long-term effects²¹. Energy in the form of glucose will be present in the blood of the diabetic.

Without insulin the glucose can neither be stored nor utilized for energy in the cells. The energy needed by the body can therefore not be supplied to cells. The change in blood glucose levels can be measured after ingesting a certain meal. The Equivalent Teaspoons Sugar (ETS) quantification unit will be used. ETS is defined by Botha²² as follows.

$$ETS = \frac{E_{CHO}}{E_{\text{teaspoons sugar}}} = \frac{GI \cdot m_{CHO}}{325} \quad (20)$$

With:

ETS = Equivalent Teaspoons Sugar

E_{CHO} = Energy content in the food available from carbohydrates (kJ or Kcal)

$E_{\text{teaspoon sugar}}$ = Energy content in a teaspoon of table sugar = 20 Kcal = 84 kJ

GI = Glycaemic index of the food

m_{CHO} = Mass of carbohydrates in the food being quantified (g)

Sucrose, glucose and fructose are three different forms of pure carbohydrates. The same weight (10g) however is equal to 2, 3.1 and 0.7 teaspoons sugar. Glucose will therefore have the largest blood glucose response, more than four times the response of Fructose. A lot of people are unaware of this fact and merely count the number of carbohydrates in their food²³.

Botha²² also showed that a near linear relationship exists between ETS intake and the increase in blood glucose level after ingesting a meal. This is because ETS is directly linked to the glucose content that can be absorbed from the food²⁴. Equation (18) can be used to show this

relationship. This equation holds for ETS values lower than approximately 15 ETS. It is not healthy to consume such high quantities of glucose at a time (See Figure 7).

The rate of the increase in blood glucose level in a meal is dependant upon the composition of the meal (GI, fibers and macronutrient composition) but also on the individual person's digestive characteristics. The peak blood glucose level is usually reached within an hour of consuming a meal. Meals with high fat percentages for example take longer to digest.

Blood glucose and exercise

When a person starts to exercise the muscles initially use the glycogen in the muscle cells. After a while the liver will transform glycogen into glucose, which is released into the blood. This glucose in the blood can then be utilized by the muscle cells for energy. Insulin enables the muscle cells to accept the glucose into the cells²⁵. Prolonged exercise will cause fat to be utilized for energy in the form of fatty acids. These processes are automatically regulated in a non-diabetic with the release of insulin and several other hormones.

During exercise two conditions might result. When there is not enough insulin in the blood during exercise, the cells cannot utilize the glucose for energy. The liver will start to release more glucose in the blood to supply the starving muscle cells with energy. This causes the blood glucose level to continue rising during exercise. Although the blood glucose level rises, there is still not enough insulin to utilize it. Fortunately insulin sensitivity increases during exercise but in some cases it may not be enough to account for the shortage in insulin.

If there is too much insulin in the blood during exercise the muscle cells will increase their glucose utilization for energy causing the blood glucose level to fall too low. It is therefore important that the long-acting insulin dosage takes the activity level of a person into account. If the long-acting insulin dosage of a person caters for the energy requirements of the person, exercising will not cause uncontrollable blood glucose disturbances during exercise.

To quantify the effect that exercise has on blood glucose level the exercise energy should be linked to the energy source (fuel) namely glucose. Botha²² showed that a linear relationship exists between the area under the insulin concentration curve (AUC_I) of a non-diabetic after consuming a meal containing a certain ETS quantity.

$$AUC_I = f_{AUCI} \cdot ets \quad (21)$$

f_{AUCI} is a proportionality constant relating to the area under the insulin concentration curve over time with the ETS that caused the blood glucose response.

The insulin is secreted to store glucose and thereby removing it from the blood. The area under the insulin concentration curve can be assumed to be nearly proportional to the amount of insulin secreted by the pancreas of a non-diabetic. This can be verified from the fact that when a Type 1 diabetic injects insulin the AUC_I is proportional to the insulin dosage (I) injected.

$$AUC_I \propto I \quad (22)$$

Equation (16) showed the linear relationship between blood glucose decrease and the insulin injected for a Type 1 diabetic with insulin sensitivity $f_{insulin}$.

$$\Delta BS_{predicted} = -f_{insulin} \cdot I_{units\ injected} \quad (23)$$

Therefore the blood glucose decrease is proportional to the area under the insulin concentration integral causing the blood glucose decrease for a Type 1 diabetic person. This is not the case with non-diabetics. Their pancreas help to control the blood glucose level continually.

$$\Delta BS_{predicted} \propto -AUC_I \quad (24)$$

A proportionality constant f_{IBS} can be defined and used to formulate Equation (25).

$$\Delta BS_{predicted} = -f_{IBS} \cdot AUC_I \quad (25)$$

Equation (25) can be substituted into Equation (21) to give the relationship between blood glucose response and ETS energy. This blood glucose response of a non-diabetic should be mimicked by the Type 1 diabetic. In Equation (26) the blood glucose will decrease by $\Delta BS_{predicted}$ when $ets_{removed}$ is stored or utilized in the cells by the action of insulin in a Type 1 diabetic.

$$\Delta BS_{predicted} = - f_{IBS} \cdot f_{AUCI} \cdot ets_{removed} \quad (26)$$

Equation (26) can be simplified by combining the two proportionality constants f_{IBS} and f_{AUCI} into a newly defined proportionality constant $f_{exercise}$.

$$f_{exercise} = f_{IBS} \cdot f_{AUCI} \quad (27)$$

$$\Delta BS_{predicted} = - f_{exercise} \cdot ets_{removed} \quad (28)$$

Botha [10] further showed the relationship between ETS blood glucose energy and the exercise activity responsible for expending the energy.

$$E_{expended} = f_{expended} \cdot ets_{expended} \quad (29)$$

$f_{expended}$ is a person specific factor for relating the energy expended during an exercise to the amount of ETS used by the body to perform the exercise. The ETS here only accounts for the percentage of energy expended during exercise that is taken from the blood glucose. The amount of ETS expended is dependant on the intensity and duration of the exercise but also on how efficiently energy from glucose is utilized by the human body during exercise.

$$ets = E_{expended} / f_{expended} \quad (30)$$

By substituting Equation (30) into (28) the reduction in blood glucose level for a Type 1 diabetic when expending energy ($E_{expended}$) during exercise can be written in terms of energy expended.

$$\Delta BS_{predicted} = \frac{f_{BS} \cdot E_{expended}}{f_{expended}} \quad (31)$$

Equation (31) can further be simplified by defining a single proportionality constant f_{exbs} .

$$f_{exbs} = \frac{f_{exercise}}{f_{expended}} \quad (32)$$

Using the newly defined f_{exbs} Equation (31) is reduced to (33)

$$\Delta BS_{predicted} = f_{exbs} \cdot E_{expended} \quad (33)$$

For Equation (28) or (33) to be used there are a few criteria that have to be met. These equations are only valid for Type 1 diabetics. While exercising glucose in the blood can only be utilized by cells when there is enough insulin in the blood to allow the glucose to enter muscle cells. The long-acting insulin dosage should cater for the daily activity level of the diabetic. Exercise routines should also be taken into account when this dosage is determined.

The calculations can only be used when the counter regulation of the body does not increase the blood glucose level. When blood glucose levels fall below approximately 3.8 mmol/l the pancreas starts secreting glucagon²⁶. Glucagon promotes the conversion of glycogen stored in the liver to glucose. This glucose is then released in the blood causing the blood glucose level to rise. This effect will therefore influence the accuracy of Equation (28) and (33) because they do not take the counter regulation of the body into account.

Counter regulation is used by the body to prevent hypoglycaemia. The blood glucose prediction model can only be used when exercises are performed while blood glucose levels stays higher than this value. It is risky for diabetics to start exercising with a low blood glucose level. When blood glucose levels reaches 3.8 mmol and lower epinephrine, growth hormone, cortisol and other hormones will also start to counter act the low blood glucose level.

For practical reasons the blood glucose prediction model will use Equation (28). Botha²² proposed a method for calculating $f_{expended}$. A good approximation of 55 kCal/mmol was used for the average person. $f_{exercise}$ was measured on a few test subjects and an average value of 0.6 mmol/ETS was found. Due to study constraints only a few test subjects could be used. More measurements are needed to get a better approximation of this value for the average Type 1 diabetic person.

By using the average value of 55 kCal/mmol we can rewrite Equation (30) as follows.

$$ets_{expended} = E_{expended} / 55 \quad (34)$$

Equation (34) can be used to calculate the exercise energy expended quantified in ETS from existing publicized energy tables. These values are calculated for the average person.

Equation (28) can then be used to calculate the reduction in blood glucose level. If the expended energy quantity is known (ETS), Equation (35) can be used.

$$\Delta BS_{predicted} = -f_{exercise} \cdot ets_{expended} = -0.6 \cdot ets_{expended} = -0.6 \cdot ets_{exercise} \quad (35)$$

An effective ETS quantity called $ets_{exercise}$ can be defined to the extent that for an average Type 1 diabetic, exercising 1 ETS will cause a reduction of 1 mmol/l.

$$\Delta BS_{predicted} = -ets_{exercise\ table} = -0.6 \cdot ets_{expended} = -0.6 \cdot ets_{exercise} \quad (36)$$

Exercise tables can be created for the average Type 1 diabetic where exercising one ETS of energy will lead to a reduction of 1 mmol/l in blood glucose level when the criteria mentioned is met.

Blood glucose prediction model

The factors can now be combined to give a prediction model with which to calculate the blood glucose level. The different factors are shortly reviewed below. They are then used to formulate the blood glucose prediction model to be used.

The increase in blood glucose level as a result of **food or beverage intake**:

$$\Delta BS_{predicted\ food} = f_{ets} \cdot ets_{meal} \quad [\text{mmol/l}] \quad (37)$$

with f_{ets} : ETS sensitivity of the diabetic [mmol / (l.ETS)]
 ets_{meal} : total amount of ETS in meal [ETS]

The decrease in blood glucose level as a result of **exercise** (using the correct long-acting dosage):

$$\Delta BS_{predicted\ exercise} = -f_{exercise} \cdot ets_{exercise} \quad [\text{mmol/l}] \quad (38)$$

with $f_{exercise}$: exercise sensitivity of the diabetic [mmol / (l.ETS)]
 $ets_{exercise}$: total amount of energy expended during exercise quantified in ETS [ETS]

The decrease in blood glucose level due to **insulin**:

$$\Delta BS_{\text{predicted insulin}} = -f_{\text{insulin}} \cdot I_{\text{units left}} \quad [\text{mmol/l}] \quad (39)$$

with f_{insulin} : insulin sensitivity of the diabetic [mmol / (l.U)]
 $I_{\text{units left}}$: short-acting insulin left in blood [U]

The difference between the predicted and current blood glucose level can be calculated as the result of the effects that food, exercise and insulin have on the blood glucose level of the diabetic.

$$\Delta BS_{\text{predicted}} = \Delta BS_{\text{predicted food}} + \Delta BS_{\text{predicted exercise}} + \Delta BS_{\text{predicted insulin left}} \quad (40)$$

The predicted blood glucose level can then be written as follows

$$BS_{\text{predicted}} = BS_{\text{current}} + \Delta BS_{\text{predicted}} \quad (41)$$

and by substituting Equation (40) into (41) the predicted blood glucose level is:

$$BS_{\text{predicted}} = BS_{\text{current}} + \Delta BS_{\text{predicted food}} + \Delta BS_{\text{predicted exercise}} + \Delta BS_{\text{predicted insulin left}} \quad (42)$$

The desired blood glucose level is denoted as BS_{control} . This level is the control set point. We can now calculate the excess blood glucose level (BS_{excess}). This value indicates the difference between the predicted blood glucose level and the desired blood glucose level.

$$BS_{\text{excess}} = BS_{\text{predicted}} - BS_{\text{control}} \quad (43)$$

If the excess blood glucose value is positive, insulin is needed to lower the blood glucose level to the control (desired) blood glucose level. Insulin sensitivity (f_{insulin}) determines the blood glucose level decrease per unit short-acting insulin. The short-acting insulin units needed to lower the blood glucose level can be calculated by dividing the excess blood glucose level by the insulin sensitivity of the diabetic.

$$\begin{aligned}
I_{\text{units needed}} &= \frac{BS_{\text{excess}}}{f_{\text{insulin}}} = \frac{BS_{\text{predicted}} - BS_{\text{control}}}{f_{\text{insulin}}} \\
&= \frac{BS_{\text{current}} + \Delta BS_{\text{predicted food}} + \Delta BS_{\text{predicted exercise}} + \Delta BS_{\text{predicted insulin left}} - BS_{\text{control}}}{f_{\text{insulin}}} \\
&= \frac{BS_{\text{current}} + f_{\text{ets meal}} \cdot \text{ets}_{\text{meal}} - f_{\text{exercise}} \cdot \text{ets}_{\text{exercise}} - f_{\text{insulin}} \cdot I_{\text{units left}} - BS_{\text{control}}}{f_{\text{insulin}}}
\end{aligned} \tag{44}$$

If the excess blood glucose level is negative it means that the predicted blood glucose level is below the control (desired) blood glucose level. This indicates a risk of hypoglycaemia. The additional ETS to be ingested can be calculated. This ETS should be eaten additionally to the ETS already used for the blood glucose calculation.

ETS sensitivity (f_{ets}) indicates the blood glucose level increase per unit ETS ingested. The additional ETS to be ingested can therefore be calculated by dividing the excess blood glucose level value with the ETS sensitivity.

$$\begin{aligned}
\text{ets}_{\text{additional needed}} &= \frac{-BS_{\text{excess}}}{f_{\text{ets}}} = \frac{-(BS_{\text{predicted}} - BS_{\text{control}})}{f_{\text{ets}}} \\
&= \frac{-(BS_{\text{current}} + \Delta BS_{\text{predicted food}} + \Delta BS_{\text{predicted exercise}} + \Delta BS_{\text{predicted insulin left}} - BS_{\text{control}})}{f_{\text{ets}}} \\
&= \frac{-(BS_{\text{current}} + f_{\text{ets meal}} \cdot \text{ets}_{\text{meal}} - f_{\text{exercise}} \cdot \text{ets}_{\text{exercise}} - f_{\text{insulin}} \cdot I_{\text{units left}} - BS_{\text{control}})}{f_{\text{ets}}}
\end{aligned} \tag{45}$$

It should be noted that diabetics should not exercise while their current blood glucose levels are already low.

These empirical equations derived in this section form the basis of several products aimed at improving the blood glucose control of Type 1 diabetics. The equations are complex and not that easy to use without the help of a computing device. Although the equations are already simplified it gives a good idea of the complex problems the diabetics face everyday trying to control their blood glucose level.

Bolus calculation device

In one embodiment of the invention, the apparatus is provided in the form of a software application for use in conjunction with on a Portable Electronic Device (PED).

The apparatus is first customized for the specific user by characterizing the user **1**. This is done by measuring and entering said user's:

- ETS sensitivity (f_{ets});
- Insulin sensitivity ($f_{insulin}$); and
- Exercise sensitivity ($f_{exercise}$).

The following less important parameters are then also considered namely:

- age;
- gender;
- height;
- normal activity level (E.g. low, medium, high);
- typical daily routine (E.g. office, house etc.);
- total daily dose of short- and long-acting insulin;
- target blood glucose level and acceptable blood glucose range; and
- any other relevant information of the user.

The following dynamic variables (daily activities) can also be entered via the input means of the PED and are taken into account when suggesting corrective action:

- blood glucose measurements **2** and time thereof;
- food and beverage intake **3** including the type, portion size, number of portions, ETS value, other nutritional information (e.g. carbohydrates, proteins, calories etc.) and the time being ingested;
- exercise and activities **4** being performed including the time, intensity and duration of the exercise;
- insulin administration log **5** – previous insulin administrations have to be accounted for when the injected insulin is still active; and
- stress **6** including the duration and intensity.

The customization values and daily activities mentioned above are then used to calculate **7** the corrective measure **8** to be taken using Equations (43) and (44) or (45) as functions of time. The counter regulation ability of the liver need not be accounted for because the target blood glucose level used in these calculations is higher than the hypoglycaemic threshold where the counter regulation hormones will start to act.

The calculation will result in one of three types of suggestions **8**:

- a suggestion to take no action; or
- a suggestion for a certain dosage of insulin; or
- a suggestion to eat an additional amount of ETS.

General information **9** regarding the analysis of daily food consumed etc. can be displayed to said user. Said invention can also be used to detect potential problems and give the user feedback **10** thereof E.g. if the device detects those, the user's sensitivities for insulin has changed.

In one embodiment of the invention the apparatus is provided in the form of a manual slide rule device. The front and rear view of said slide rule are shown in Figure **10a** and **10b** respectively. The slide rule device consists of three parts: a main centre ruler **11**, a large sleeve **12** and a small sleeve **13**. The main ruler **11** is received in the large sleeve **12** and is movable relative to each other, while the large sleeve **12** is received in the small sleeve **13**, which is also movable relative to the large sleeve.

The main sleeve **11** has printed on one side a blood glucose scale **19** and on the rear side an insulin dosage scale **18** and a scale for suggesting additional ETS to be consumed **22**. The large sleeve has printed on one side an exercise and food ETS energy scale and a first marker **14** to point to a blood glucose value on the blood glucose scale **19** on the centre ruler **11**. The remaining surface of the large sleeve is transparent **17**. The small sleeve has instructions printed on one side with a second marker **23** to point to exercise or food ETS energy scale **15** and on the rear side a third marker that is set to point to the correct insulin scale **18** according to the measured insulin sensitivity of said user.

The device must first be customized for the patient. This is done by first determine the ETS sensitivity of said user. The resolution of scale **26** for ETS food is then selected so that the distance between two resolution points on the blood glucose scale **19**, divided by the distance

between two resolution points on the ETS food scale **26** equals the measured ETS sensitivity of said user.

The same is done for exercise sensitivity namely the distance between two resolution marks on the blood glucose **19** scale divided by the distance between two resolution marks on the ETS exercise scale **15** should equal the measure exercise sensitivity of the patient. Similarly the insulin sensitivity can be accounted for by selecting the distance between two insulin scale **18** resolution points so that the distance between two successive blood glucose scale **19** resolution points divided by the distance between two successive insulin scale **18** resolution points equals the measured insulin sensitivity of said user. The slide rule device can pre-printed with each of these scales **19, 26, 15** and **18** according to the corresponding sensitivity values. Several scales can also be printed on the device with selection pointers **24** and **23** indicating which scales to use.

The operation of the device can be explained with reference to Figure 9. The slide rule is a simplified implementation of the bolus calculation Equations (43), (44) and (45). It therefore does not have inherent intelligence to compensate for previous insulin injections etc. It does however provide a useful tool with which to calculate bolus insulin required. Figure 9A shows the blood glucose scale **19**, ETS food scale **26**, ETS exercise scale **15** and insulin scale **18** which can be seen in Figure 9D. The large sleeve is moved relative to the centre ruler so that the first marker **14** points to the measure current blood glucose level on scale **19**. The small sleeve is then moved from the first marker **14** upwards and relative to the large sleeve so that the second marker **23** indicates the amount of ETS being ingested. The amount of ETS being ingested can be determined by adding up the ETS value of the corresponding food and beverage items making up the meal being ingested obtained from an ETS value booklet (not shown). The small sleeve is then moved downward by the amount of ETS energy being expended during exercise (if any) according to the exercise scale **15**. This resulting blood glucose level can be seen in Figure 9B. By turning over the slide rule device a third marker **24** (printed to indicate the correct insulin sensitivity scale to be used) indicates the corrective measure to be taken which can be either a insulin dosage to be injected, a suggestion to take no action or a suggestion to eat additional ETS (block **22** – in this case a fourth marker **21** will point to the amount of additional ETS to be ingested). Figure 9D shows how this calculation is done on a linear scale. A reference booklet having ETS values for food, beverages and exercise.

could accompany the slide rule device.

In a second embodiment of the invention, the corrective action calculation device is provided in the form of a software application for use in conjunction with a portable electronic device, such as a handheld computer, proprietary device, personal computer or other electronic or mechanical device.

The inventive method can be implemented on any of these devices including, but not limited to: a handheld computer, PDA, personal computer, notebook, laptop, desktop computer, micro computer, mobile phone, tabloid computer or any other electronic or mechanical device capable of performing the necessary calculations.

A typical system of this type will consist of the following components:

- input means for receiving data and parameters (E.g. keyboard, keypad, voice command system, stylus etc.);
- a processor calculating said bolus suggestions; and
- output means for outputting said calculated suggestions and other information (E.g. display, voice output, dials etc.)

The software application may include accessing means for accessing an electronic storage medium that contains lookup table. The software application may include the electronic storage medium, such as a database that stores algorithms, data and parameters.

Two possible variations for the software application are shown in Figure 14 and 15. Figure 14 shows the bolus calculator implemented on a handheld computer (PDA) while Figure 15 shows the application implemented on a mobile communication device. The software application includes accessing means for accessing a logbook **14a**, **15a** to list relevant such as food intake, exercise, insulin administration, blood glucose measurements etc. which are input by a user via the device's input means.

Food or beverages can be added to the logbook by selecting Food, selecting a type of food **14b**, **15d** and the sub category **14c**, **15e** of the food and the specific food item **15f**. The number or fractions of portions **14d**, **15g** can then be set and added to the meal.

To add exercise to the logbook, exercise is selected, a type of exercise **14e**, **15h** is chosen and the time and duration of the exercise is set **14f**, **15i**. A blood glucose value **15j**, **15k** can also

be logged by selecting blood glucose measurement and entering the time and value of the measurement.

To calculate the bolus, insulin is selected. The user needs to complete four steps, namely measuring the current blood glucose level **14h** and entering the time of the measurement, confirming or entering the last short acting insulin administration and time thereof, confirming or entering the amount of ETS being ingested **14j** (obtained from the logbook) and the amount of ETS exercise energy to be expended during exercise in the next few hours **14k**. A bolus suggestion will then be calculated and can be either a suggestion for a certain amount of short acting insulin, a suggestion to take no action or a suggestion to eat a certain amount of food ETS. For this calculation, Equations (43),(44) and (45) will be used. Certain other effects namely the mixed meal and second meal effects will also be accounted for in the calculations.

The device should first be customized for the specific patient, after the patient has been characterized. After characterization the sensitivities for ETS, insulin and exercise can be entered into the device **14l, 14n, 15t, and 15u**.

Similar devices exist at present but these do not use a linear unit such as ETS, as an energy quantification system that is used in Equation (43), (44) an (45).

Another embodiment of the invention is shown in Figures 16 and 17. In this embodiment, a device similar to the slide rule device described earlier is disclosed.

The test procedure as previously described can be followed. ETS sensitivity $f_{BS/ets}$ value can be calculated using Equation (17).

$$f_{BS/ets} = \frac{\Delta BS_{test}}{ets_{meal}} = \frac{BS_{post\ meal} - BS_{prior\ meal}}{ets_{meal}} \quad (17)$$

Referring to Figure 16A, the device according to this embodiment comprises three concentric cardboard wheels, each printed on one side. All three wheels can be rotated relative to each other around the middle point of the concentric wheels. A back wheel 30 is larger than an upper wheel 28 and centre wheel 29, which are the same size. The back wheel 30 has a blood glucose scale printed on it. The centre wheel (shown in Figure 16C) has several ETS sensitivity values printed on it, and it has a first pointer **29** on the edge of the wheel, which is used to point to a blood glucose value.

