Developing a link between ingested carbohydrate energy and cardiovascular disease

J P Laubscher (B. Sc. Eng)

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ABSTRACT

Cardiovascular Disease (CVD) is the most widespread modern disease in the Western world. There is a substantial amount of evidence suggesting that blood glucose energy plays a role in the formation and progression of the disease.

The staff at Human-Sim (Pty) Ltd have developed a concept that they believe can be used to help decrease the risk of CVD. This concept can be used to quantify blood glucose energy extracted from any foodstuff. This method of quantification of blood glucose energy has been called the Equivalent Teaspoon Sugar (*ets)* concept.

To link the *ets* concept with CVD, two studies were done. In the first study risk factors obtained from cohort studies linking the HbA_{1c} percentage with CVD risk were used. The HbA_{1c} percentage is a representation of the mean blood glucose level over a certain period of time.

Through simulating the effect of *ets* intake on blood glucose levels using the simulation model Diabetic Toolbox, it was found that an increase in *ets* intake results in an increase in mean blood glucose levels in diabetic patients. This increase was linked with an increase in the HbA_{1c} percentage and hence the link with CVD risk was made. However, the increase in mean blood glucose due to *ets* intake is not sufficiently significant to create an accurate link between *ets* intake and CVD.

The second study used risk factors obtained from cohort studies linking glycaemic load intake with CVD risk. This proved to be much more effective than the first study. Since glycaemic load can be expressed through *ets,* a link between *ets* intake and CVD was made.

Stress is also a well-known factor that is associated with the increase of CVD. With empirical measurements and simulations, it was found that the effect stress has on blood sugar levels can be approximated with an effect similar to that of

ingested carbohydrates. The effect stress has on blood glucose energy could be linked to an increased risk of CVD. The results correlated very well with cohort studies done where stress was viewed as a risk factor of CVD. This research can lead to a new way of quantifying stress.

The effect exercise has on CVD was also investigated. A decrease in CVD risk is associated with the amount of energy expended during exercise in KCal. During exercise, blood glucose energy is used. The amount of blood glucose energy used can be expressed as *ets-expended* during exercise, which in turn was linked to a decrease in the risk of CVD.

In conclusion, a correlation does exist between blood glucose energy and CVD. The *ets* concept quantifies blood glucose energy and can thus be used to control blood glucose energy. Research shows that the risk of CVD can be reduced if a person controls his energy intake, manages his stress and exercises regularly. All of these above factors can be quantified with the *ets* concept which is an easy to understand unit of blood glucose energy. The *ets* concept can be used as a tool to help a person keep his blood glucose energy levels at a healthy level considering carbohydrate intake, stress and exercise and thus reduce the risk of CVD.

SAMEVATTING

Die hoof oorsaak van sterftes in die westerse wêreld kan toegeskryf word aan kardiovaskulêre siektes. Moderne navorsing toon dat bloedglukose energie 'n belangrike rol speel in die formasie en progressie van die siekte.

Die maatskappy, Human-Sim (Pty) Ltd het 'n konsep ontwerp wat toegespits kan word op die voorkoming van kardiovaskulêre siektes. Die konsep is 'n maatstaf van bloedglukose energie van kos-soorte. Die konsep staan bekend as die *ets*-konsep. Die verband tussen bloedglukose energie en kardiovaskulêre siektes maak dit moontlik om die verband tussen die *ets*-konsep en kardiovaskulêre siektes te toon. Daar is twee studies gedoen om die verband tussen kardiovaskulêre siektes en *ets*-konsep te bewys.

In die eerste studie is daar gekyk na gepubliseerde literatuur wat die verband tussen geglukosileerde hemoglobien A1c (HbA1c) en kardiovaskulêre siektes toon. HbA1c vlakke verteenwoordig die gemiddelde bloedglukose vlak van 'n persoon vir die laaste 8-12 weke. Daar is 'n positiewe verband tussen kardiovaskulêre siektes en HbA1c vlakke gevind.