The upper wheel has a rectangular transparent or see through window **27**, showing the relevant sensitivity values on the centre wheel. The upper wheel also has a second pointer **28** to point to a blood glucose level. Characterization with this device is done by simply pointing with the second pointer 28 on the upper wheel to the blood glucose level prior to the meal $BS_{prior\ meal}$ and the first pointer on the centre wheel **29** to point to the blood glucose level after the test meal $BS_{post\ meal}$. The sensitivity value in the rectangular window **27** next to the corresponding number of ETS in the meal ets_{meal} is the patient's ETS sensitivity, $f_{BS/ets}$.

The Insulin sensitivity $f_{BS/I}$ value can be calculated using Equation (15).

$$f_{BS/I} = \frac{\Delta BS_{test}}{I_{units\ test}} = \frac{BS_{prior\ insulin} - BS_{post\ insulin}}{I_{units\ test}} \quad (15)$$

Again a slide rule device is proposed to do the calculation. The test procedure as previously described should be followed. The characterization device shown in Figure 17a comprises three concentric cardboard wheels, each printed on one side. All three wheels can be rotated relative to each other around the middle point of the concentric wheels. The back wheel **33** (Figure 17D) is larger than the upper wheel and center wheel. The back wheel has a blood glucose **33** scale printed on it. The centre wheel (Figure 17C) has several insulin sensitivity values printed on it, and it has a first pointer **32** on the edge of the wheel, which is used to point to a blood glucose value. The upper wheel (shown in Figure 17B) has two rectangular transparent windows **34** and **35**, showing the relevant sensitivity values on the centre wheel. The upper wheel has a second pointer **31** to point to a blood glucose level. Characterization with this device is done by simply pointing with the second pointer on the top wheel **31** to the blood glucose level prior to the insulin administration $BS_{prior\ insulin}$ and the first pointer on the centre wheel **32** to point to the blood glucose level after the insulin administration $BS_{post\ insulin}$. The sensitivity value in one of the rectangular windows **34** or **35** next to the corresponding number of insulin units administered in the test procedure $I_{units\ test}$ is the patient's insulin sensitivity, $f_{BS/I}$.

The insulin and ETS sensitivity slide rule wheels can be fixed together back to back on each other to create one device, which can be used to determine both insulin and ETS sensitivity.

A apparatus according to the invention could be incorporated into existing equipment to regulate blood sugar. The apparatus may be provided in the form of a software application.

Figure 18 shows a condensed flow diagram for a software application to calculate ETS sensitivity and insulin sensitivity of a patient. The software application makes use of the characterization test procedure as described earlier. The user (E.g. medical doctor) of the software application is given instructions, step-by-step, and is prompted to enter measured blood glucose values of patient (E.g. diabetic being characterized) at certain times.

Said software application can be implemented on any device including, but not limited to the following: handheld computer, PDA, proprietary device, personal computer, notebook, laptop, desktop computer, micro computer, mobile phone, tablet computer or any other electronic or mechanical device able of performing the necessary calculations.

To characterize a patient, the patient has to fast for at least two hours and must have a relatively stable blood glucose level before starting with the procedure. The user is prompted to measure the blood glucose level of the patient. The user then enters the blood glucose level. If the blood glucose level is higher than a predetermined safety threshold BG_{high} the software application will prompt the user to start with the insulin sensitivity test first (which will cause the blood glucose level to drop). If the blood glucose level is lower than the safety threshold BG_{high} the patient is given a carbohydrate rich meal containing a known amount of ETS. The software application prompts the user to enter the ETS value of the meal. The user is then prompted to measure and enter the blood glucose values of said patient after 30 minutes and then 60 minutes after the meal. The ETS sensitivity is then calculated by taking difference between, the maximum of the two measured values at 30 and 60 minutes, and the initial blood glucose value, and dividing the result by the amount of ETS in the test meal. If the calculated ETS sensitivity value falls within a predetermined range, the value is displayed. If it is not within said range, the software application will prompt the user to repeat test at a later time.

The user is then prompted to measure and enter the blood glucose value of the patient. If it is higher than a predetermined safety threshold, the test can be continued. In this case an appropriate number of short acting insulin units is administered. The software application will prompt the user for this insulin administration and to enter the insulin dosage. The user will then be prompted to measure and enter blood glucose values after 45 and 105 minutes. The insulin sensitivity can then be calculated by, taking the difference between the blood glucose value prior to the insulin administration and the minimum value of the blood glucose values taken at 45 and 105 minutes, and dividing it by the amount of insulin units administered. If this calculated sensitivity value is within a predetermined range of sensitivities, the sensitivity

value will be displayed. If it is not within this range the user will be prompted to repeat the test at a later stage. This test procedure is described in more detail above.

In a still further embodiment of the invention, the apparatus is provided in the form of a blood glucose simulation application. It uses the energy values quantified in ETS to represent food being ingested, energy being stored in the liver, exercise energy being expended, exercise attempted and the energy made available by the counter regulation system. The interaction between these different energies can easily be demonstrated on the simulation application. It can be used to educate both diabetics and non-diabetics on the topic of blood glucose control, diabetes, stress and the prevention of illnesses etc.

The blood glucose prediction Equation (42) can be expanded to a more accurate one if the counter regulation ability (release of glycogen as glucose on response of glucagon or other hormones) of the liver is included.

$$BS_{predicted} = BS_{current} + \Delta BS_{predicted\ food} + \Delta BS_{predicted\ exercise} + \Delta BS_{predicted\ insulin\ left} + \Delta BS_{counter} \quad (46)$$

$\Delta BS_{counter}$ can be calculated by the following set of rules or conditions:

- The maximum value that $\Delta BS_{counter}$ can be is the maximum increase of blood glucose level caused by the glucose being released by the counter regulation system (liver). This is a value that can be estimated and it is known that it decreases with the time after being diagnosed as a Type 1 diabetic. It is also temporarily influenced by alcohol intake, Type 2 diabetic medications etc.
- The counter regulation system will try to keep blood glucose levels close to normal if it drops below a certain threshold value. This means that blood glucose levels will stay relatively constant until the glycogen stores in the liver are depleted.
- The counter regulation system will elevate blood glucose levels, even when they are already high, when there is not enough insulin to utilise energy. This happens both with daily activities and exercise. This means that the counter regulation system will elevate the blood glucose level when a person exercises and does not have enough readily available insulin in his/her blood, even if the blood glucose level is already high. Although the blood glucose level is already high, the cells cannot utilize the energy efficiently without insulin. This means that the person will have some difficulty in exercising. One advantage though is that when a person starts exercising

the insulin resistance starts decreasing, meaning that less insulin is necessary for the exercise.

The layout of the diabetic simulator application is shown in Figure 19. There are four choices for the simulation characterization namely a quick estimation, accurate characterization and two demonstration characterizations for two different persons with Type 1 diabetes. The Quick estimation is shown in Figure 19b. Here all the body characteristics necessary including, but not limited to, height, weight, activity level, years diagnosed, control blood glucose range, total daily dose long acting insulin, total daily dose short acting insulin, and blood glucose response for different foods and insulin. Estimated characterization values can be calculated by using the information entered but it should be noted that it is not an accurate method of characterization because it relies on the memory of the person being characterized. The accurate characterization shown in Figure 19b makes use of the characterization procedure as described earlier. The body characteristics and insulin regime is again necessary but also the sensitivity values for food, insulin and exercise. The two demonstration characterizations have two sets of preprogrammed parameters for all the body characteristics and sensitivity values of two different persons.

The simulation model can be customized further as shown in Figure 19d where sensitivity values, counter regulation ability etc. can be altered.

Figure 19e shows the main interface of the blood glucose simulation application. The location and function of each component can be described as follows:

Blood glucose oval 36: This oval gradually changes colour as the blood glucose value changes. If the blood glucose value is outside the control range, it turns red; if it is close to the target value it turns green; blood glucose values between these two values will cause oval to gradually change colour from green to red.

Blood glucose value 47: The blood glucose value can be displayed in either mmol/l or mg/dl or any other concentration unit.

Manual blood glucose adjustment 46, 45: The blood glucose values can be adjusted manually by clicking on buttons 46 and 45. This can be used to simulate the scenario where the user starts of with a high or low blood glucose value.

Arrows 38, 39, 40, 41, 42, and 43: These arrows are used to represent the quantities of energy they represent in ETS except for the insulin arrow 39, which is measured in U. By dragging these arrows up and down with said input means of device, the values can be altered. Some of these arrows are dependant upon each other and therefore a change in one of these magnitudes might trigger a change in one or more of the other magnitudes.

Arrow 38 – Energy eaten: This arrow represents the food being ingested. The magnitude of this arrow can be changed by either dragging the value, or selecting food button 48 and selecting food or beverage from the database. Figure 19f shows the main food categories; Figure 19g shows an example of the subcategories and food items while Figure 19h shows how the portion size and number of portions are selected. The blood glucose value will generally increase for an increase in energy being eaten, Equation (18).

Arrow 39 – Insulin: The short acting insulin can be changed by dragging the arrow to the left or right. This insulin will generally cause the blood glucose level to fall, Equation (16), except where the counter regulation system is active or where insulin is rather being used for exercise meaning that the body is in utilisation mode rather than storage mode.

Arrow 40 – Energy being stored: When the body is in storage mode, insulin is being used to store glucose (from CHO in meal) in the liver and other cells of the body. Equation (16) can be used to calculate the amount of glucose that is being stored. When energy is needed for exercise, the body will rather go into utilization mode, meaning that less glucose is being stored and more utilized. This means that available insulin is being used for utilization. If there is however too much insulin, utilization and storage will take place at the same time and may lead to hypoglycaemia if the counter regulation system cannot successfully counteract.

Arrow 42, 41 – Exercise being attempted and exercise energy being expended:

When a person exercises, glucose is utilized by the cells for energy. This utilization of energy can only take place if there is enough insulin in the blood. Fortunately a person's insulin sensitivity temporarily increases up to a factor four during exercise. This means

that less insulin is needed for utilizing energy during exercise than for energy used for normal metabolism etc. Arrow 42 represents the exercise being attempted. If there is not enough insulin in the blood, the actual exercise energy being expended, Arrow 21 will be less than the attempted exercise energy. The counter regulation system will react as if there is not enough glucose in the blood and more glucose will be release by the liver, causing the blood glucose level to rise.

Arrow 43 – Energy being released from liver (Counter regulation system): The conditions for the energy being released from the liver namely, $\Delta BS_{counter}$ were discussed earlier in this section.

Maximum counter regulation mark 44: The liver can produce a maximum amount of glucose by converting glycogen in response to the hormone glucagon being secreted. Type 1 diabetics often inject too much insulin resulting in hypoglycaemia and thereby putting stress on their livers for glucose production. This ability gradually decreases with time and after about four years; the maximum counter regulation ability may have decreased by up to 80%. This value can also decrease temporarily after consuming alcohol.

Insulin regime button 51 / Stress & Illness: This allows the user to graphically demonstrate (Figure 19k and 19l) how to calculate an appropriate insulin regime and bring it into balance with daily energy requirements, food intake, stress levels and exercise.

In a further embodiment of the invention, the apparatus is incorporated into a blood glucose-regulating device. This device, similar to an insulin pump, also allows the administration of glucose for low blood glucose levels. Said device is therefore capable of controlling both low and high blood glucose levels. Figure 20 shows the block diagram for the system. The device consists of the following components:

- Input means **60** for entering blood glucose control range, target blood glucose value, sensitivity values and other information or commands required.
- Output means **53** for communicating the status of device;
- Blood glucose sensor **61** for monitoring blood glucose levels. This can be either an integrated system or an external unit capable of communicating with the device.

The frequency of blood glucose measurements is dependent upon the type of blood glucose monitor being used. Higher sampling rates will result in better control.

- Dispensing units for insulin **54** and glucose **55**. These separate units are responsible for the administration of glucose and insulin and the control algorithm of said device determines the rate of administration.
- Processing unit **58**: This is the core processor responsible for analyzing input data with stored parameters and using them in the control algorithm. This processor communicates with the other internal and/or external components of the system. The processor includes the inventive software application or bolus calculator which uses Equations (43), (44) and (45) to determine after food intake the required corrective action. This can be either a suggestion to take no action, a suggestion to inject a certain dosage of insulin, or a suggestion for additional ETS to be ingested. The device can automatically administer the insulin or ETS or the user can be prompted with the suggestion and be instructed to proceed. Equation (45) can also be used to calculate the amount of ETS to be administered in the event of hypoglycaemia.

It should be noted that this device would make use of a continuous control algorithm rather than a discrete control algorithm.

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DRAWINGS

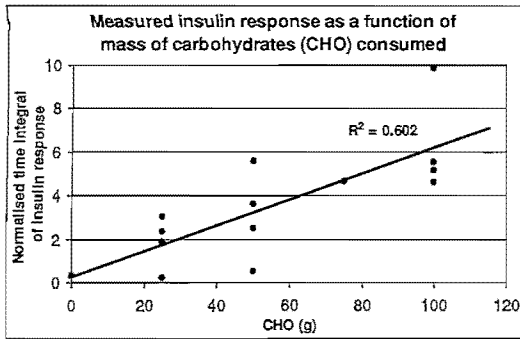


Figure 1a

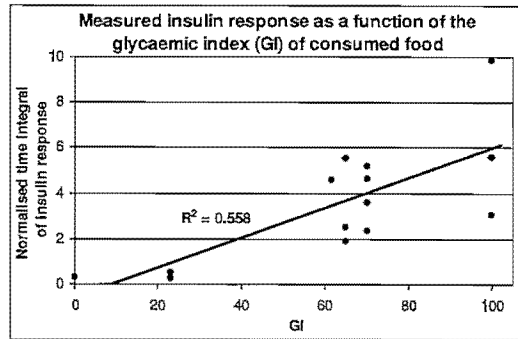


Figure 1b

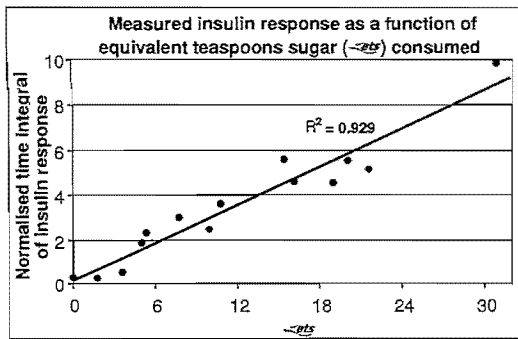


Figure 2

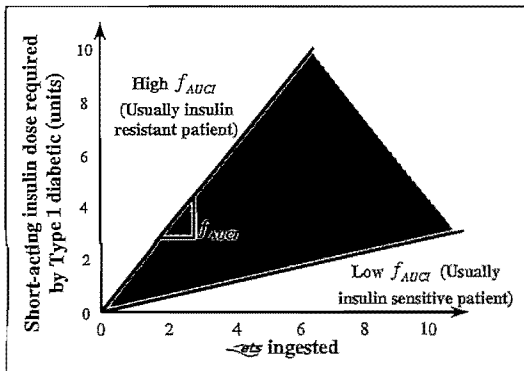


Figure 3a

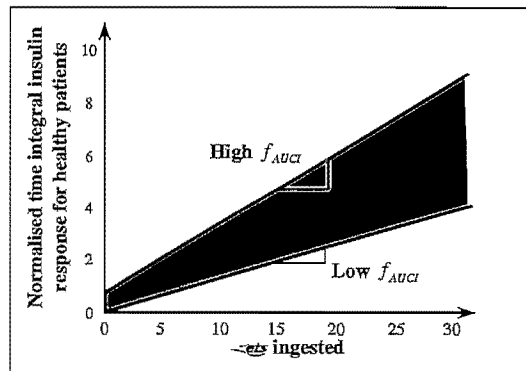


Figure 3b

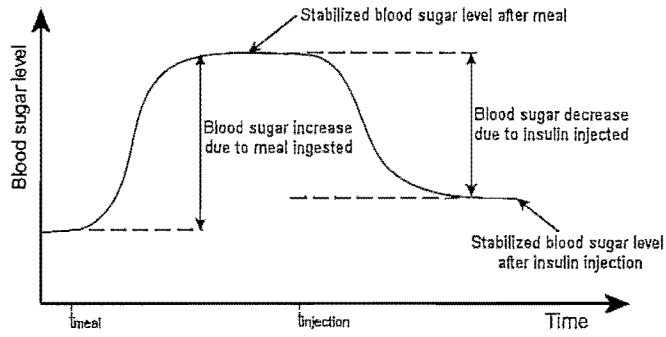
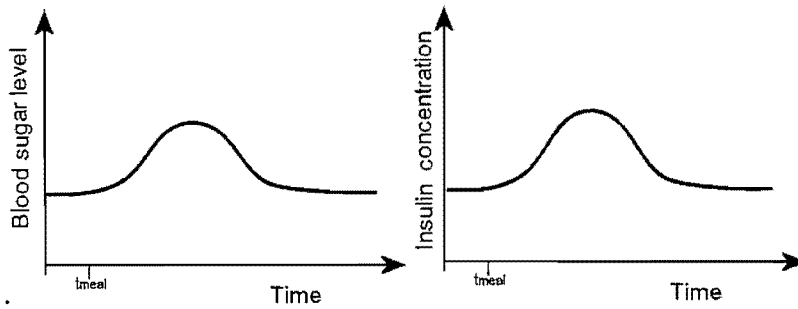
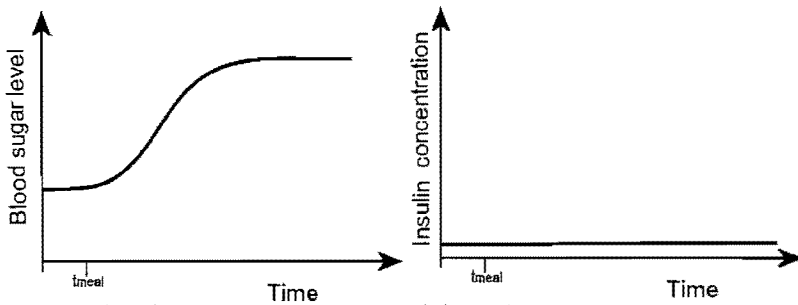


Figure 4



Illustrative blood glucose and insulin concentration curves of a non-diabetic person after ingesting a meal containing carbohydrates

Figure 5



Illustrative blood glucose and insulin concentration of a Type 1 diabetic after ingesting a meal containing carbohydrates (not using short-acting insulin).

Figure 6

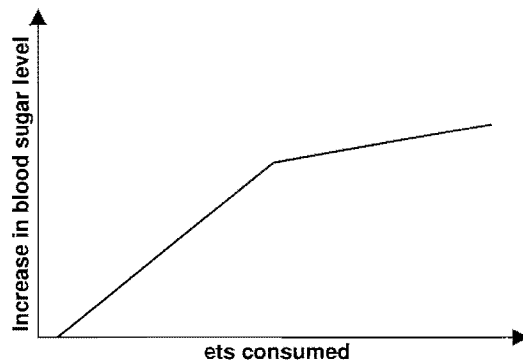


Figure 7

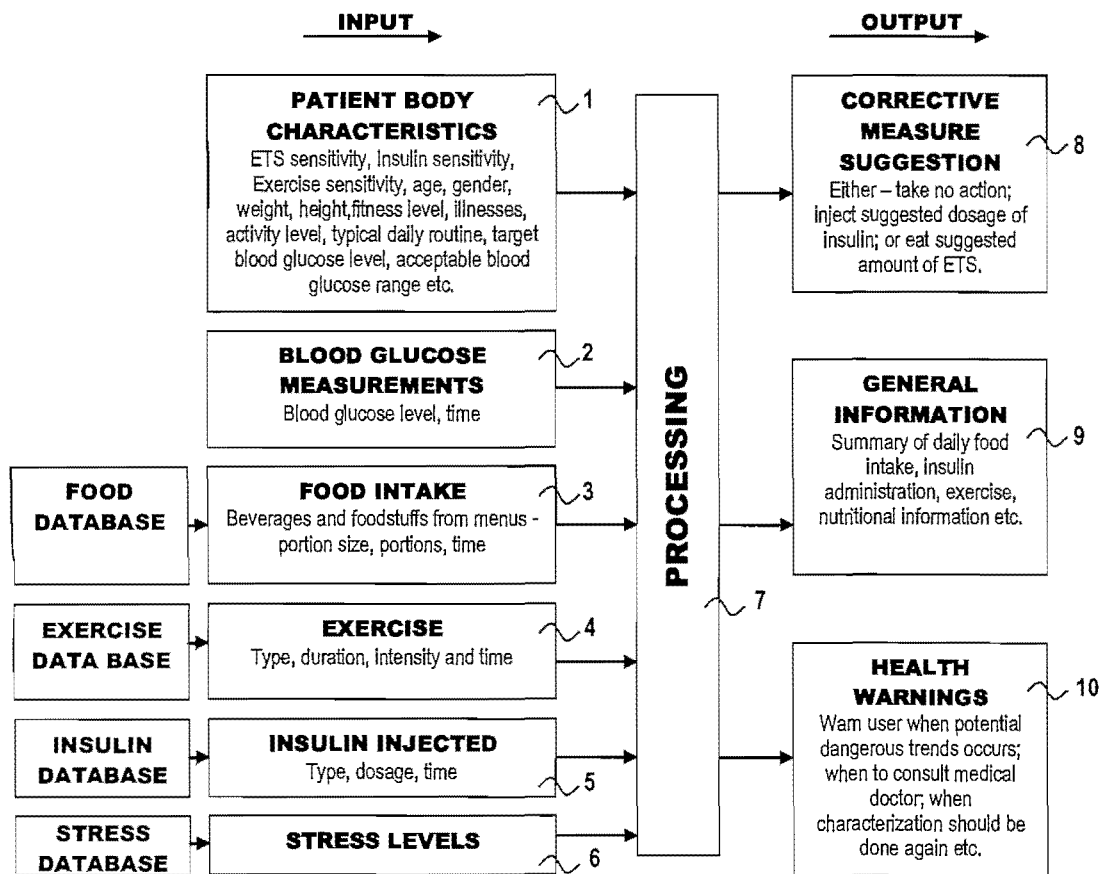


Figure 8

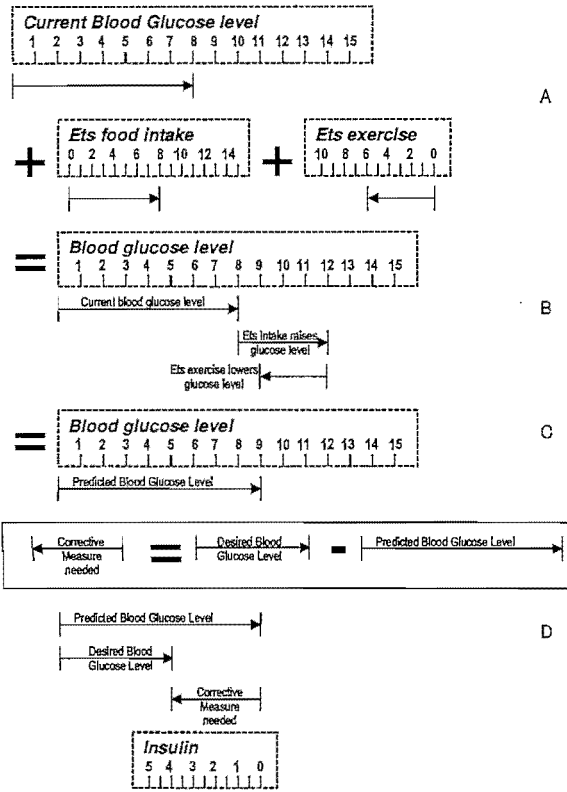


Figure 9

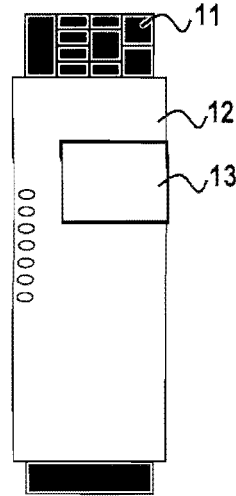


Figure 10a

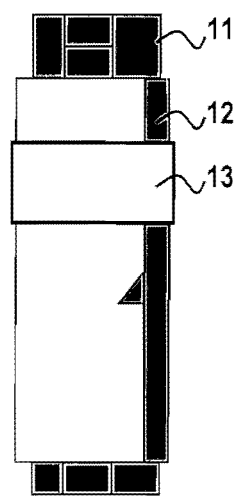


Figure 10b

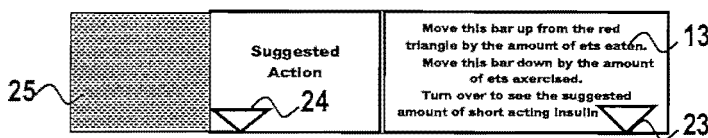


Figure 13

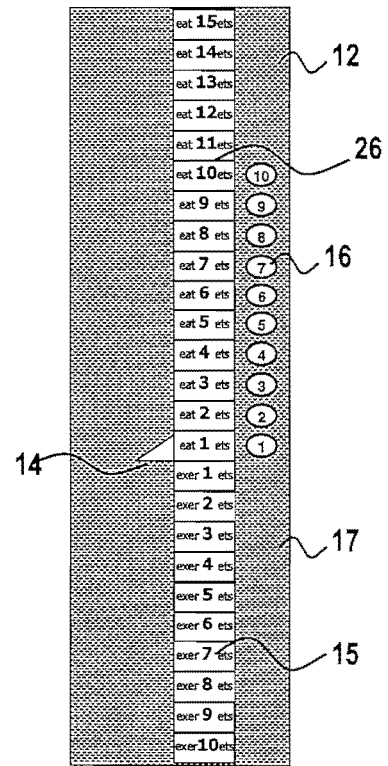


Figure 11

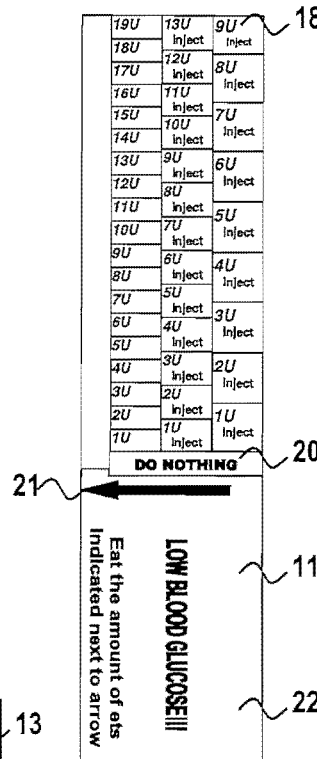


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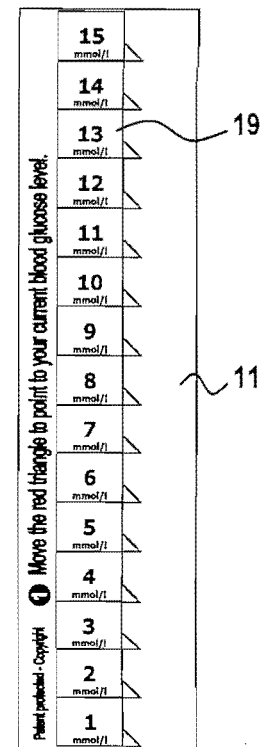


Figure 12b

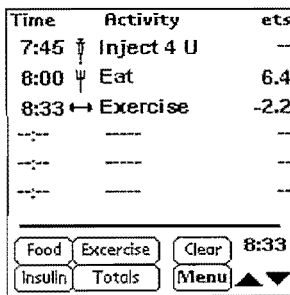


Figure 14a

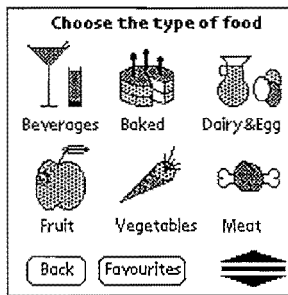


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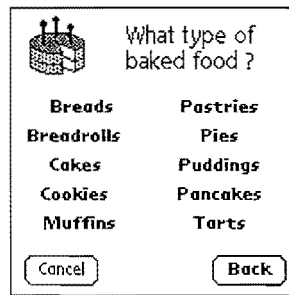


Figure 14c

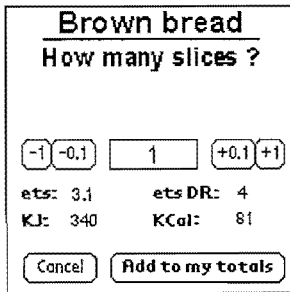


Figure 14d

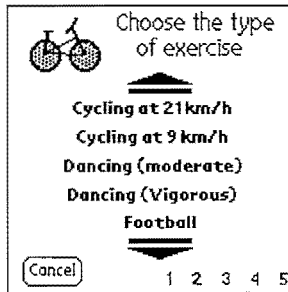


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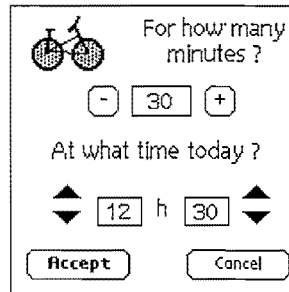


Figure 14f

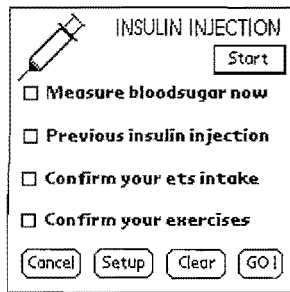


Figure 14g

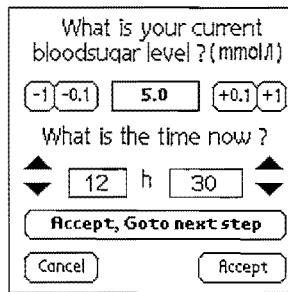


Figure 14h

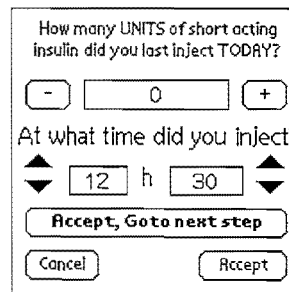


Figure 14i

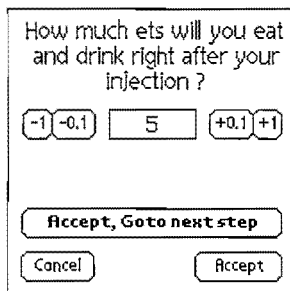


Figure 14j

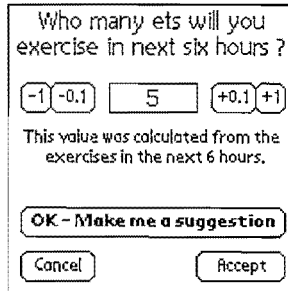


Figure 14k

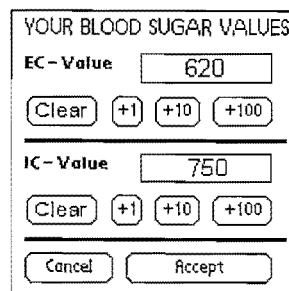


Figure 14l

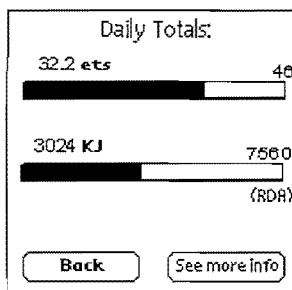


Figure 14m

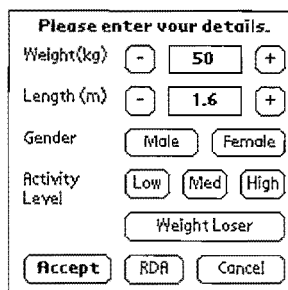


Figure 14n

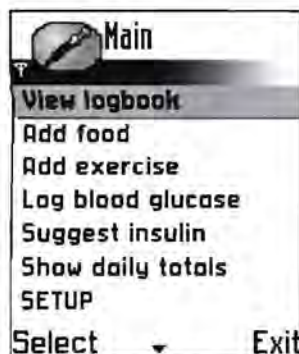


Figure 15a

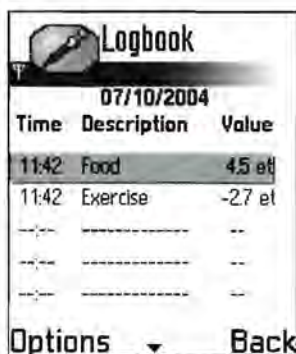


Figure 15b



Figure 15c

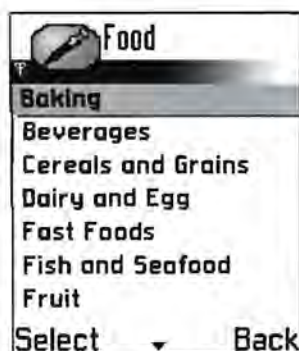


Figure 15d



Figure 15e



Figure 15f

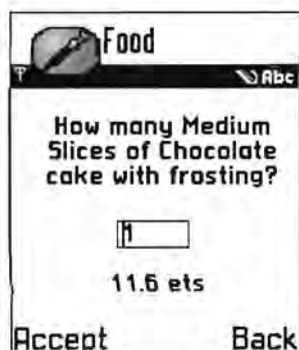


Figure 15g

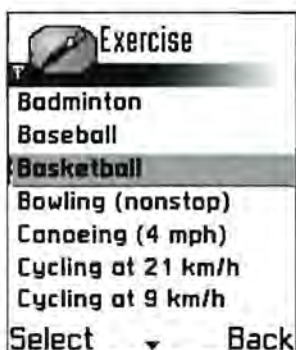


Figure 15h

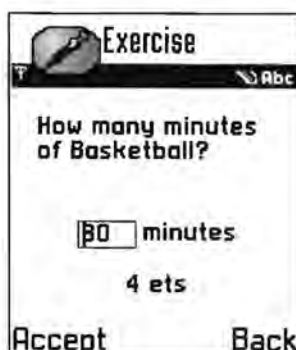


Figure 15i

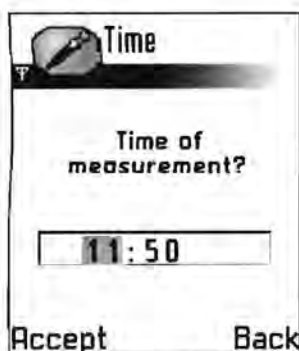


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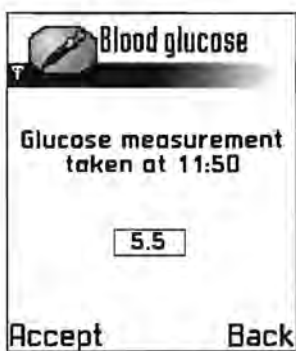


Figure 15k



Figure 15l

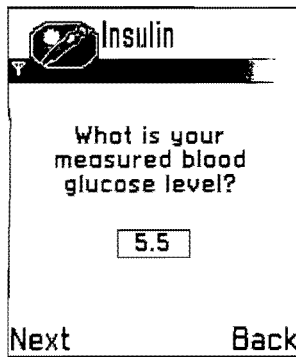


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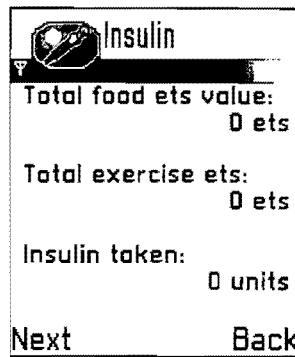


Figure 15n

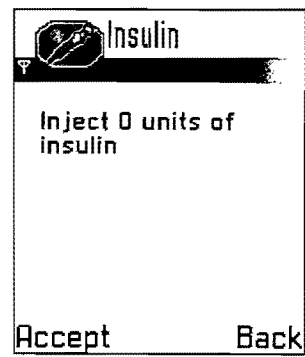


Figure 15o

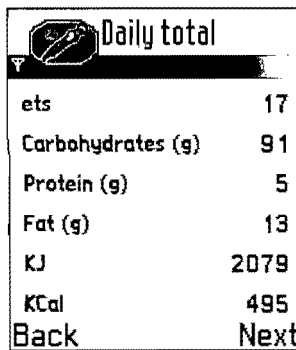


Figure 15p

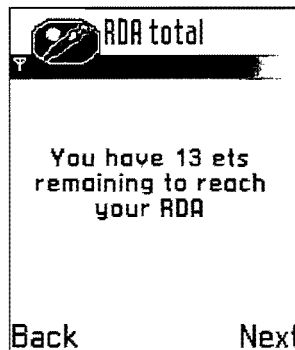


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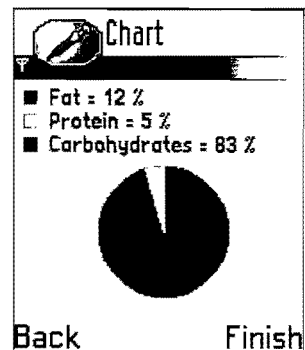


Figure 15r

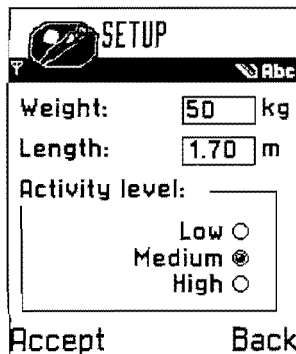


Figure 15s

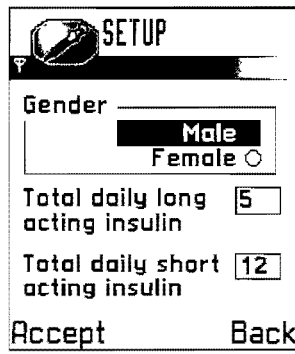


Figure 15t

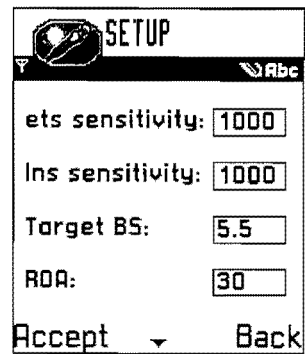


Figure 15u

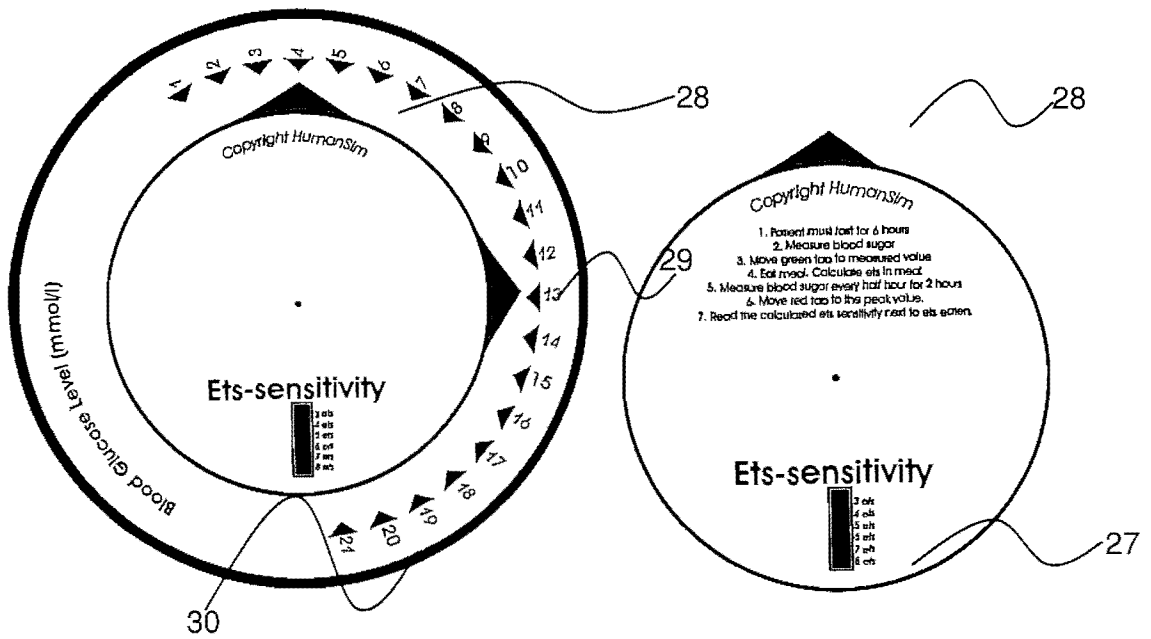


Figure 16a

Figure 16b

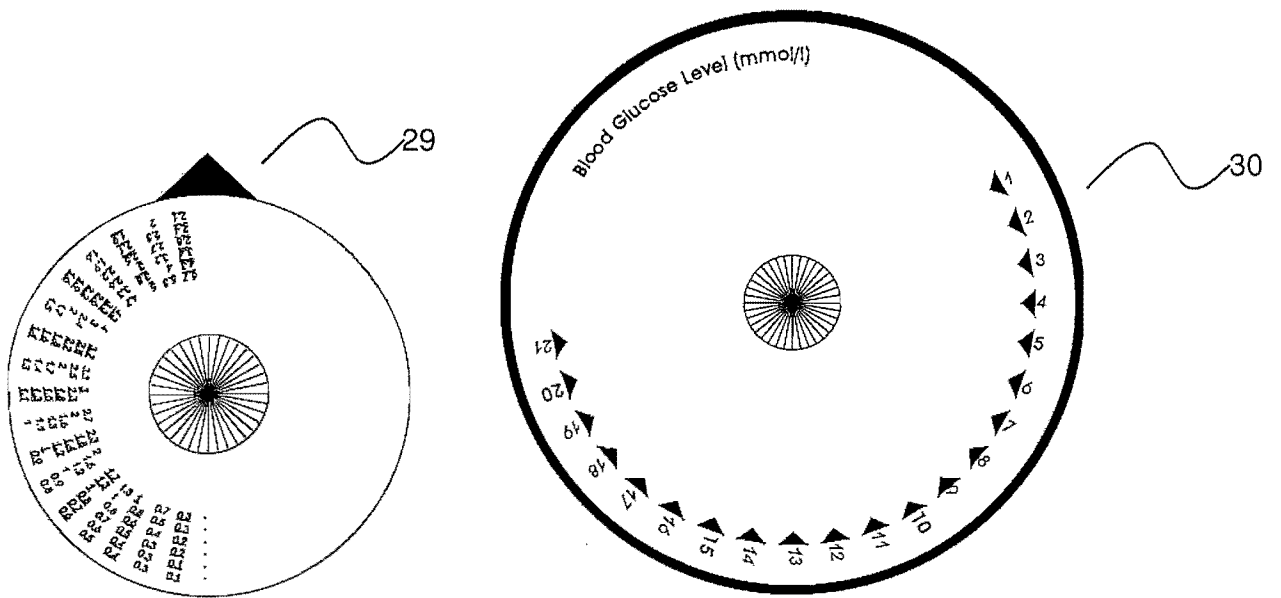


Figure 16c

Figure 16d

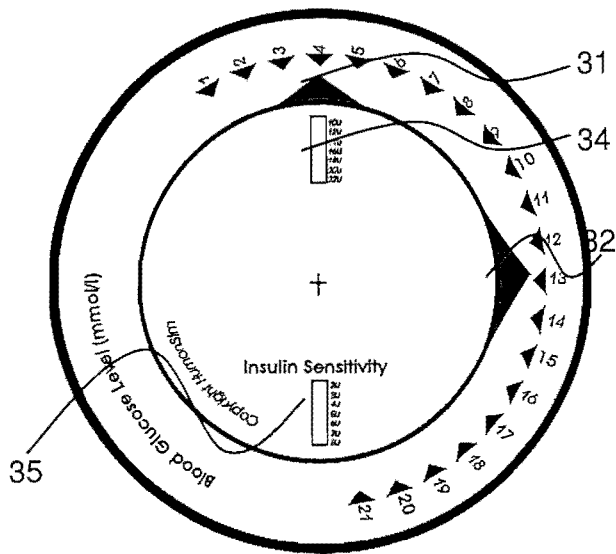


Figure 17a

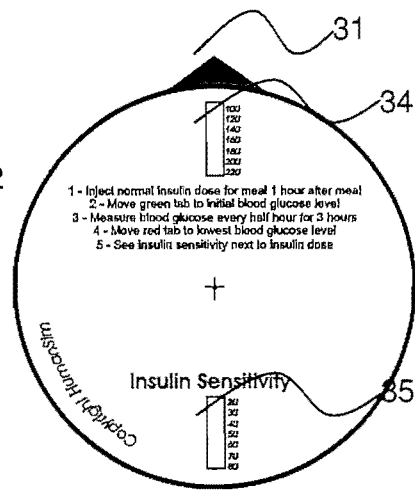


Figure 17b

- 1 - Inject normal insulin dose for meal 1 hour after meal
- 2 - Move green tab to initial blood glucose level
- 3 - Measure blood glucose every half hour for 3 hours
- 4 - Move red tab to lowest blood glucose level
- 5 - See insulin sensitivity next to insulin dose