Die effek van koolhidraat inname (gekwantifiseerd in *ets* hoeveelhede) op die gemiddelde bloedglukose vlakke van 'n tiepe 2 diabeet, is gesimuleer. Daar is gevind dat 'n toename in *ets* inname, veroorsaak dat die gemiddelde bloedglukose vlakke toeneem. Hierdie toename in gemiddelde bloedglukose vermeerder die risiko vir kardiovaskulêre siektes. Die toename in gemiddelde bloedglukose vlakke is nie van so 'n aard om 'n merkwaardige toename in risiko vir kardiovaskulêre siektes te veroorsaak nie.

In die tweede studie is literatuur ondersoek wat die verband tussen glisemiese belading en risiko vir koronêre hartsiektes toon. Daar is 'n positiewe verband tussen die inname van glikemiese belading en risiko vir koronêre hartsiektes. Glikemiese belading kan uitgedruk word in *ets* en dus kon *ets* met 'n risiko faktor vir koronêre hartsiektes gekoppel word.

Stres 'n nadelige effek op die mens se kardiovaskulêre gesondheid. Deur impieriese meetings en simulering is gevind dat die effek van stress op 'n persoon se bloedglukose vlakke soortgelyk is aan die effek van koolhidraat inname op bloedglukose vlakke. Omdat *ets* 'n maatstaf is van bloedglukose energie is dit moontlik om stress vlakke in *ets* te kwantifiseer.

Die toename in kardiovaskulêre risiko a.g.v die toename in bloedglukose energie veroorsaak deur stress is bereken. Die resultate is vergelyk van studies wat die direkte invloed van stress op kardiovaskulêre risiko toon. Die resultate toon 'n merkwaardige ooreenkoms wat die rol van bloedglukose energie in kardiovaskulêre siektes bevestig.

Die effek van oefening op kardiovaskulêre siektes is ook geondersoek. Daar is gevind dat daar 'n indirekte verband bestaan tussen die kilokalorië verbrand tydens oefening en kardiovaskulêre siektes. Die *ets* konsep kan gekoppel word aan kilokalorië verbrand tydens oefening en kan dus gekoppel word aan 'n vermindering in risiko vir kardiovaskulêre siektes tydens oefening.

Daar is gevind dat die hoeveelheid bloedglukose energie verbruik tydens oefening dubbel die effek het op die vermindering van kardiovaskulê siektes as wat die toename in bloedglukose (veroorsaak deur koolhidraat inname) het op die vermeerdering van risiko vir kardiovaskulêre siektes.

Die studie toon dat bloedglukose energie het 'n merkwaardige invloed op die formasie en progressie van kardiovaskulêre siektes. Die *ets*-konsep kwantifiseer bloedglukose energie. Deur navorsing is die verband tussen die *ets*-konsep en kardiovaskulêre siektes vasgestel. Navorsing bewys dat die risiko vir kardiovaskulê siektes beinvloed word deur koolhidraat inname, stress en oefening. Al hierdie faktore beinvloed bloedglukose energie en kan deur *ets* gekwantiseer word. Die *ets*-konsep is 'n ideale eenheid wat gebruik kan word om bloedglukose beheer mee toetepas om sodoende die risiko vir kardiovaskulê siektes te verminder.

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NOMENCLATURE

LIST OF ABBREVIATIONS

Ets	Equivalent Teaspoon Sugar
HbA1c	Glycated haemoglobin A_{1c}
CVD	Cardiovascular disease
CHD	Coronary heart disease
IH	Ischaemic heart disease
LDL cholesterol	Low Density Lipoprotein Cholesterol
HDL cholesterol	High Density Lipoprotein Cholesterol
VLDL cholesterol	Very Low Density Cholesterol
RDA	Recommended Daily Allowance

SYMBOLS

AUC_{Food}	Area under the curve of the food being digested
$AUC_{Reference}$	Area under the curve of the reference food in the test
E_{CHO}	Converted carbohydrate energy potential
$E_{teaspoon\ \ sugar}$	Energy available from a teaspoon of sugar
$E_{Expended}$	Total amount of energy expended by the body
$G_{Blood(t)}$	Blood glucose concentration at a specific time
$G_{Blood(t-1)}$	Blood glucose concentration at a previous time step
$\dot{G}_{Digest}$	Glucose energy flow from a digestive system to the bloodstream
$\dot{G}_{Store-Out}$	Glucose energy flow from the primary storage to the bloodstream
$\dot{G}_{Store-In}$	Glucose energy flow from the bloodstream to the primary storage
$\dot{G}_{Exercise}$	Glucose energy flow from the bloodstream to the energy expenditure
$G_{Blood(Average)}$	The mean blood glucose level of a certain period of time
GI	Glycaemic Index
GI_{CHO}	Conversion potential of energy from ingested food (approximated with GI)
GL	Glycaemic Load