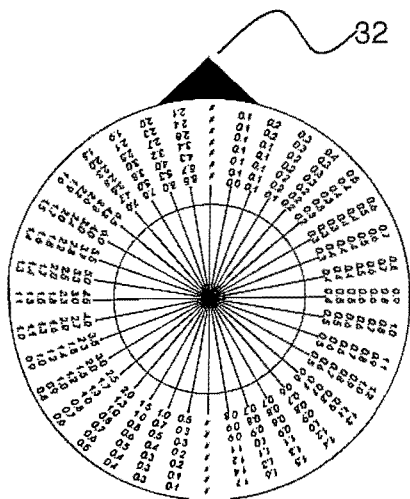


Figure 17c

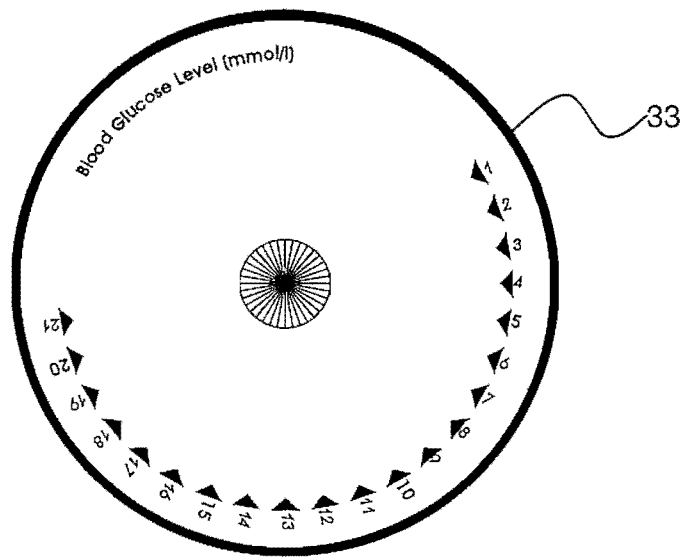


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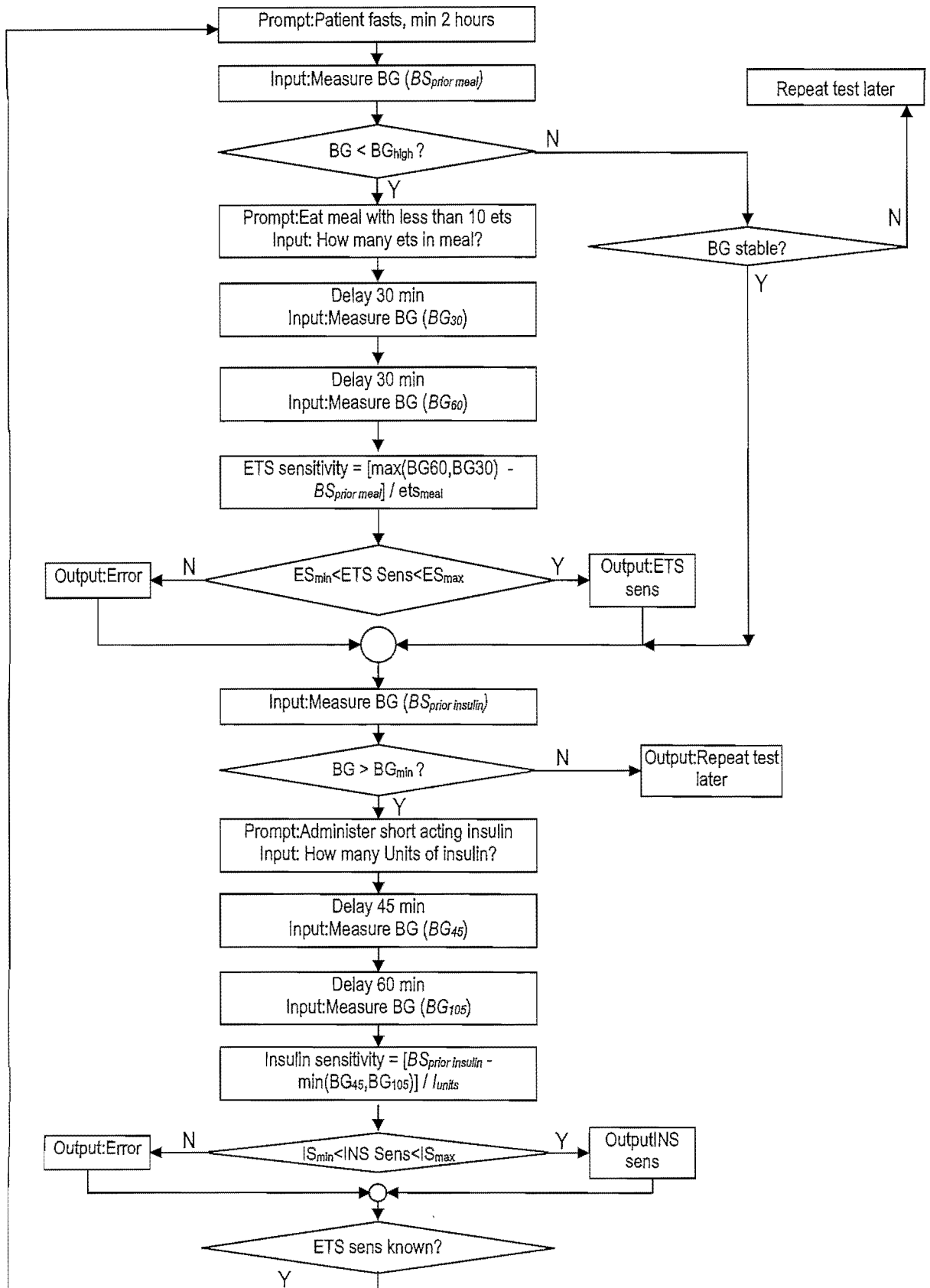


Figure 18

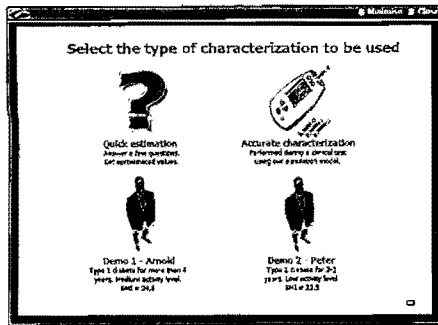


Figure 19a

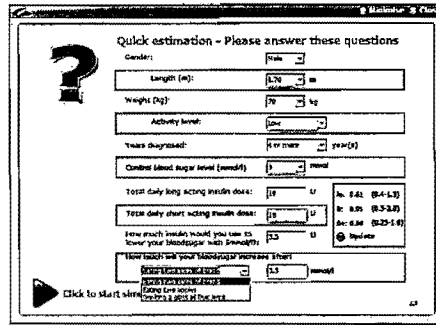


Figure 19b

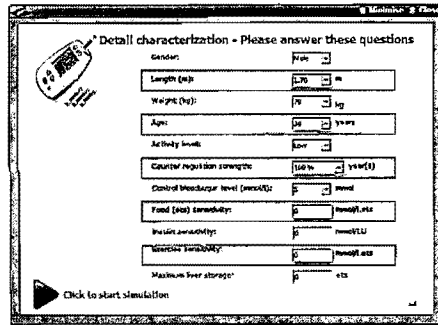


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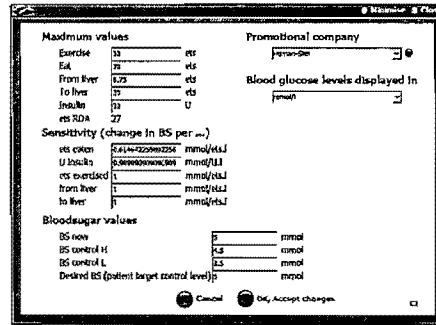


Figure 19d

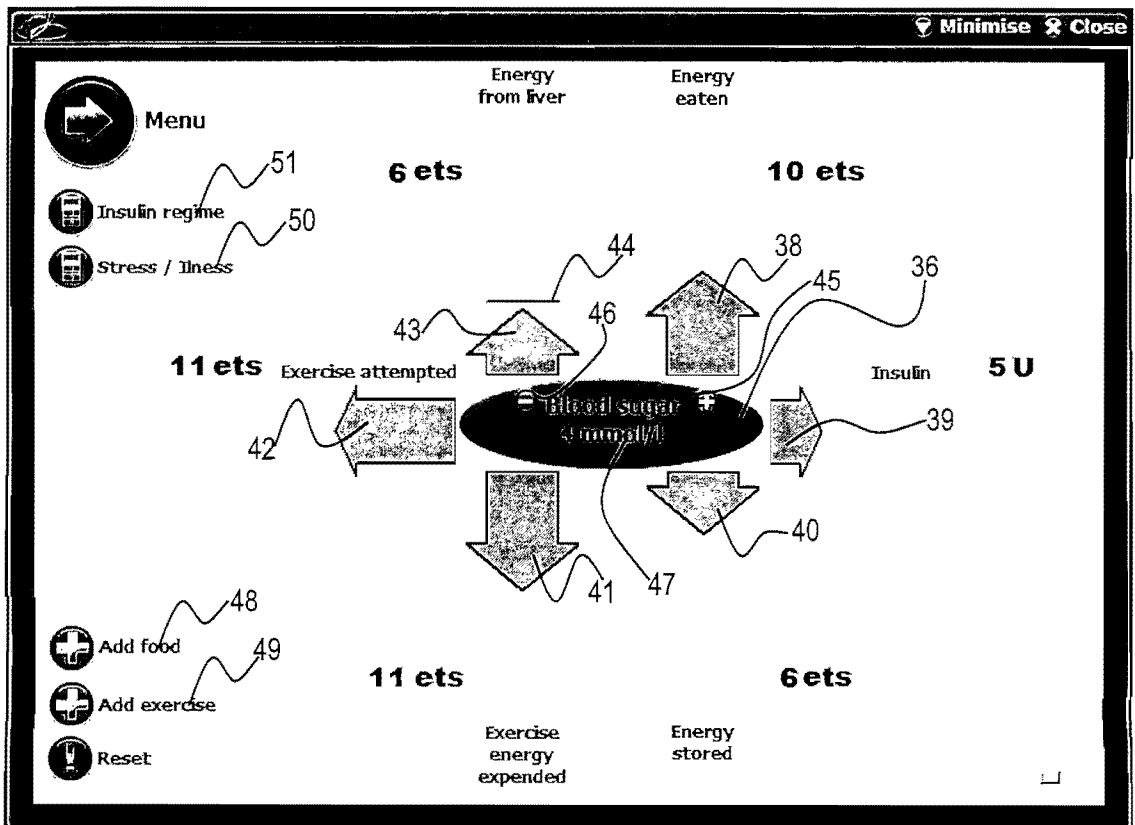


Figure 19e

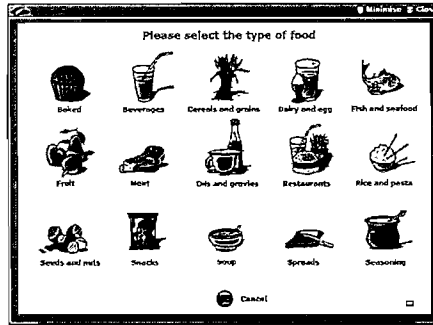


Figure 19f

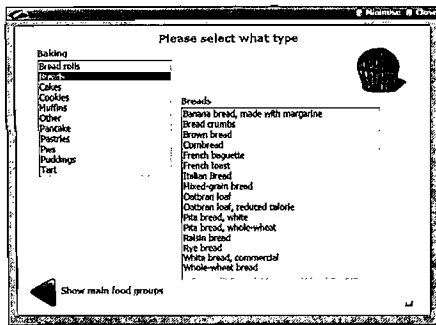


Figure 19g

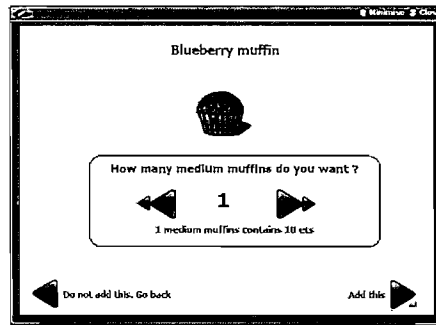


Figure 19h

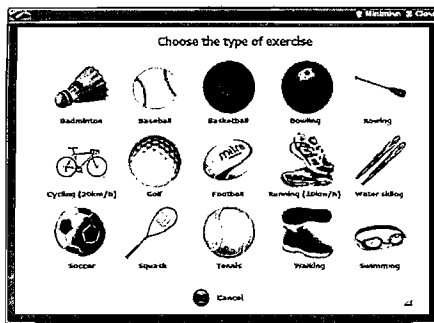


Figure 19i

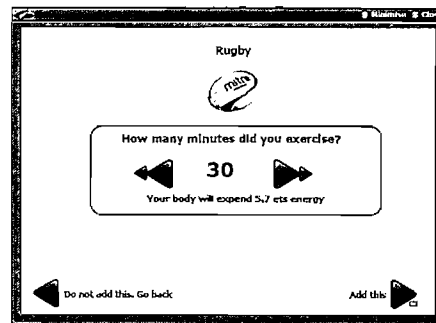


Figure 19j

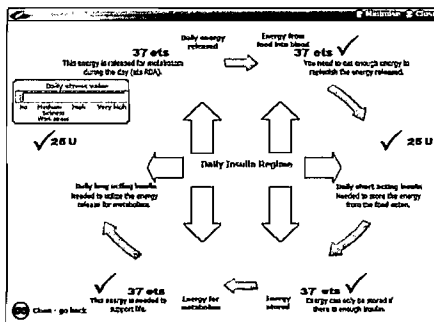


Figure 19k

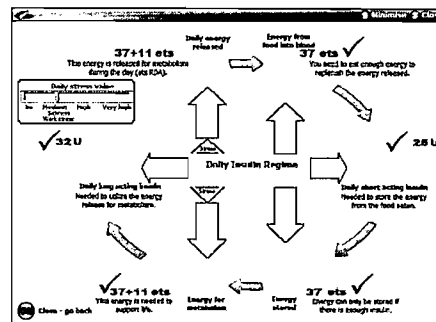


Figure 19l

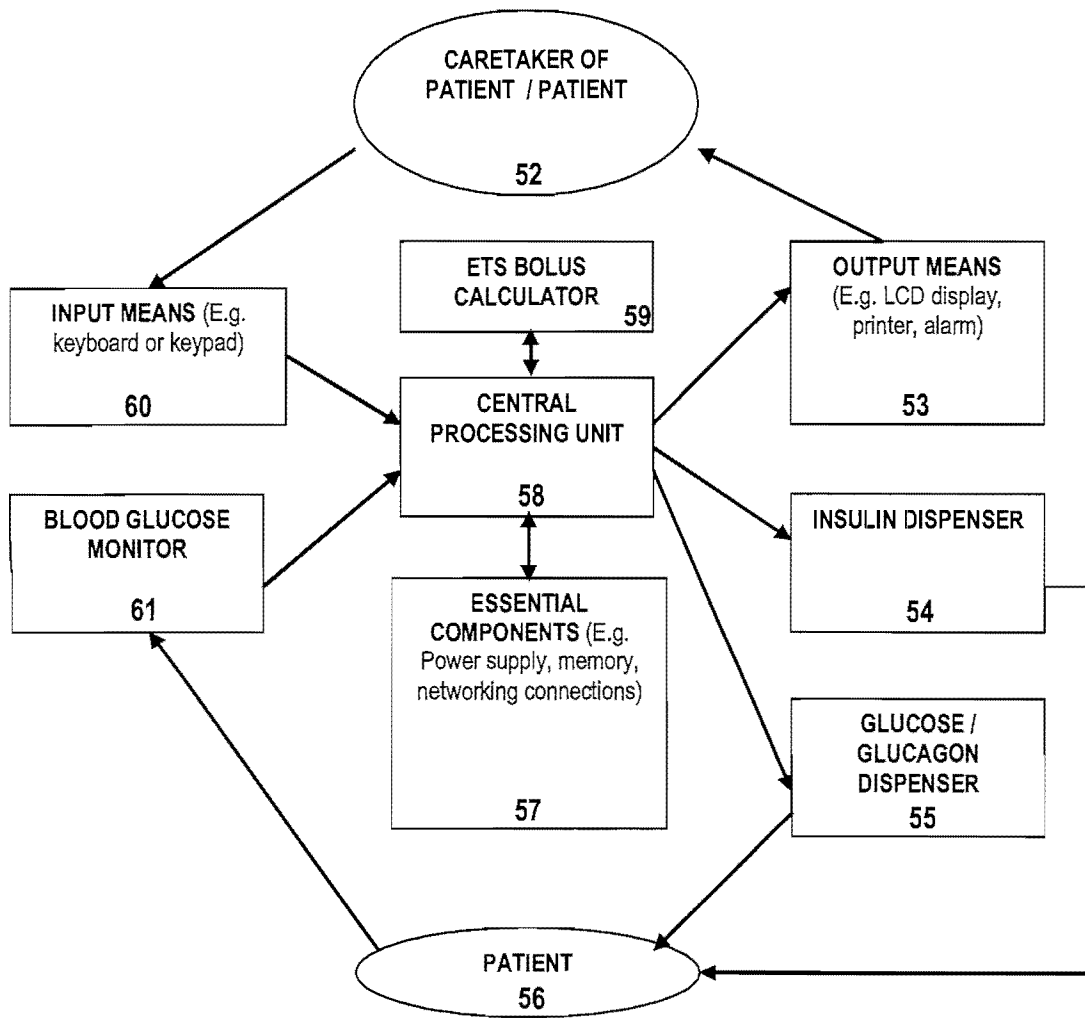


Figure 20

GLYCAEMIC CONTROL OF TYPE 1 DIABETICS USING THE ETS CONCEPT

Human-Sim (Pty) Ltd.
Protocol HS_DIAB_004v2 – 21 June 2005
Glycaemic control of Type 1 diabetics using the ETS concept

1. JUSTIFICATION

1.1 Literature review

Diabetics either do not produce enough insulin or cannot utilise it efficiently¹. Insulin administration is therefore essential for many diabetics to control their blood glucose levels. Most of these diabetics find it difficult to control their blood glucose levels². One of the reasons is that the carbohydrate (CHO) counting method, that is often used, is not very accurate³. Therefore a more practical relationship between insulin response and food taken in is needed to promote better glycaemic control.

After ingesting a meal, the carbohydrates from said meal are converted to blood glucose. In a healthy person the pancreas secretes insulin. Insulin promotes the storage of glucose in the liver (as glycogen) and also in other cells. Insulin is also required by cells so that they will absorb glucose to provide them with energy. Without insulin, the glucose will remain in the blood because it cannot be stored or utilised for energy. This results in high blood glucose concentrations. This condition is called hyperglycaemia. Hypoglycaemia or low blood glucose occurs when too much insulin is secreted¹.

The pancreas of a Type 1 diabetic does not secrete insulin¹. Before or after meals the diabetic has to inject an appropriate dosage of short-acting insulin, called a bolus. The bolus has to counteract (lower) the effect that the meal will have on the blood glucose of the diabetic. It is difficult to match the bolus to a specific meal⁴, especially if there is some inconsistency in eating habits. Boluses are often determined by trial and error. This means that diabetics often stick to rigid meal plans because they are nervous to experiment with new meals.

Unfortunately bolus calculations are made even more complex by the following factors:
(Please note that this list is not exhaustive but merely reflects to some common problems.)

- The blood glucose level prior to a meal can be too low or too high. This means that less or more insulin respectively should be administered than just the bolus⁴.
- There might be some active short-acting insulin left in the blood. This residual insulin will have a lowering effect on the blood glucose level. The onset, peak and duration of the type of insulin used, gives us an indication of how much active insulin is left in the blood.
- Residual effect of previous meal or snack. If a snack or meal was taken a short while before the next meal or snack, there might be a residual rising effect on blood glucose from the first meal.
- Stress and illness tend to cause elevated blood glucose levels⁴.

The major stumbling block, however, is matching the bolus insulin to the meal. One of the conventional methods of calculating bolus is the carbohydrate counting method⁴. An insulin to CHO ratio is calculated for the specific patient. There are various ways in which this ratio can be determined – for example the 500/450 rule proposes dividing 500 by the total dose of daily insulin (TDD). This number is a rough approximation of the grams of carbohydrate covered by one unit of insulin. In other words, to calculate the bolus for a specific meal, the total number of grams CHO in the meal is divided by the insulin-to-CHO-ratio. This answer tells us how many units of short-acting insulin should be injected for the meal.

A potential problem with the 500/450 rule is that it is assumed that every diabetic, regardless of his/her weight, eats the same amount of carbohydrates per day. With some trial and error this ratio can be improved to provide better glycaemic control. Another problem is determining the correct amount of carbohydrate grams for a specific meal. This is an almost impossible task without books, food tables and properly labeled food packaging.

The quality of bolus calculation using the carbohydrate counting method can be examined by using measurements by Lee and Wolever⁵. These measurements give insulin response curves for different healthy test subjects ingesting different amounts of CHO (0 to 100 grams) with varying GI values (23 to 100).

The time integrals ($\int BI(t)dt$) of the Lee and Wolever⁵ blood insulin (BI) response curves for one subject are normalised and plotted against the amount of CHO consumed (Figure 1). Pearson's R^2 were calculated⁶ for linearised trend fits through the plotted data. The R^2 -value for the CHO method is 0.602. The worst spread is at 50g CHO, namely a factor 12.

where AUC_I is the area under the insulin curve and $\langle \text{ets} \rangle$ is the amount of $\langle \text{ets} \rangle$ ingested. The full derivation of Equation 1 is not included in this trial protocol and will be made available on request⁸.

The Lee and Wollever⁵ measurements were used again to investigate the quality of insulin predictions using the $\langle \text{ets} \rangle$ method. The results are shown in Figure 2. The linear trend line for the $\langle \text{ets} \rangle$ method yields an R^2 -value of 0.929, which is significantly better than the $\langle \text{ets} \rangle$ carbohydrate counting method. An average R^2 value of 0.807 for the correlation coefficients is obtained by using another dataset for 15 test subjects from Wolever and Bolognesi³. In both these trials the $\langle \text{ets} \rangle$ concept proved to be more accurate than the carbohydrate counting method.

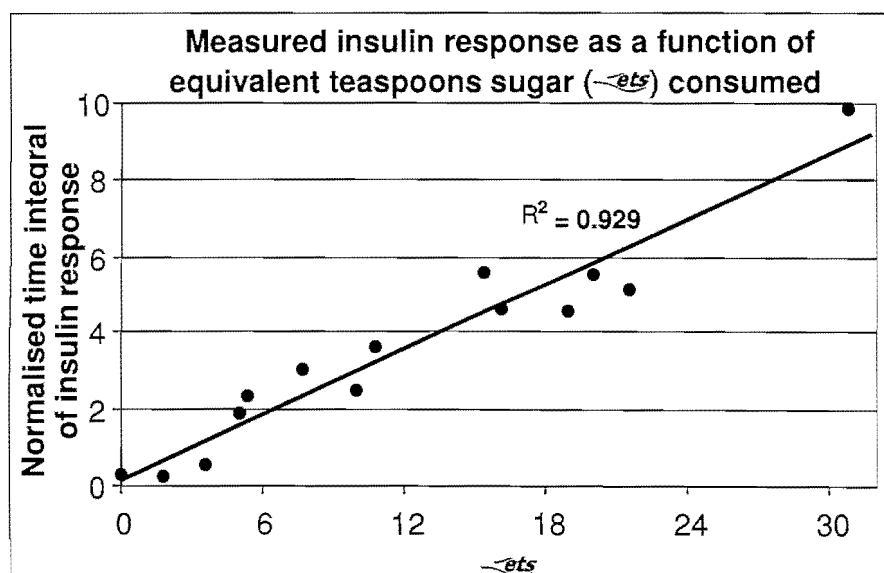


Figure 2 – Measured insulin response as a function of equivalent teaspoons sugar consumed

1.2 Problem and Hypothesis

The main **problem** being addressed is the following:

Type 1 diabetics struggle to control their blood glucose levels. One of the main reasons for this is inaccurate bolus calculation. Hyperglycaemia can be caused by injecting too little bolus insulin while injecting too much bolus insulin can cause hypoglycaemia. Conventional methods for bolus calculation such as CHO counting are not very accurate. Therefore most diabetics do not easily achieve good glycaemic control. Furthermore the literature survey shows that $\langle \text{ets} \rangle$ is a better predictor for insulin requirements than CHO counting.

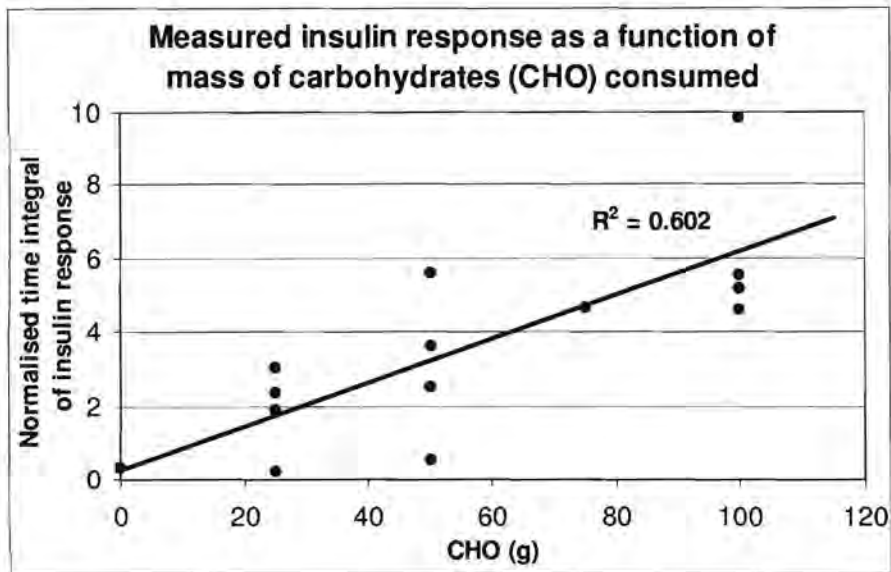


Figure 1 – Measured insulin response a function of mass of CHO consumed

Although these measurements were made on healthy subjects, it gives us a good indication of how carbohydrate ingestion should be taken into account when calculating boluses for Type 1 diabetics. Figure 1 shows that the carbohydrate counting method is not an accurate method for calculating boluses. At the ingestion point of a 50g of CHO meal, the bolus can be incorrectly calculated by a factor of up to 12.

The need for a better insulin prediction method (bolus calculation) than CHO counting is obvious. Wollever and Bolegnesi³ succeeded in doing this. They developed an empirical model based on measurements in seven healthy subjects. Unfortunately the resulting non-linear empirical equations have not found popular use, as they are difficult to use by the average diabetic.

A new method for bolus calculation is proposed for the purpose of this clinical trial. The new method makes use of the Equivalent Teaspoons Sugar (~~ets~~) concept. It is theoretically derived using energy balance techniques⁷, namely the ingested CHO / blood sugar energy balance. A theoretical approach is preferred to an empirical one as theory *inter alia* leads to better insight. The simple linear link between insulin response and ~~ets~~ is given by Equation (1).

$$AUC_I = f_{AUCI} \text{ ~~ets~~ } \quad (1)$$

The **hypothesis** is therefore:

By using the ~~ets~~ concept for three months on a test group of Type 1 diabetics familiar with CHO counting, HbA1C levels can be lowered by at least 1%.

A secondary objective is to determine whether fewer occurrences of hypo- and hyperglycaemia were encountered. This information will be obtained from the questionnaires.

The use of the ~~ets~~ concept as a system will therefore be tested in a practical but controlled environment.

1.3 Benefits arising from the experiment

If the hypothesis holds true the following benefits will arise for Type 1 diabetics using the ~~ets~~ concept for bolus calculation:

- Test subjects will have improved (lower) HbA1C levels at the end of the clinical trial.
- There will be fewer occurrences of hyper- and hypoglycaemia meaning less of the associated diabetes risks.
- Subjects will have the opportunity to improve their meal choices. All ~~ets~~ bolus calculation devices provide the user with information regarding their meal choices. This will help the diabetic to make better or healthier dietary choices.
- Test subjects will be introduced to a new but easier way to calculate their bolus. The bolus calculation system was designed to be easy to use and user-friendly.

The same benefits might apply to the general diabetic population at a later stage.

1.4 Objectives

The primary objective of this clinical trial will be to determine whether the ~~ets~~ concept (in other words using the ~~ets~~ bolus calculator) can be used in practice to improve glycaemic control of the Type 1 diabetes test subjects. To verify this, the HbA1C levels before and after

the trial will be compared. The patients will also provide data of all occurrences of hypo- and hyperglycaemia. This will be compared to the frequency of occurrences before the trial.

Secondary objectives of this trial are the following:

- to find out whether the ~~ets~~ bolus calculator is user-friendly;
- to find out whether the ~~ets~~ concept is easy to use;
- to find out whether test subjects prefer the ~~ets~~ concept above the CHO counting method; and
- to find out whether the ~~ets~~ bolus calculator will gain user acceptance.

2. Materials and Methods

2.1 Model system and justification of the model

The hypothesis will be tested using a Paired-t test of mean difference equal to zero. A sample size of 19 will have 90% power to detect a difference in means of 1.0, assuming a standard deviation of differences of 1.25, using a paired t-test with a 0.05 two sided significance level. A conservative reduction in mean HbA1C levels of 1% were used for this calculation. It should be noted that this is a pilot study and the outcome will be used to determine whether a future trial with more test subjects will be conducted.

2.2 Experimental design

The test group will consist of a small number (20) of test subjects selected on a random basis, and which meet the following requirements. The test subject must:

- have been diagnosed with Type 1 diabetes for a period of more than one year;
- be at least 14 years old (male or female);
- be familiar with the carbohydrate counting concept to calculate bolus insulin (in other words the patient must be able to make informed choices regarding their insulin regime);
- be familiar with the use of a cellular phone (~~ets~~ bolus calculator is implemented as a software program downloaded onto a cellular phone);
- be able to read and understand English;

- be using either an insulin pump or insulin pen for administering insulin;
- and must be living in Gauteng or surrounding areas.

People falling into one of the following categories will not be permitted to participate in the trial:

- infants;
- children;
- adolescents;
- pregnant women (woman who fall pregnant during the study will be required to end participation in the clinical trial);
- woman who are breastfeeding;
- people with mental and or psychological conditions that could influence their judgemental ability; and/or
- any person for which the clinical trial might hold a considerable risk.

All test subjects will follow the same experimental procedure, namely calculating their boluses using the ~~ets~~ bolus calculator. There is, however, a slight distinction between test subjects: those using insulin pumps and those who don't. An insulin pump constantly delivers insulin to the diabetic (basal insulin) but can also be commanded to infuse a certain amount of short-acting insulin units (bolus insulin). The diabetics who do not use insulin pumps inject their long-acting bolus insulin once or twice a day and more frequently after meals. They can either use a syringe for injection or an insulin pen. Clinical trials have shown that insulin pump therapy improves glycaemic control.

2.3 Observations / analytical procedures

Two questionnaires will be provided to the test subjects, one at the onset of the trial and the other at completion of the trial.

The first questionnaire will be used to obtain the following information:

- age,
- gender,
- weight at onset of trial,
- height,
- number of years diagnosed as a Type 1 diabetic,

- typical daily routine during week and weekend,
- frequency and intensity of any exercises,
- frequency of occurrences of hypo- and hyperglycaemia,
- Skill level of cellphone usage,
- knowledge of CHO counting and insulin-to-carb-ratio,
- total daily long-acting insulin and total daily short-acting insulin dosage,
- breakdown of insulin regime (including type and brands) of insulins,
- type of insulin therapy (pump, pen, syringe, other),
- brand and model of blood glucose monitor being used,
- frequency of blood glucose measurements on a typical day,
- medical history relating to diabetes or other chronic diseases,
- other diabetic and non-diabetic medication used,
- ~~ets~~ sensitivity value as measured,
- insulin sensitivity value as measured,
- HbA1C as measured.

Because this trial primarily focusses on the causality between blood glucose control and ets-Bolus calculation the baseline examination will consist of the pre-trial questionnaire completed by the trial subject and reviewed by the trial doctor and also the HbA1C level measured on the day the clinical trial commences. The trial doctor will also decide whether the subject is suitable for participation in the clinical trial based on the criteria set out in section 2.2.

The second questionnaire at completion of the clinical trial will be used to gather the following additional information:

- Weight at completion of trial,
- typical daily routine during weeks and weekends of clinical trial,
- frequency and intensity of any exercises,
- frequency of occurrences of hypo- and hyperglycaemia,
- total daily long-acting insulin and total daily short-acting insulin dosage,
- HbA1C as measured,

It will also include an evaluation regarding the use of the bolus calculation device including questions like:

- Is it easy to use?

- Is it user-friendly?
- Are the food and exercise databases complete?
- Is it difficult to find a specific food?
- Is it easy to calculate the bolus with?
- Are the subjects able to trust the suggested values?
- Are the calculations reliable?
- Is it difficult to operate the cellular phone?

Pre-trial and post-trial medical examinations

All trial subjects will be required to consult the trial doctor prior to beginning the clinical trial for a full medical examination where all long term and more recent medical conditions will be observed and noted. This examination will be repeated after the trial has been completed. Any relevant information resulting from these examinations will be reported to the ethical committee.

Characterization process

A quick characterization process will be performed on the test subjects to determine their ~~ets~~ and insulin sensitivity. These sensitivity values will then be used to customize the bolus calculators for the specific diabetic test subject.

~~ets~~ sensitivity measurement

The patients will be required to fast for at least three hours before the characterization procedure starts. The blood glucose level of subject will be measured (BS_{init}) and then they will be given a meal with a known quantity of ~~ets~~ (ets_{meal}). The blood sugar level will then be measured after 60 minutes and again after 15 minutes (BS_{final}). If the blood glucose level has stabilized the ~~ets~~ sensitivity ($SENS_{ets}$) value can be calculated using the following equation:

$$SENS_{ets} = (BS_{final} - BS_{init}) / ets_{meal}$$

If the initial measured blood glucose level is too high and has stabilized, the insulin sensitivity measurement can be performed first.

Insulin sensitivity measurement

The requirement for this test is that the blood glucose level of the test subject should be high and stable (typically after performing the ~~ets~~ sensitivity test - eating without administering bolus insulin). Again the initial blood sugar level is measured before injecting insulin (BS_{init}). An appropriate number units of short-acting insulin ($U_{insulin}$) should then be injected to lower the blood glucose back to or close to normal. (4-5 mmol/l). The blood glucose is then monitored for at least half an hour after the insulin activity is negligent ($t > 30\text{min} + t_{insulin\ onset} + t_{insulin\ duration}$). After the blood glucose level has stabilized (BS_{final}) the insulin sensitivity ($SENS_{insulin}$) can be measured using the following equation:

$$SENS_{insulin} = -(BS_{final} - BS_{init}) / U_{insulin}$$

Initial product setup procedure

The ~~ets~~ bolus calculation device requires the following information to be entered. These values are then used to customize the algorithms to the specific patient. The parameters needed are:

- Weight [kg];
- Height [m];
- Activity level [low, medium, high];
- $SENS_{insulin}$;
- $SENS_{ets}$;
- Total daily dose of long-acting insulin [TDD_{sai}]; and
- Total daily dose of short-acting insulin [TDD_{lai}].

Handout of information booklets, logbooks and devices

Booklets will be handed out to the diabetic subjects. These booklets will contain the following information:

- Introduction to the ~~ets~~ concept;
- How ~~ets~~ counting works;
- The difference between ~~ets~~ and carbohydrates;
- Instructions for using the bolus calculation device;
- Where to get help; and
- Daily instructions.

Everything that the subjects need to know for the clinical trial will be covered in the booklet. There will be contact information where they can get help with the device and diet. Logbooks will also be handed out to patients for use during the clinical trial.

Briefing session for test subjects:

All test subjects will be briefed before starting the trial. The information booklet will be used to brief the patients. At the end of the briefing session there will be an opportunity for questions. The trial doctor, Dr L. Johnson will be present during the briefing session.

Typical daily routine

Test subjects are required to use the ~~ets~~ bolus calculation device daily. They should use the calculation device to calculate bolus insulin. Here are two typical scenarios and what to do:

Scenario 1: Test subject eats three meals per day and injects insulin prior to each meal. In this scenario the patient should enter all the food and beverages to be consumed. The suggested bolus insulin should then be injected right before eating the meal.

Scenario 2: Test subject eats three large meals and three small snacks per day. The subject usually injects insulin right before each larger meal. The suggested bolus insulin should then be injected right after the meal. It is not necessary to inject boluses for each snack, as the elevated blood sugar level caused by the snacks is taken into account by the bolus algorithm.

If the patient feels uncomfortable with the suggested bolus dosage, the subject has to use his or her own discretion and rather inject an appropriate dosage that he or she feels comfortable with.

All the food, exercise, insulin and measured blood glucose levels entered by the test subject are stored in database. This database can be downloaded from the cellular phone for later analysis.

Trial data captured

The following data will be recorded by the device when entered by the user:

- food and beverages consumed,

- exercise,
- measured blood glucose values,
- suggested bolus insulin and actual bolus insulin injected.

This data can then be downloaded from the device onto a personal computer for further analysis.

It is required that the test subject keeps track of all occurrences of hypo- and hyperglycaemia in a logbook. Here the date, exact time, type of blood glucose event, duration and corrective measure taken are of importance.

Monitoring subject compliance

The trial doctor and/or one of the trial investigators will phone all trial participants at least once a week. The purpose being to monitor their compliance with the trial protocol, to discuss their blood glucose control, help them with any technical problems which they might have encountered and to find out whether any adverse events or serious adverse have occurred. A record of date, time and information of these conversations will be kept by all the relevant trial investigators and trial doctor.

The data capturing ability of the cellphone program will also help to assess the compliance of the trial subjects during the trial once the clinical trial has been terminated. Trial subjects will be encouraged to report any adverse events, serious adverse events or illnesses immediately to the trial doctor or trial investigators. This reporting will help to assess the safety and relevant risks of the trial subjects. See also section 4 and 5 for the procedures to deal with adverse and serious adverse events and report them.

Trial Doctor

The principal trial investigator, Dr L Johnson will be available during all trial related visits. Trial participants will receive her telephone numbers in order to contact her in case of an emergency. Trial participants will also receive contact numbers for the other trial investigators. Trial participants will be encouraged to contact Dr Johnson if any adverse events or illnesses occur during the duration of the trial.

2.5 Data analysis

All data entered into the bolus calculator are stored on the cellular phone and can be downloaded at the termination of the clinical trial onto a personal computer. The data gathered during the clinical trial will be used to statistically analyse the following:

- Initial and final HbA1C levels of test subjects;
- Occurrences of hypoglycaemia before and during the trial;
- Occurrences of hyperglycaemia before and during the trial; and
- Any other changes in glycaemic control.

An improvement in these factors is a good indication of improved glycaemic control.

The questionnaires to be completed by the test subjects will be used to determine the following.

- Did the subjects find it easy to calculate their bolus insulin?
- Did they trust and use the amount suggested by the device?
- Did they find the device useful?
- Would they continue to use the device?
- Did they learn something that could help them to control their blood glucose levels in the future?

3. Project management

This clinical trial will be managed by Human-Sim (Pty) Ltd. with the guidance of personnel at the practice of Dr. Louise Johnson. Table 1 provides a list of the relevant persons and their respective responsibilities.

Person	Responsibilities	Company / Practice
Prof. Dr. E.H. Mathews	Trial funder	Human-Sim (Pty) Ltd., Faerie Glen
Mr. R. Pelzer	Trial management	Human-Sim (Pty) Ltd. , Faerie Glen
Mr. G. Bolt	Trial assistant, Data analysis	Human-Sim (Pty) Ltd. , Faerie Glen
Mr. K. Laubscher	Data analysis	Human-Sim (Pty) Ltd. , Faerie Glen
Dr. S.L. Johnson	Trial physician	Dr. L.Johnson Practice, Montana Hospital
S. Heyderych	Trial dietician	Dr. L.Johnson Practice, Montana Hospital
Dr. P.J. Becker	Bio-statistical	Medical Research Council,

	consultations	Pretoria
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Table 1 – Trial personnel

4. Reporting

A final report will be generated from the statistical analysis of the trial data. The report will include, but not limited to, the data, statistical analysis, experimental procedures, results, conclusion and recommendations. Any adverse and/or serious adverse event(s) and/or other safety issue(s) will be included in the report.

Adverse events, serious adverse events and intercurrent illnesses will be identified by reporting of such events by the trial doctor, trial investigators or the trial subject. The trial investigators in conjunction with the trial doctor will determine whether the causality of the adverse event, serious adverse event or illness is and report the event and the actions taken to remedy the situation to the ethical committee.

If the adverse or serious adverse event(s) or illness is not of a serious nature and does not pose a significant risk to health and well being of the trial subject, the trial subject will be informed thereof and given the opportunity to make an informed choice to either terminate or continue with trial participation. If however the adverse or serious adverse event or illness poses a significant risk to the health and well being of said trial subject, the trial subject will be asked to cease participation.

Furthermore if it is found the adverse event identified in one of the trial subjects poses a risk to other trial subjects, the other trial subjects will be informed thereof. If the risk of such an event is significant, the other trial subjects who are at risk for the same adverse or serious adverse events, will be asked to end their participation in the clinical trial.

All adverse events and/or serious adverse events will be followed-up weekly by the trial doctor and trial investigators until such time that the trial investigator deems the event to have no further significant risk to health and well-being of the trial participant. All reporting from follow-up actions will be included in the post-trial report to the ethical committee.

5. Deviations & Records

In the unlikely event of problems with poor blood glucose control as a result of the use of the system or any other adverse or serious adverse event, the test subject will be taken out of the clinical trial. Test subjects can at any time at their own will decide to abort the clinical trial.

Participants will be taken out of the trial group when one of the following conditions are met:

- ❑ Participant or guardian of participant decides to withdraw participant from the clinical trial;
- ❑ Suggestion by the trial doctor or research coordinator to end participation;
- ❑ Adverse event occurs that prevent further participation;
- ❑ Serious adverse event occurs that prevent further participation;
- ❑ Uncontrolled blood glucose levels resulting from change in insulin regime; or
- ❑ A serious medical condition occurs that was caused directly or indirectly by participation in the clinical trial.

Patients who withdraw from the clinical trial at own will or are taken out of the trial group, will be asked to allow a HbA1C test to be performed, within three days from last day of trial participation, with their permission. A blood sample is necessary to measure the HbA1C level. Patients who do not participate in the clinical trial for the full three months duration of the trial will also be asked to complete the post-trial questionnaire within three days from the last day of their trial participation.

Any deviations from this protocol will be submitted in writing to the ethical committee for approval.

6. *Ethical considerations*

Test subjects will be required to complete and sign a patient informed consent (PIC) document where they will be informed of the purpose, duration and implications of this trial. They will also be informed about the risk involved and the support system in place to help them, should any problems arise.

Test subjects may at any time decide to discontinue their participation in the clinical trial. Discontinuation of the trial treatment will not have any considerable effect, as the treatment merely tries to optimize bolus insulin dosages. Trial subjects are not obliged to give reasons

for withdrawing prematurely from the trial. Investigators will however make an effort to ascertain the reasons, while respecting the subject's rights.

Any deviation (excluding changes in protocol to eliminate immediate hazards to trial subjects) from this protocol will be reported to the ethical committee for approval. All other parties involved will also be informed of any such deviations whether they are critical of nature or not.

7. Budget

Human-Sim (Pty) Ltd. will be responsible for all costs towards:

- Bolus calculators,
- Costs towards the venue,
- HbA1C level test laboratory charges,
- Other costs directly relating to the clinical trial.

The following costs are covered by the test subject or his or her medical aid:

- Insulin (all types);
- Diabetic medication;
- Diabetic consumables (e.g. blood glucose test strips, monitors, lancets etc.); and
- any other medication being used.

Trial subjects will receive no remuneration for their participation in the clinical trial as participation is voluntarily.

8. Duration and time schedule

The total duration of this clinical trial is three months.

Day 1&2: Briefing session (approximately 2 hours) in the afternoon or evening. Measurement of HbA1C levels. Handout of bolus calculation devices. Trial subjects complete Pre Clinical trial Questionnaire. Session will be repeated over two days for the convenience of trial subjects who cannot attend the first session.

Day 2-8: Test subjects starts calculating their bolus insulin by using the ~~ets~~ concept.

Day 8&9: Information, feedback and support session.

Day 8-90: Test subjects continue to use ~~ets~~ concept for bolus calculation

Day 90: Measurement of HbA1C levels. Test subjects return bolus calculation devices.
Trial subjects complete Post Clinical Trial Questionnaire.

Day 90-100:Data analysis and report generation.

9. References

1. Pickup J.C. & Williams G., "*Textbook of Diabetes*", Blackwell Scientific Publications, Oxford, London (2002)
2. Walsh J., Roberts R.& Jovanovic-Peterson L., "*Stop the rollercoaster – How to take charge over your blood sugars in diabetes*", Torrey Pines Press, California (1996)
3. Wolever, T. M. S. & Bolognesi C., "*Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects*", J. Nutr. **126**, 2798-2806 (1996)
4. Beaser R.S & Hill J.V.C., "*The Joslin Guide to Diabetes*", Fireside, New York (1995)
5. Lee, B. M. & Wolever, T. M. S., "*Effects of glucose, sucrose and fructose on plasma glucose and insulin responses in normal human: comparison with white bread*", Eur. J. Clin. Nutr. **52**, 924-928 (1998)
6. Mendenhall, W. & Sincich, T. "*Statistics for Engineering and the Sciences 4th Edition*", (Prentice Hall, Englewood Cliffs, New Jersey, 07632, USA, 1995).
7. Mills, A. F., "*Heat transfer*" (Richard D. Irwin, Inc., Homewood, IL 60430, USA, 1992)
8. Mathews E.H., "*A practical relationship between insulin response and ingested carbohydrates*", Unpublished highly confidential article (2002)

GLYCAEMIC CONTROL OF TYPE 1 DIABETICS USING THE ETS CONCEPT

PROTOCOL HS_DIAB_004

Version 1.3 – 21 June 2005

PATIENT INFORMED CONSENT FORM

Human-Sim thanks you for your time and willingness to help us with this clinical trial. It is our company's goal to improve the health of diabetics by improving their blood glucose control. Without your help this would not be possible. In order for you to participate in our trial, we need your informed consent. Please read through this agreement and sign it on the last page if you agree to participate in this clinical trial. Please do not hesitate to ask should you have any questions.

RESEARCH

The purpose of this clinical trial is to determine whether ETS-counting (a concept developed from research done by Human-Sim, South Africa) as opposed to Carbohydrate-counting can improve blood glucose control for Type 1-diabetics. Data analysed of Canadian researchers Lee, Wollever and Bolognesi showed ETS to be a more accurate predictor of insulin response than carbohydrates. A cellular phone software application will be used to calculate boluses using ETS-counting. By entering a current blood glucose level, selecting the food and beverage items to be consumed and exercises to be performed, the program will suggest a bolus. This clinical trial will therefore investigate the ETS-counting concept in a practical environment by using a cellular phone application.

SELECTION PROCEDURE

Between 10 and 20 test subjects will participate in the clinical trial. Trial subjects were selected on a random basis from Dr. L. Johnson's practice (convenience samples) and had to meet certain inclusion requirements e.g. be at least 14 years old and need to be familiar with the carbohydrate counting concept. Participants in this clinical trial will not be allowed to plan to become pregnant, be pregnant or breastfeeding for the duration of the trial. Adequate contraception must be used for the duration of the trial. If a participant does however fall pregnant, the participant will be required to withdraw from the clinical trial.

TRIAL PROCEDURES

The trial will be initiated by a briefing session at Dr. L. Johnson's practice at the Montana Hospital in Pretoria. The ETS-concept will be explained to all participants and demonstrations will be given on operating the cellular phone and the bolus insulin calculation software. Each participant will receive a cellular phone with the bolus calculation software. A blood sample will be taken to test Glycohemoglobin levels (HbA1c). This gives an indication of the quality of blood glucose control for the period of three months prior to the trial. A simple procedure will then be performed on test subjects to determine sensitivities to ETS and insulin. Blood glucose levels will be monitored while first ingesting a meal and then afterwards injecting short acting insulin. The calculated values will then be entered into each individual's cellular phone to customize it for the specific participant. Participants will then for three months calculate their boluses with the device. Technical support will be available to all participants. At the end of the trial Glycohemoglobin levels will be tested again and compared with the initial values. Participants will also receive a questionnaire at the end of the clinical trial. Participants will have to return the cellular phones at the end of the trial.

POSSIBLE BENEFITS TO PARTICIPANTS

Benefits of participating in this trial may include:

- improved blood glucose control,
- fewer occurrences of hypo- and/or hyperglycaemia and
- a better understanding of blood glucose control.

These benefits can however not be guaranteed. Participation in this clinical trial also helps the international scientific community to further diabetic research and could eventually improve the lives of many diabetics.

PARTICIPATION

Participation in this clinical trial is voluntary. Participants may at any time decide to stop participating without supplying a reason. The research company strongly urges participants not to withdraw from the trial, as this will have an effect on the statistical significance of the research. There are however no foreseeable risks involved by withdrawing from the trial. The research institution or study doctor will inform participants if new information becomes available that might influence their willingness to continue the study. The research company

reserves the right to terminate the clinical trial at any stage on their discretion, should it become necessary.

CONFIDENTIALITY

All records identifying participants will be kept confidential, to the extent permitted by the applicable laws and/or regulations and will not be made publicly available. If the results of this trial are published, the subject's identity will remain confidential. All participants have the right to see, copy and correct some of their personal health information related to the research as long as this information is held by the study doctor (Dr. L. Johnson) or research institution (Human-Sim (Pty) Ltd.). The participant agree that the Monitors, Auditors, the Ethics Committee and the Regulatory Authorities be granted direct access to the participant's medical records for verification.

CONTACT INFORMATION

Should the participant require any help or assistance the following people could be contacted at any time:

Technical assistance, ETS-concept information etc.

Ruaan Pelzer	083 391 6672	012 991 5110
Gerhard Bolt	082 937 3337	012 991 5110

Medical emergencies

Dr. L. Johnson	082 821 9680	012 548 5409
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I hereby declare that I am willing to participate in the clinical trial as discussed in this document. I am aware that participation will involve some changes to my insulin regime and that I may at any stage decide to withdraw from the clinical trial.

SIGNED

_____ Name of participant, parent or guardian	_____ Signature of participant, parent or guardian	_____ Date signed
_____ Name of investigator or designated person	_____ Signature of investigator or designated person	_____ Date signed

A signed copy of this document will be handed to you, the participant.

APPENDIX D: PRE-TRIAL QUESTIONNAIRE

PRE CLINICAL TRIAL QUESTIONNAIRE- ETS BOLUS CALCULATOR

Please complete the following questionnaire. If you are not sure what is being asked, please consult one of the assistants or doctors. We appreciate your time and effort in helping us with this clinical trial.

Date:

YOUR DETAILS

Full name:

Contact numbers:

Home:	<input type="text"/>
Work:	<input type="text"/>
Mobile:	<input type="text"/>

Contact addresses:

Residential:	<input type="text"/>
Postal:	<input type="text"/>
Email:	<input type="text"/>

YOUR DAILY ACTIVITIES

How often do you exercise?	<input type="text"/>	<small>E.g. 3 times a week</small>	
What type(s) of exercise or sport?	<input type="text"/>	<small>E.g. cycling</small>	
Typical duration of exercise?	<input type="text"/>	<small>E.g. 30 minutes</small>	
Typical daily activity level during week?	<input type="checkbox"/> Low	<input type="checkbox"/> Moderate	<input type="checkbox"/> High
Typical daily routine?	<input type="text"/>		
At what time do you normally go to bed?	<input type="text"/>		
At what time do you normally get up in the morning?	<input type="text"/>		

YOUR MEALS AND SNACKS

How many meals do you have per day?

How many snacks do you have per day?

Do you count your calories?

Yes No

YOUR BODY

Gender: Male Female

Age:

Height:

Weight:

HbA1C: (Leave this space open)

IF YOU ARE USING AN **INSULIN PEN** OR **SYRINGE** AND NOT AN INSULIN PUMP
PLEASE COMPLETE THIS PAGE:



YOUR LONG-ACTING INSULIN (BASAL)

Type:	E.g. Lantus
Total daily dose:	U

At what time(s) do you inject? How many units?

Basal dosage 1	Basal dosage 2
Time: ___ h ___	Time: ___ h ___
Units: ___ U	Units: ___ U

SHORT-ACTING/MIXED INSULIN (BOLUS)

Type:	E.g. Actrapid
Total daily dose:	U

Please give us an indication of the typical dose and time of your boluses:

Bolus 1	Bolus 2	Bolus 3	Bolus 4	Bolus 5
Time: ___ h ___	Time: ___ h ___	Time: ___ h ___	Time: ___ h ___	Time: ___ h ___
Units: ___ U	Units: ___ U	Units: ___ U	Units: ___ U	Units: ___ U

METHOD OF INSULIN ADMINISTRATION

Pen Syringe Other, please specify _____

YOUR BLOOD GLUCOSE MONITOR (METER)

Type or brand of meter:	
How many times per day do you measure your blood glucose level?	

YOUR BLOOD GLUCOSE (SUGAR)

What is your target blood glucose level? Between mmol/l and mmol/l

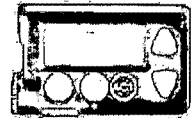
How often do you get Hypo's (low blood glucose)?

At what time(s) are you most likely to get a hypo?

- Early morning Morning Afternoon Early evening
 Late in the evening (before going to bed) While sleeping for a short while
 While sleeping for a long while

How often do you have a problem with high blood glucose levels?

IF YOU ARE USING AN **INSULIN PUMP** PLEASE COMPLETE THIS PAGE:



YOUR INSULIN REGIME

Type of insulin:	E.g. Actrapid
Total daily basal dose:	U
Total daily bolus dose:	U = + + + +

Please give us an indication of the typical basal dosages and the times of your boluses:

Bolus 1	Bolus 2	Bolus 3	Bolus 4	Bolus 5
Time: ___ h ___	Time: ___ h ___	Time: ___ h ___	Time: ___ h ___	Time: ___ h ___
Units: ___ U	Units: ___ U	Units: ___ U	Units: ___ U	Units: ___ U

YOUR BLOOD GLUCOSE MONITOR (METER)

Type or brand of meter:	
How many times per day do you measure your blood glucose level?	

YOUR BLOOD GLUCOSE (SUGAR)

What is your target blood glucose level? Between mmol/l and mmol/l

How often do you get Hypo's (low blood glucose)?

At what time(s) are you most likely to get a hypo?

- Early morning Morning Afternoon Early evening
 Late in the evening (before going to bed) While sleeping for a short while
 While sleeping for a long while

How often do you have a problem with high blood glucose levels?

- End of questionnaire -

Thank you for your time

POST CLINICAL TRIAL QUESTIONNAIRE- ETS BOLUS CALCULATOR

Please complete the following questionnaire. If you are not sure what is being asked, please consult one of the assistants or doctors. We appreciate your time and effort in helping us with this clinical trial.

YOUR DETAILS

Full name:

Date:

YOUR DAILY ACTIVITIES

Did you make any changes to your daily routine during the clinical trial (E.g. Did you go on holiday or exercise more or less than usual etc.)? Please elaborate if relevant.

YOUR BODY

Weight kg

HbA1C level (leave this space open) %

YOUR BLOOD GLUCOSE (SUGAR)

At what time(s) were you most likely to get a hypo, if any, during the clinical trial?

- Early morning
- Morning
- Afternoon
- Early evening
- Late in the evening (before going to bed)
- While sleeping for a short while
- While sleeping for a long while

Did you encounter any problems with your blood glucose control during this clinical trial that you normally do not encounter? Please elaborate if necessary.

SOFTWARE APPLICATION

Please answer these questions regarding the bolus software.

DID YOU FIND THE SOFTWARE PROGRAM EASY TO USE?

Very difficult I managed Very easy

DID YOU EASILY FIND FOOD AND EXERCISES IN THE DATABASES?

Very difficult I managed Very easy

DID YOU FIND IT EASY TO CALCULATE YOUR INSULIN BOLUSSES?

Very difficult I managed Very easy

IF YOU HAVE MADE USE OF A SIMILAR DEVICE IN THE PAST, PLEASE RATE THE BOLUS CALCULATOR ACCORDINGLY

Worse The same Great improvement

NOKIA CELLULAR PHONE

Please evaluate the ease-of-use of the cellular phone.

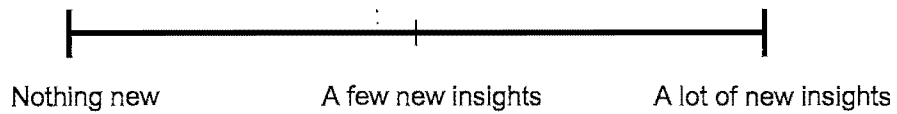
DID YOU FIND IT EASY TO OPERATE THE CELLPHONE (E.G. MAKE A PHONE CALL)

Very difficult I managed Very easy

EDUCATIONAL VALUE

Please evaluate the educational value of the bolus software.

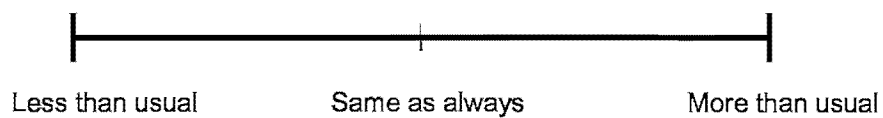
DID YOU LEARN ANYTHING REGARDING YOUR BLOOD GLUCOSE CONTROL?



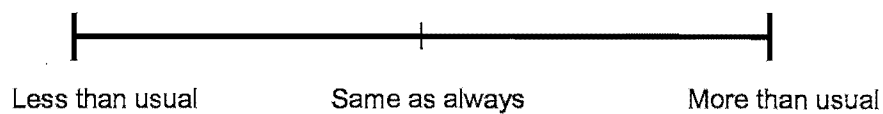
BLOOD SUGAR CONTROL

Please tell us more about your blood sugar control during the clinical trial.

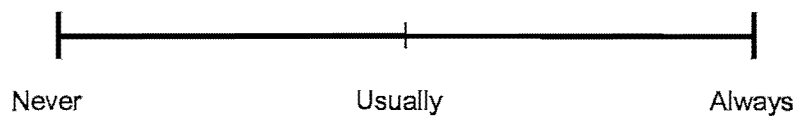
HOW OFTEN DID HYPO'S (LOW BLOOD SUGARS) OCCUR?



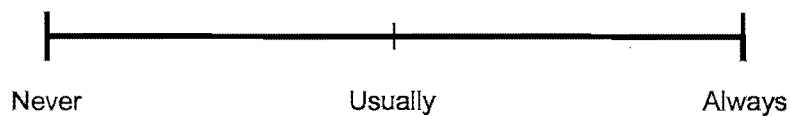
HOW OFTEN DID YOU MEASURE HIGH BLOOD SUGAR LEVELS?



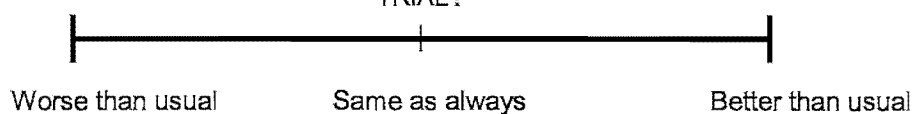
DID YOU TRUST THE BOLUS SUGGESTIONS MADE?



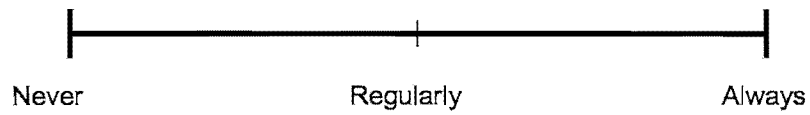
DID YOU FIND THE SUGGESTIONS THAT WERE MADE TO BE RELIABLE?



HOW DID YOU FIND YOUR BLOOD GLUCOSE CONTROL TO BE DURING THE CLINICAL TRIAL?



HOW OFTEN DID YOU USE THE DEVICE?



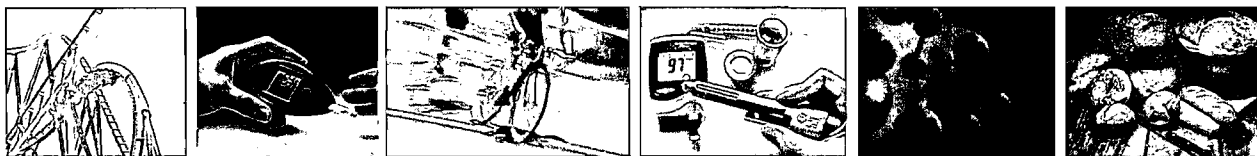
WERE YOU TREATED FOR ANY MEDICAL CONDITION DURING THE CLINICAL TRIAL (E.G. ANY OPERATIONS, INFECTIONS, ILLNESSES ETC.)? PLEASE ELABORATE.

A large, empty rectangular box with a thin black border, intended for the respondent to provide details about any medical conditions during the trial.

ANY COMMENTS OR SUGGESTIONS TO IMPROVE THE BOLUS CALCULATOR DEVICE?

A large, empty rectangular box with a thin black border, intended for the respondent to provide comments or suggestions for improving the bolus calculator device.

End of questionnaire - Thank you for your time!



USER'S GUIDE FOR ETS-BOLUS CALCULATION CELLPHONE

Equivalent Teaspoons Sugar **ets[®]**

R PELZER

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ALL INVENTIONS MENTIONED ARE PATENT PROTECTED**

HELP / ASSISTANCE

DURING THE DURATION OF THIS CLINICAL TRIAL, YOU MAY AT ANY TIME CONTACT US FOR HELP OR ASSISTANCE. PLEASE DO NOT HESITATE TO CONTACT US SHOULD YOU EXPERIENCE ANY PROBLEMS OR HAVE ANY QUESTIONS.

FOR TECHNICAL ASSISTANCE (E.G. PROBLEMS WITH THE PHONE OR SOFTWARE) CONTACT EITHER

- RUAAN PELZER, 083 391 6672 OR
- HENRY TOWNSEND, 082 575 2336

YOU CAN ALSO CONTACT US AT OUR PRETORIA OFFICE ON 012 809 1051.

IF YOU HAVE A MEDICAL EMERGENCY OR NEED MEDICAL ASSISTANCE PLEASE CONTACT DR. LOUISE JOHNSON ON ONE OF THE FOLLOWING NUMBERS:

- 012 548 5409 (PRACTICE AT MONTANA HOSPITAL)
- 082 821 9680

ALTERNATIVELY, YOU MAY ALSO PHONE YOUR GENERAL PRACTITIONER OR LOCAL HOSPITAL TO ASSIST YOU IN CASE OF A MEDICAL EMERGENCY.

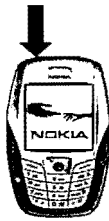
CONTENTS

1 – USING THE CELLPHONE	4
2 – OPENING THE <i>ets</i> -BOLUS SOFTWARE	6
3 – THE LOGBOOK	7
4 – BLOOD GLUCOSE MEASUREMENTS	9
5 – EXERCISES	11
6 – FOOD	13
7 – HOW TO CALCULATE INSULIN BOLUSES	18
8 – DAILY TOTALS	21
9 – SETUP	22
10 – WHAT IS <i>ets</i> , HOW CAN IT HELP ME?	25

1 - USING THE CELLPHONE

Here is a brief summary of the most important phone functions.

TURN THE PHONE ON



Press and hold top button, ...Wait a few seconds, Enter PIN (when asked) and press #

TURN THE PHONE OFF

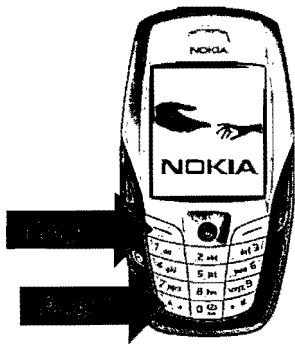


Press and hold top button *

* Make sure the keypad is not locked

LOCK OR UNLOCK THE KEYPAD

First press "*" and then *

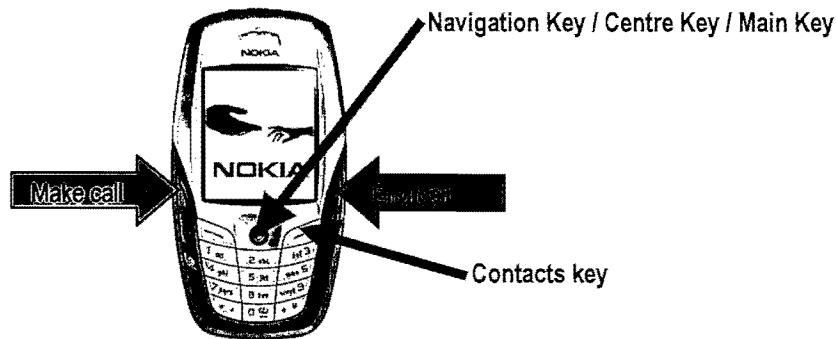


HOW TO MAKE A TELEPHONE CALL

Make sure the keypad is unlocked. Enter the telephone number and press the green button (left). Press the red button (right) to end the call.

...Or...

View your phone book by pressing "Contacts". Use the Main Key (also called the centre or navigation key to move up and down) to select the person to phone and press the green key to make the call.

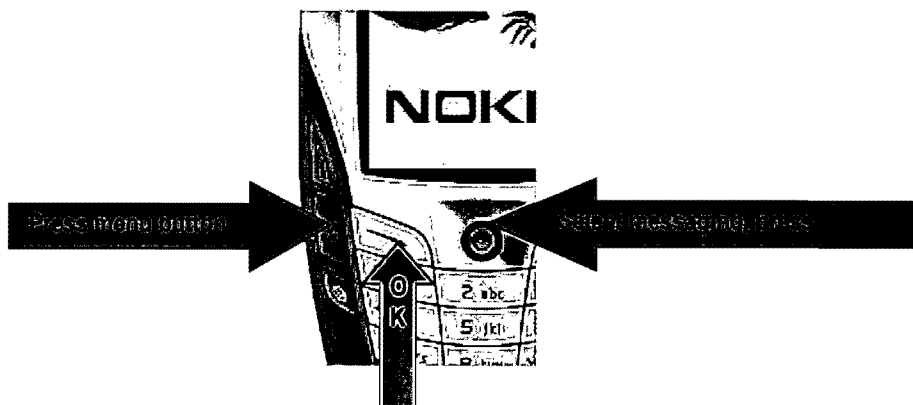


HOW TO RECEIVE A TELEPHONE CALL

To answer a call, press the green button (left). To end the call, press the red button (right).

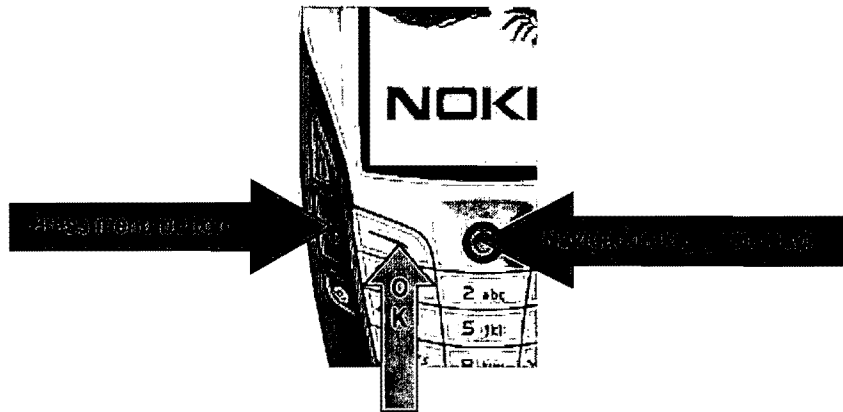
HOW TO SEND AN SMS

To create an SMS, press the menu button. Use the navigation key to move to messaging and then press the navigation key. Select "New message" by pressing the navigation key. Select Text message by pressing the navigation key. While in the "To" box, press the navigation key again to view your contact list. Select all the recipients by moving to them with the navigation key and then pressing the navigation key (to flag as a recipient). When you are done, press OK. Type your message in the message box. When you are finished, press "Options" and select "Send"

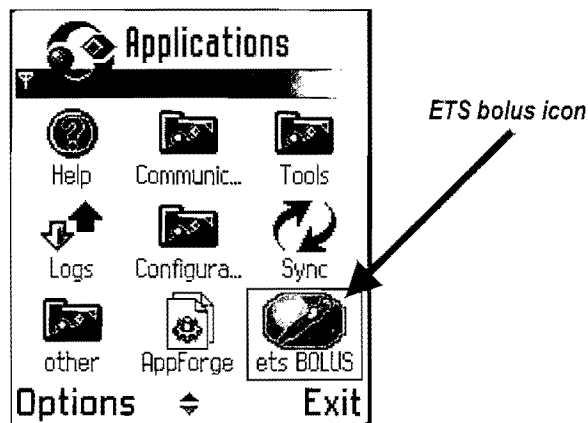


2 - OPENING THE ETS-BOLUS SOFTWARE

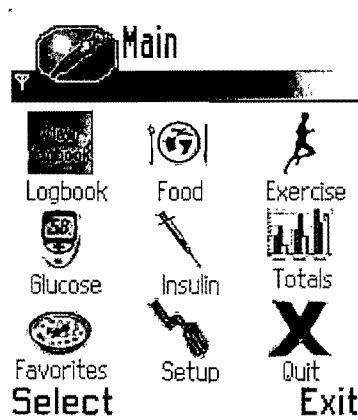
To start the ETS-bolus software, make sure that the phone is turned on and the keypad is unlocked. Press the menu button.



Use the navigation key to move to the **ets Bolus Icon**. Press the **MainKey** to open the software program. You will have to browse down to see the icon.



After a few seconds, the following screen will be displayed. You are now ready to use the bolus calculator.

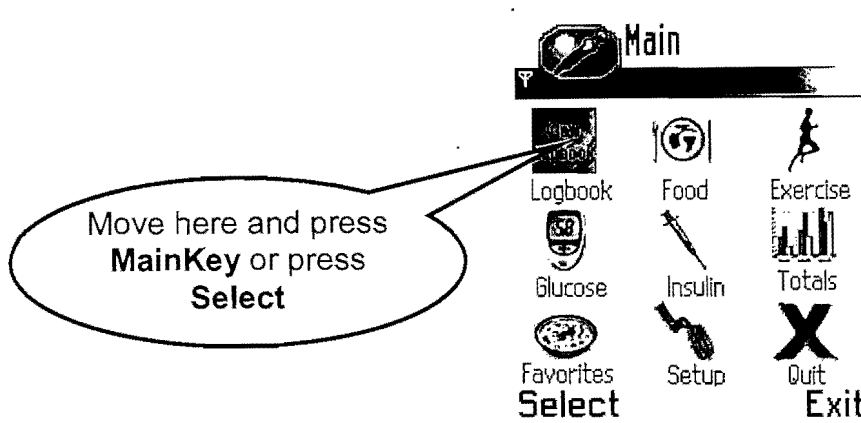


The different program options will be discussed in the next sections.

LOGBOOK

The logbook displays activities for the day entered into the cellphone. These activities include food intake, exercise, blood glucose measurements and insulin boluses.

TO VIEW THE LOGBOOK



WHAT'S IN THE LOGBOOK?

Logbook		
25 Apr 2005		9:20
Time	Description	Value
09:18	Food	8ets
09:18	Blood glucose	8mmol/l
09:19	Insulin	4U
10:30	Exercise	-3.7ets

Back		Options

The **date and time** are displayed on top - make sure that it is correct!

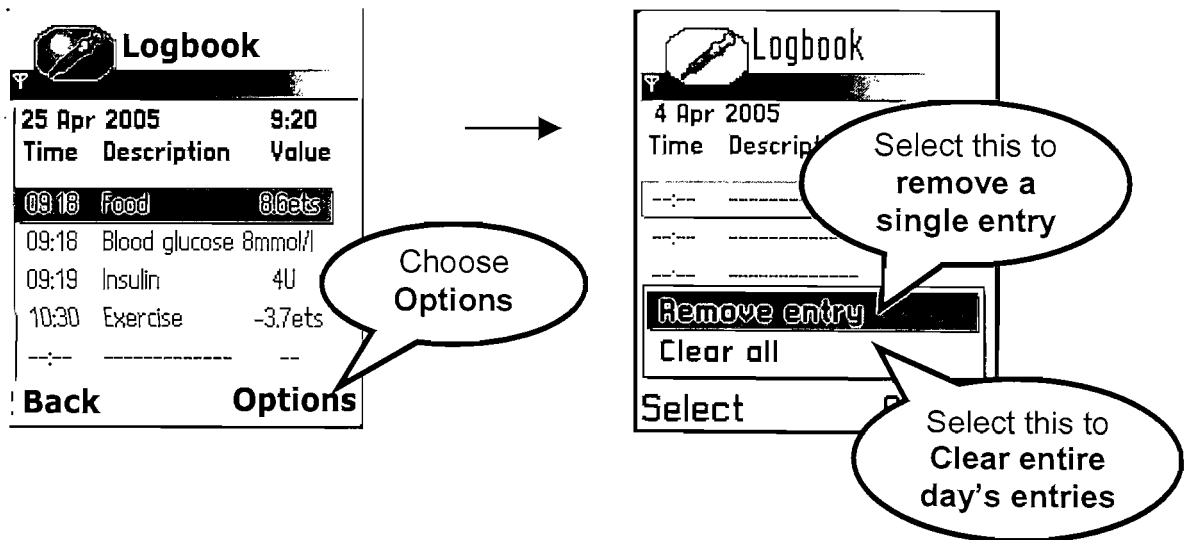
The **times of events** are shown in the left column, the *different actions* in the middle and the *magnitude* in the right hand column.

Food is measured in *ets* (equivalent teaspoons sugar that goes into the blood). **Exercise** is shown as negative *ets* (sugar is taken out of the blood). **Insulin** in Units (U) and **blood glucose values** in mmol/l.

The *ets Bolus Calculator* uses this information to calculate bolusses.

HOW TO REMOVE LOGBOOK ENTRIES

Move up or down to highlight the entry you want to remove. Then choose **Options** and select whether you want to **remove entry** (single entry) or **Clear all** (removes all the entries for the day).

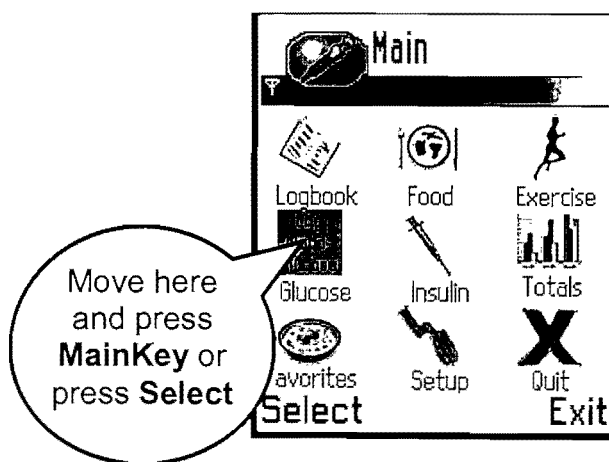


4 - BLOOD GLUCOSE MEASUREMENT

You can use the logbook to store measured blood glucose values. *If you are not going to administer an insulin bolus, you can use this option to store your blood glucose value. If you are going to take a bolus, go directly to **Insulin** – you will be prompted there to enter your current blood glucose level.*

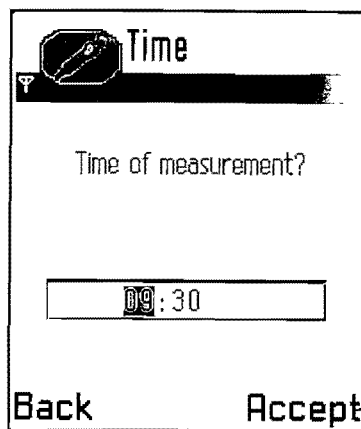
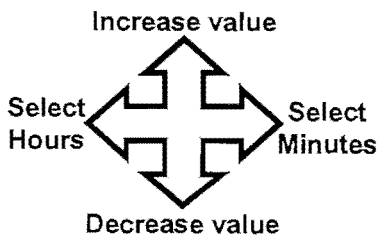
TO ENTER A BLOOD GLUCOSE VALUE

While in the Main menu, select **Glucose**



Enter or confirm the **time of the measurement**

Use MainKey to:



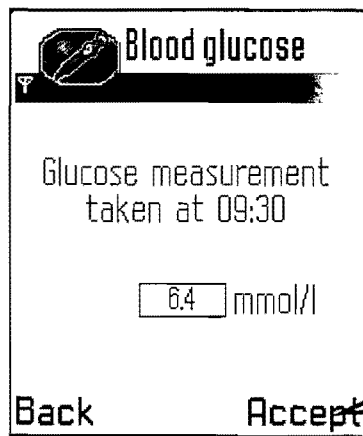
Enter the **blood glucose value**

Use MainKey to:

Increase value



Decrease value



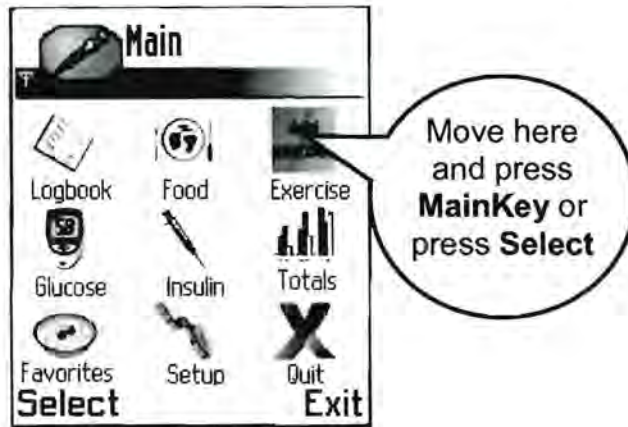
By pressing **Accept** the blood glucose value will be stored in the logbook.

5 - EXERCISE

It is important to enter your exercises, if any, into the logbook. This will reduce your insulin bolus in order to reduce the risk of hypoglycemia. Bolus calculations take exercises up to six hours in advance into account.

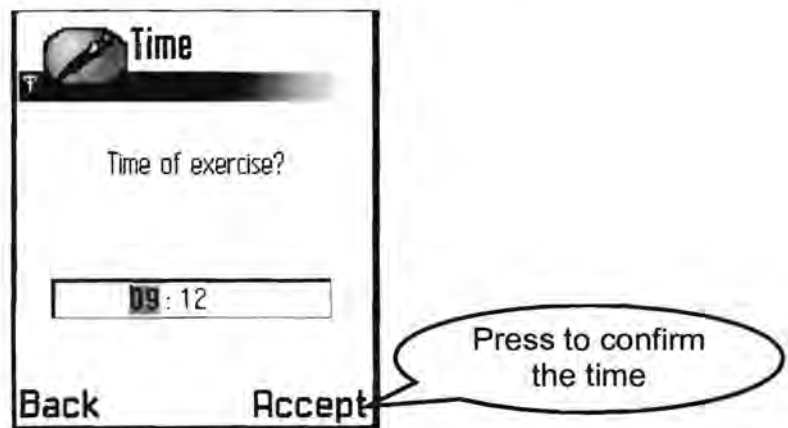
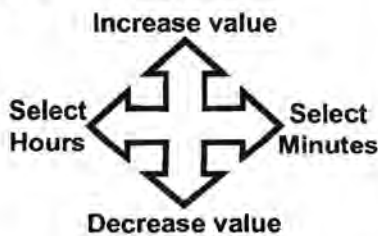
TO ENTER AN EXERCISE

While in the Main menu, select **Exercise**



Enter or confirm the **time of the exercise**. Remember that exercises should be entered in advance before the bolus calculation preceding the exercise!!!

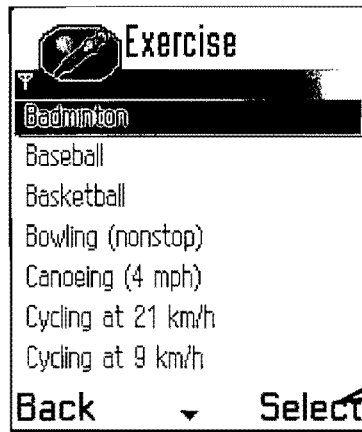
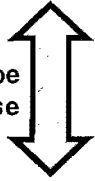
Use MainKey to:



Select the type of exercise

Use MainKey to:

Select type
of exercise

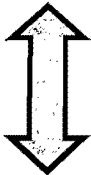


Press to select the
exercise

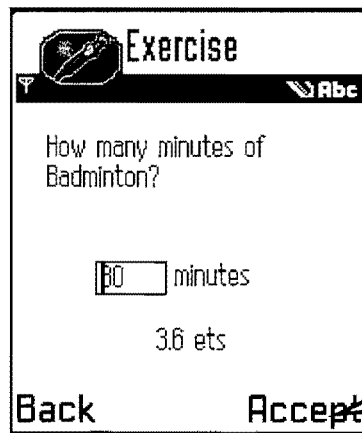
Enter the duration of the exercise

Use MainKey to:

Increase minutes



Decrease minutes



Press to confirm
the duration

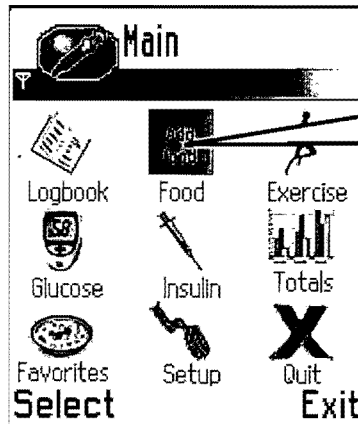
By pressing **Accept** the exercise will be stored in the logbook.

6 - FOOD

The *ets Bolus Calculator* has a database that contains more than 1500 food items.

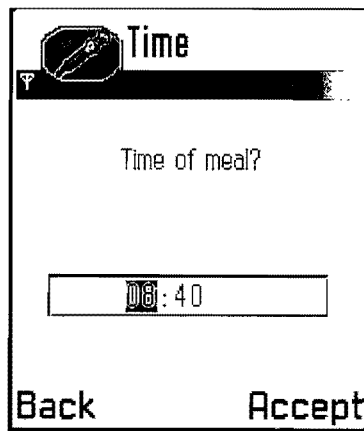
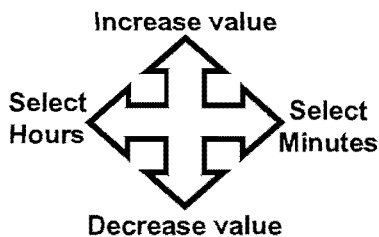
TO VIEW FOOD OPTIONS

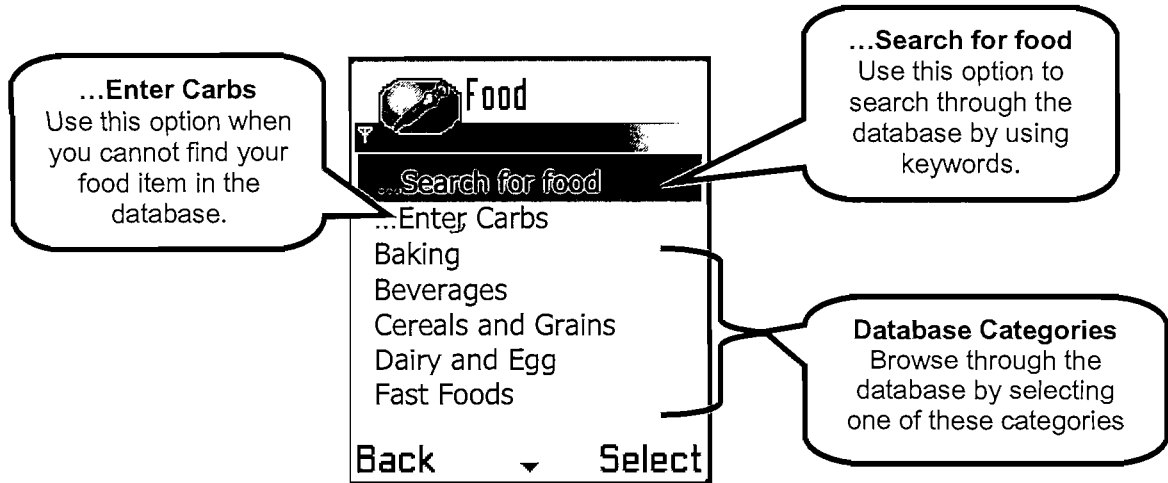
While in the Main menu, **select Food**



Enter or confirm the **time of the meal**

Use MainKey to:



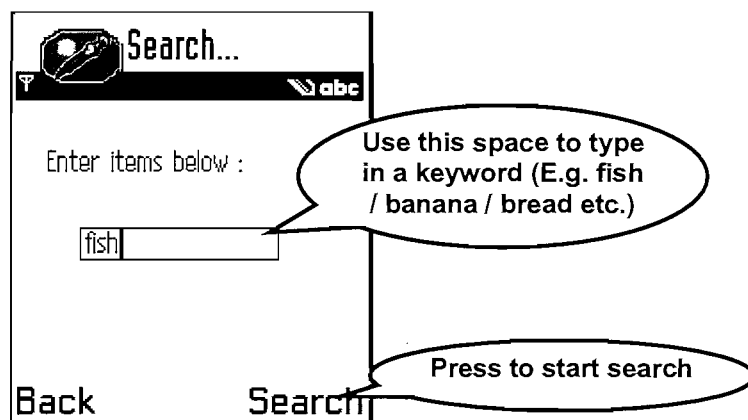


You now have three options. They are:

- ❑ **...Search for food:** This option allows you to enter keywords to search for. E.g. “chocolate” will return items such as “chocolate milk”, “chocolate cake” etc.
- ❑ **...Enter carbs:** This is the carb counter. If you cannot find the food item in the database but know how many grams of carbohydrates there are in the food, you can use this option.
- ❑ **Browse through the database:** This option allows you to browse through the database, which is neatly categorized.

...SEARCH FOR FOOD

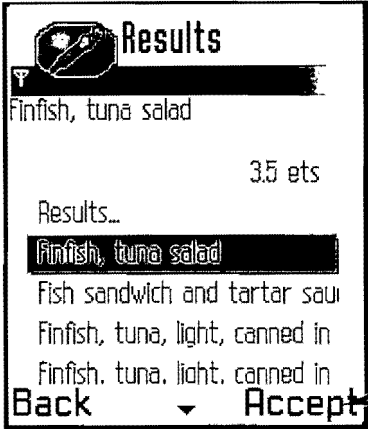
If you quickly want to find an item in the database select **...Search for food**. The following screen will be displayed.



Your results will be displayed. Select the item you are looking for and press **Accept** to select the food item or press **Back** to search over again.

Use MainKey to:

Select the food item



Results

Finfish, tuna salad

3.5 ets

Results...

Finfish, tuna salad

Fish sandwich and tartar sau

Finfish, tuna, light, canned in

Finfish, tuna, light, canned in

Back Accept

Press to accept your choice

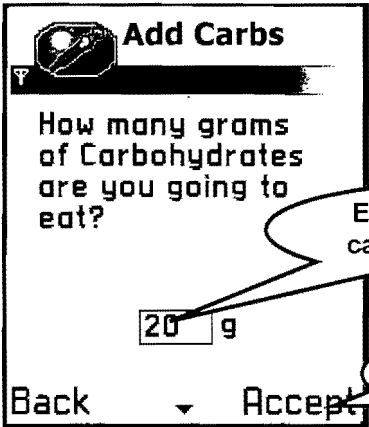
...ENTER CARBS

This is the carb counter. If you cannot find the food item in the database but know how many grams of carbohydrates there are in the food, you can use this option. The following screen will be displayed.

Use MainKey to:

Decrease grams

Increase grams



Add Carbs

How many grams of Carbohydrates are you going to eat?

20 g

Back Accept

Enter the grams of carbohydrates here

Press to add the carbs

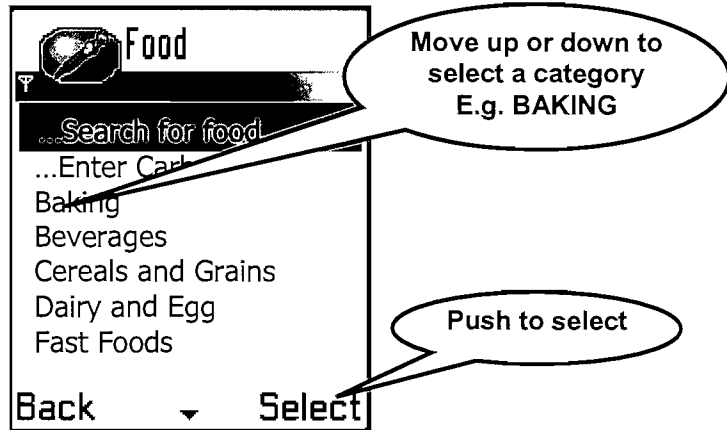
By pressing **Accept** the amount of carbohydrate grams will be converted to ets and added to your logbook. Remember to take the portion size into account when entering the grams of carbohydrates. Rather use the *...Search function* or *Browse through the database* to add food items to your logbook. These two methods will provide you with more accurate results.

BROWSE THROUGH THE FOOD DATABASE

If you want to add a specific food item, you can browse through the database to select it. Let say, for example, we want to add a hot cross bun. First select the Food option from the Main Menu.

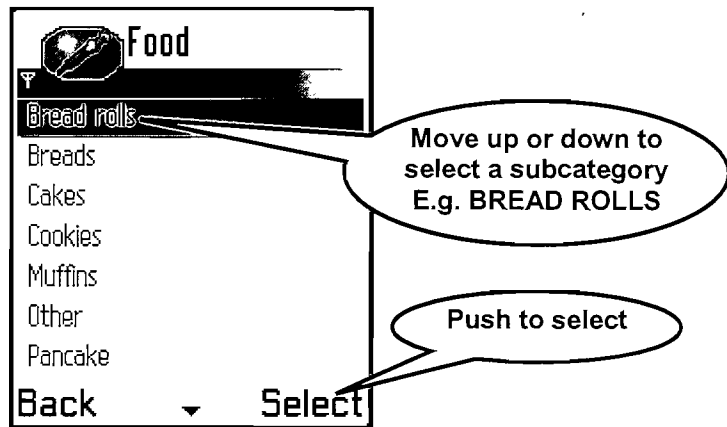
Step 1 – Select the main food category

For our example, select Baking



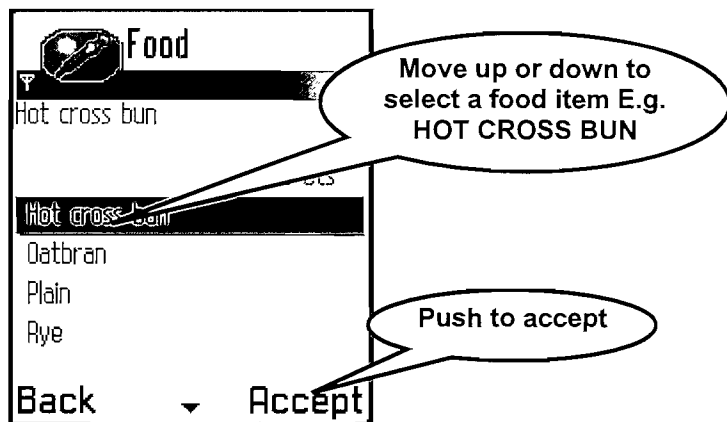
Step 2 – Select the food sub-category

For our example, select Bread rolls



Step 3 – Select the specific food item

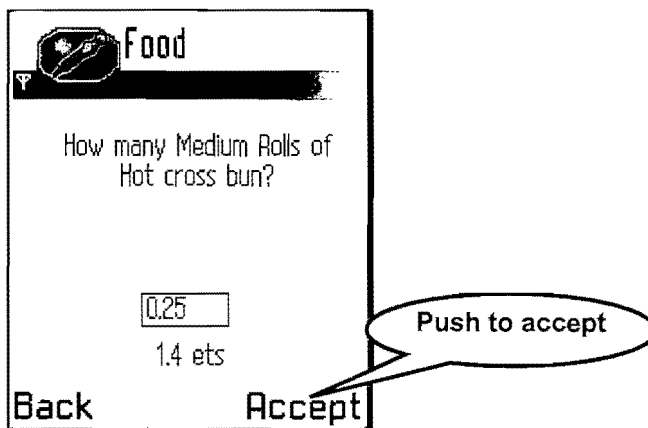
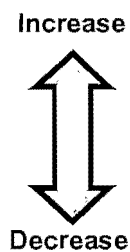
For our example, select Hot cross bun



Step 4 – Specify the number of portions

For our example, lets say we are just going to eat a quarter Hot cross bun. Move the main key up and down to specify the number of portions.

Use MainKey to:



By pushing **Accept** the specified number of portions will be added to the logbook.

7 – HOW TO CALCULATE INSULIN BOLUSES

In order to calculate your insulin bolus by using the cellphone – you must make sure that:

- You have entered all the food and beverage items you are about to eat into the logbook. When asked the time of the meal, please enter the time that you will be taking the meal.
- You have entered any exercises that you will be doing within six hours of the insulin bolus being calculated.

If you have entered your food, beverages and exercises correctly, it will be easy to calculate your insulin bolus.

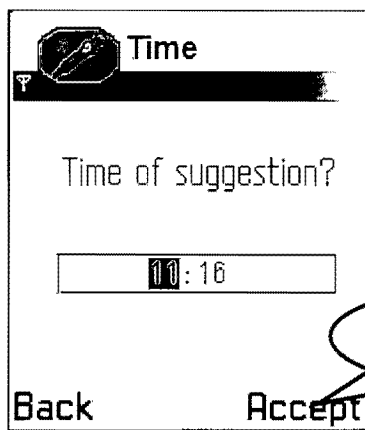
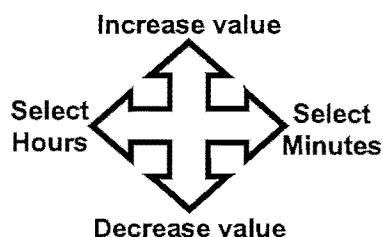
Step 1

From the main menu, Move to **Insulin** and press **Select** (or press the **MainKey**).

Step 2

Enter the time of the suggestion (insulin bolus) – usually the current time.

Use MainKey to:

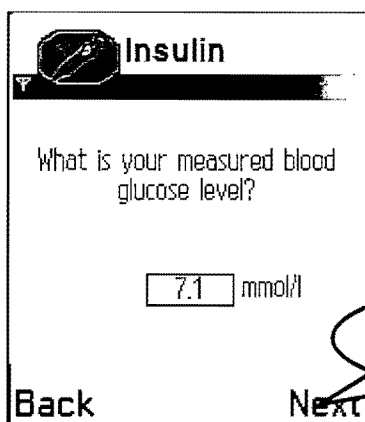
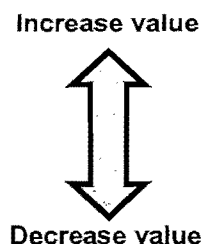


Press to confirm the time

Step 3

Measure and enter your current blood glucose level. Press **Next** to continue.

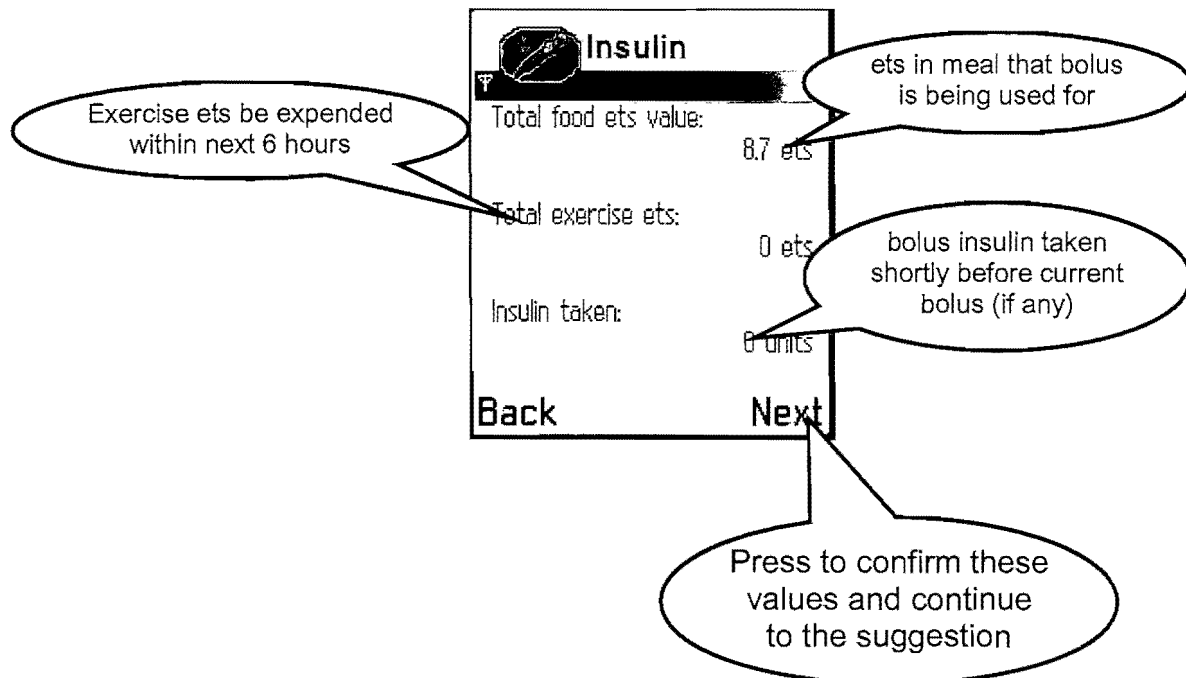
Use MainKey to:



Press to confirm and continue

Step 4

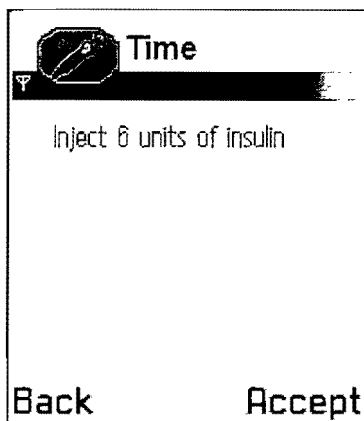
Check the food, exercise and insulin values. To confirm press **Next**. If you do not agree, go back.



It is important that you check these values. If an extremely high or low ets count is shown for food, it is possible that the wrong time was used for the meal, or the number of portions was specified incorrectly etc. If you suspect these values not to be accurate, first remove the relevant meal items from the logbook and re-enter them. Make sure that you do not enter any items twice!

Step 5

Using the information from the logbook a suggestion will be made. There are four types of suggestions that can be made:



Bolus insulin suggestion If your predicted blood glucose level is too high a suggestion will be made for an appropriate insulin bolus. If you strongly disagree with this suggested bolus, you must use your own discretion.

Suggestion to eat additional ets If your predicted blood glucose level is too low, a suggestion will be made to eat additional ets (carbohydrate rich food) to raise your blood glucose level.

Suggestion to take no action If your predicted blood glucose level is close to your target blood glucose level, then a suggestion will be made to take no action (in other words – no bolus insulin or additional ets should be taken).

Suggestion cannot be calculated If your meal contains too much ets, or it is detected that a very large insulin bolus is needed, the suggestion will not be displayed. This safety feature is to prevent the system from making extremely high insulin boluses that could possibly result in a hypo when administered. If you do get a message that the bolus could not be calculated – you will have to use your own discretion to determine your insulin bolus. There are ways to prevent this from happening: ensure that you do not consume a very high amount of carbohydrates (ets), especially when your current blood glucose level is already high.

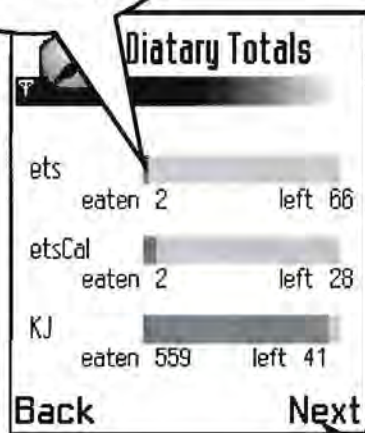
8 - DAILY TOTALS

Daily totals give a summary of your food intake including ets, etsCal and calories. It also shows the composition of your daily food intake. Remember ets gives you an indication of how much glucose there is in your diet. You don't have to worry about these values for now, they are only here for your information.

TO VIEW THE DAILY TOTALS



Red shows the amount eaten; Green shows the amount left for the day



% Protein, Fats and Carbohydrates



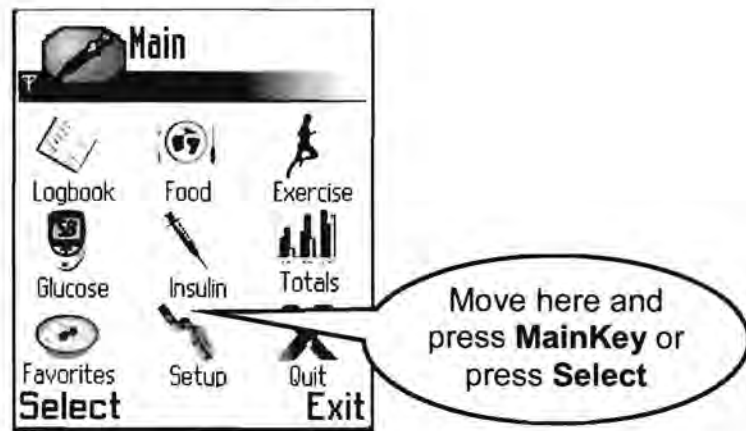
Press Next

9 – SETUP (DON'T USE SETUP BY YOURSELF!)

It is very important that the values that are entered in the setup, are correct. The bolus calculator will not be able to make accurate calculations if these values are not correct. The setup values have to be set before the device can be used. One of the trial assistants will help you to enter the correct values. It is important that you do not change these values by yourself! You do not have to read through this section.

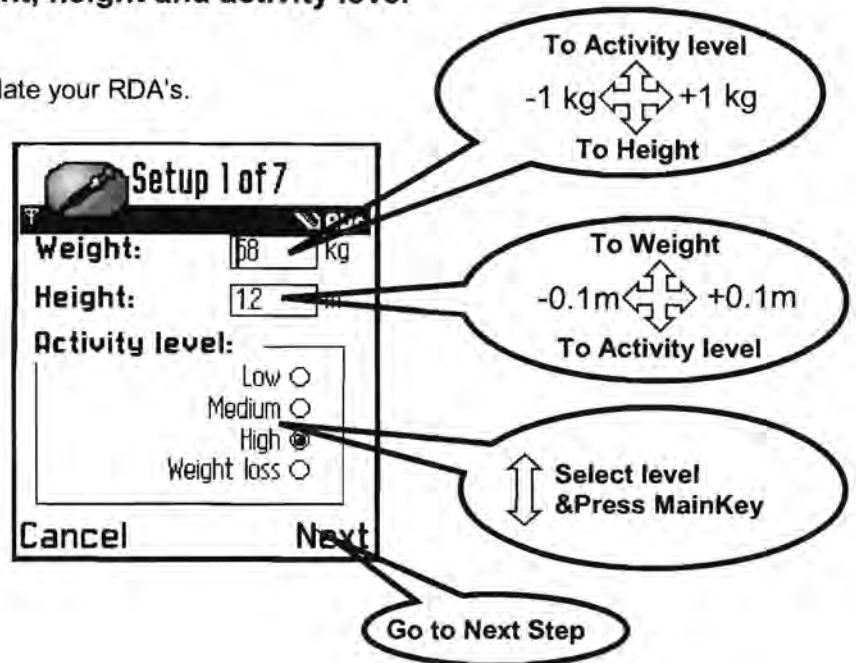
TO VIEW SETUP

Select **Setup**



Step 1 – Enter your weight, height and activity level

These values are used to calculate your RDA's.



Step 2 – Enter your gender and insulin regime

If you are using an insulin pump, one of the research assistants will help you to determine your total daily long acting insulin (basal) dose.

The screenshot shows the 'Setup 2 of 7' screen with the following elements and callouts:

- Gender:** A dropdown menu currently set to 'Male'. A callout bubble indicates that pressing the up/down arrows will toggle between 'To Male; Short Acting' and 'To Female; Long Acting'.
- Total daily long acting insulin:** A numeric input field with '10'. A callout bubble shows a four-way arrow with '-1 U' on the left and '+1 U' on the right, labeled 'To Long acting'.
- Total daily short acting insulin:** A numeric input field with '10'. A callout bubble shows a four-way arrow with '-1 U' on the left and '+1 U' on the right, labeled 'To Long Acting'.
- Navigation:** 'Back' and 'Next' buttons are at the bottom. A callout bubble labeled 'Go to Next Step' points to the 'Next' button.

Step 3 – Enter your age in years

The screenshot shows the 'Setup 3 of 7' screen with the following elements and callouts:

- Text:** 'Please enter your age below'.
- Age Input:** A numeric input field containing '15'. A callout bubble shows a four-way arrow with '-1 Year' on the left and '+1 Year' on the right.
- Navigation:** 'Back' and 'Next' buttons are at the bottom. A callout bubble labeled 'Go to Next Step' points to the 'Next' button.

Step 4 – Select the glucose units you prefer

Blood glucose meters sold in South Africa are usually calibrated in mmol/l.

The screenshot shows the 'Setup 4 of 7' screen with the following elements and callouts:

- Text:** 'Please select the unit you prefer below'.
- Unit Selection:** Two radio buttons are shown: 'mmol/l' (which is selected) and 'mg/dl'.
- Callout:** A bubble shows a vertical double-headed arrow between 'mmol/l' and 'mg/dl' with the text 'Press to toggle'.
- Navigation:** 'Back' and 'Next' buttons are at the bottom. A callout bubble labeled 'Go to Next Step' points to the 'Next' button.

Step 5 – Enter your blood glucose setup

One of the research assistants will determine these values for you and enter them. **DO NOT CHANGE THESE VALUES BY YOURSELF!**

Setup 5 of 7

ets sensitivity: 1000

Ins sensitivity: 1000

Target BS: 100 mg/dl

Back Next

Callouts:

- To Target... -50 +50 To Ins sens...
- To ets sens... -50 U +50 U To Long acting
- To Ins sens... - + To ets sens...
- Go to Next Step

Step 6 – Enter your RDA values

These RDA's (Recommended Daily Allowances) gives an indication of how much energy you need during a day. These energy values are calculated to maintain your weight at a certain daily activity level. It also takes your age, weight, gender and height into account.

Setup 6 of 7

Please supply your target values

Suggested values in red

ets : 68 39

etsCal : 30 30

KCal KJ 600 590

Back Next

Callouts:

- To KCal/KJ -50 U +50 U etsCal
- To ets -50 U +50 U To KCal/KJ
- To etsCal -50 U +50 U To ets
- Go to Next Step

Step 7 – Confirm values

Make sure that all these values are correct. If they are not correct press BACK until you see the information that needs correction, and change it. Then press NEXT until you see the confirmation screen again, check the information again and press ACCEPT if everything is correct.

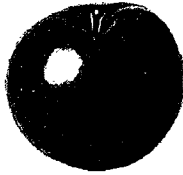
Confirm Setup

Male	1.2 m	58 kg
Activity level	High	
Insulin	10U Lng, 10U Shrt	
EtsSensitivity	1000	
InsSensitivity	1000	
Target Glucose	100 mg/dl	
Ets ADA	68 ets	
EtsCalADA	30	

Back Accept

Callout: Press ACCEPT if these values are correct. If not press BACK to change them.

REMEMBER DO NOT CHANGE THE SETUP VALUES BY YOURSELF !



381g Apple
= 50g Carbs
= 5.8 *ets*



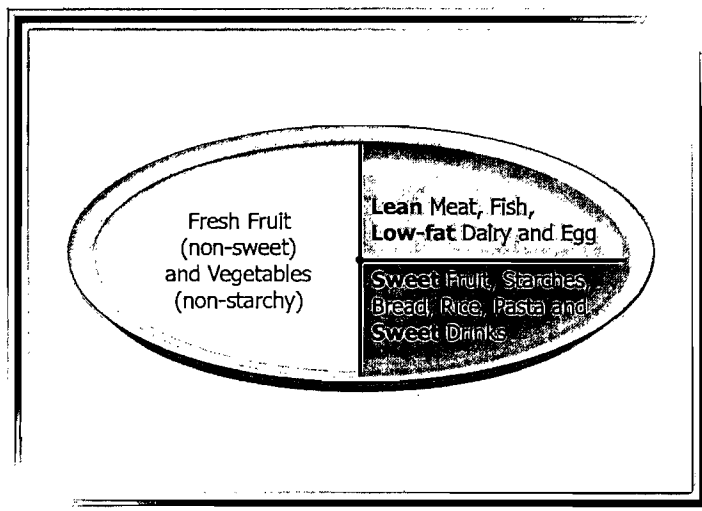
111g Hi Fiber Bran
= 50g Carbs
= 6.6 *ets*



63g Special K
= 50g Carbs
= 13.7 *ets*

All three quantities have the same amount of carbohydrates (50g) but a different amount of *ets*. Can you see why counting carbohydrates can be problematic? Remember the higher the *ets*, the higher the rise in blood glucose!

Tip: It is important to balance your meals otherwise you may become hungry between meals and may not get all the fiber and micronutrients you need. We propose the easy-to-use $\frac{1}{2}$ - $\frac{1}{4}$ - $\frac{1}{4}$ rule. By using the weight of the food, try to balance your meal as follows:



Remember to choose low-fat foods!

There is a relationship between your *ets* intake, the increase in your blood glucose level and therefore also the bolus insulin you need for a meal. *ets* allows us to calculate this increase in blood glucose level more accurately than when using carbohydrates. This means that if we eat less *ets*, less insulin will be needed.

If you want to choose low *ets*-foods there are a few general guidelines:

- Rough unrefined food (e.g. rye bread with full grains & seeds) are usually lower in *ets* than their refined equivalents (white bread).
- Colourful vegetables are usually not that high in *ets*. Starchy vegetables like potatoes are very rich in *ets* and will cause high surges in your blood glucose. Try to avoid french fries.
- Fruit juice is often high in *ets*. Many fruit can be squeezed into a single bottle. The fibre you get from eating a whole fruit is also beneficial for you thus rather eat whole fruit than drinking fruit juice.

To summarise: By eating less *ets* , less glucose is released into the blood meaning that less insulin is needed. Counting *ets* helps us to calculate better insulin bolusses.

Clinical trial results: Glycaemic control of Type 1 diabetics using the ets-concept														
Patient ID	1	2	3	4	5	6	7	8						
Blood glucose (Pre-trial)														
Time of hypo	SL	EE	LE	A,SL	EM	SS	EM	EM,EE,SL						
Problems	-	No problem BGO better	Effort entering info	No	Perceived BG higher	No	No	No						
Software application									n	Mean %	Std Dev %	0%Rating	50%Rating	100%Rating
Software easy to use?	90	81	66	56	92	89	90	67	8	86	15	Very difficult	I managed	Very easy
Easy to find databases items?	89	59	62	73	73	87	78	65	8	80	12	Very difficult	I managed	Very easy
Easy to calculate bolus?	89	78	46	64	91	88	89	?	7	85	18	Very difficult	I managed	Very easy
Rate device to similar?	-	-	-	77	-	-	69	-	2	79	6	Worse	The same	Great improvement
Nokia cellular phone														
Easy to operate Nokia phone?	89	89	49	79	91	81	90	65	8	86	16	Very difficult	I managed	Very easy
Educational value														
Learn BG control?	88	56	73	22	91	52	89	52	8	71	26	Nothing new	A few new insights	A lot of new insights
Blood glucose control														
Frequency hypos	4	17	3	32	17	13	46	12	8	20	16	Less than usual	Same as always	More than usual
Frequency highs	4	38	46	72	46	16	24	50	8	40	23	Less than usual	Same as always	More than usual
Trust suggestions	89	80	55	70	46	74	46	52	8	70	18	Never	Usually	Always
Reliable suggestions	88	79	55	76	46	85	46	53	8	72	19	Never	Usually	Always
State of BG control	87	77	49	71	70	69	71	53	8	74	13	Worse than usual	Same as always	Better than usual
Frequency use	87	90	-	34	69	35	24	79	7	65	30	Never	Regularly	Always
Other														
New medical conditions	No	No	Operations x 2	No	No	Flu	No	No						
Adverse events during study	No	No	No	No	No	No	No	No						
Serious adverse events during study	No	No	No	No	No	No	No	No						
Pre-trial														
Activities & Routine														
Frequency of exercise	2/week	3/week	3/week	3/week	-	2/week	1/week	3/week						
Type of exercises?	Weights, Walk	Gym, Cardio	Walk	Gym	-	Cycling	Walk	Gym, Cardio						
Duration exercises	30-45 min	60min	30min	60min	-	20min	30min	58min						
Activity level	Average	Average	Average	Average	Average	Average	High	Average						
Daily routine	Office	Student, Gym	Teacher	Housewife	Office	Office	Student	Lecturer						
Sleep time	22h00	22h00	23h00	22h00	23h30	22h00	22h00	21h00						
Wake time	06h00	7h00	06h00	07h00	6h30	4h00	5h30	06h00						
Meals														
Meals per day	3	3	2	3	3	3	3	3						
Snacks per day	2	2	4	2-3	1	0	4	3						
Body characteristics														
Gender	F	F	F	F	M	F	M	M						
Age	44	20	51	49	52	40	22	53						
Height	1.6	1.69	1.58	1.75	1.8	1.64	1.63	1.8						
Weight (onset)	93	60	71	66	67	79	61	75						
Insulin														
Basal	Ultratard	Lantus	Lantus	Lantus	Lantus	Lantus	Lantus	Lantus						
TDD Basal	40	10U	28-30U	16U	18U	18-20U	34U	24U						
Bolus	Actrapid	NovoRapid	NovoRapid	Humalog	Novorapid	Humalog	NovoRapid	NovoRapid						
TDD Bolus	30	15U	30U	6-9U	30U	18U	44U	18U						
Type Insulin Admin	Pen	Pen	Pen	Syringe	Syringe	Pen	Pen	Pen						
BG Monitoring														
BG Monitor	Accucheck	Optium	Accucheck	Accutrend	Optium	Accucheck	Optium	Accutrend						
BG Measurements/day	2-3	2	2	1	2	3-6	2	2						
BG Control Target Range	7-10	4.5-6	8-10	7-9	6-10	6-8	4-8	4.5-6						
BG Control (During trial)														
Hypo's / week	2-5/week	Very seldom	0/week	1/week	1/week	1-2/week	1/week	Very seldom						
Likely hypo	-	LE	EM, SL	SS	M	SS	EM	SL						