$f_{Expended}$	Efficiency factor for converting ingested *ets* into expendable blood glucose energy
k_{CHO}	Maximum amount of energy available from carbohydrates
m_{CHO}	Mass of carbohydrate contained in the food
MBG	Mean blood glucose level

INTRODUCTION

1.1. Background

Cardiovascular Disease (CVD) is the most widespread modern disease in the Western world [1] [2]. CVD is the product of a pathogenic process associated with the development of arteriosclerotic plaque in the arteries [3] [4]. Arteriosclerosis consists of the formation of fibro-fatty and fibrous lesions, preceded and accompanied by inflammation. It often takes years to become clinically apparent [3].

Arteriosclerosis is a multi-factorial process associated with genetic, environmental and lifestyle factors. Arterial wall damage results from the many complex interactions between noxious stimuli and the healing responses of the arterial wall. The mechanisms of arteriosclerosis are also not completely clear [3].

Blood viscosity is a major factor in blood rheology and plays an important role in determining the shear stresses exerted on the artery walls. Researchers found that the shear stress plays an important role in stimulating the endothelium [12] [13] [14].

Variations in the shear stress can have such a stimulating effect that arteriosclerotic lesions can result. A high blood viscosity level amplifies the variations in shear stress creating too low and too high shear stress areas. These areas are prone to arteriosclerotic lesion formation. A high blood viscosity level is viewed as an independent risk factor of CVD and can possibly be an initiating factor of CVD [12] [13] [14].

Blood lipids are also known risk factors of CVD. High levels of LDL cholesterol and triglycerides and low levels of HDL cholesterol are known to increase the risk of CVD. These factors can possibly be one of the initiating factors in the formation

of arteriosclerosis, which ultimately lead to CVD [3] [4] [10].

There is a substantial amount of evidence which suggests that a high blood glucose level and carbohydrate intake play a role in the formation and progression of the disease [5] [6].

Glycated haemoglobin (HbA_{1c}) concentration is an indicator of average blood glucose concentration over three months and has been suggested as a diagnostic or screening tool for diabetes [24].

Research shows that there is a significant correlation between HbA_{1c}, blood lipids and blood viscosity. An increase in the HbA_{1c} percentage is associated with an increase in LDL cholesterol, blood viscosity and a decrease in HDL cholesterol, all of which are linked with CVD [3] [4] [10].

HbA_{1c} concentrations predict mortality continuously across the whole population distribution in people with diabetes and at concentrations below those used to diagnose diabetes [10].

High carbohydrate diets can raise plasma fasting triglycerols, primarily by enhancing hepatic synthesis of Very Low Density (VLDL) cholesterol, and can also reduce High Density (HDL) cholesterol, all of which are associated with CVD. A prospective done by Simin Liu *et al* clearly indicates the increase in coronary heart disease (CHD) risk caused by the consumption of a high glycaemic load diet. This study indicates that glycaemic load intake can be used to predict mortality of CHD [15].

Both HbA_{1c} percentage and carbohydrate intake are associated with blood glucose energy. Since high HbA_{1c} levels are associated with high mean blood glucose levels the HbA_{1c} percentage is an indication of high blood glucose energy level over a period of time. Carbohydrate intake is responsible for an increase in blood glucose levels, thus high carbohydrate intake increases the blood glucose energy. It is this increase in blood glucose energy that is associated with

increased risk of CVD [10] [15].

Psychological stress and depression are also known to increase the risk of CVD [57] [62]. Stress triggers the counter regulation system to secrete hormones that both raise the blood glucose concentration as well as impairing insulin action [58]. This increase in blood glucose energy is one of the reasons for the increase in CVD risk.

During exercise blood glucose energy is used. Exercise is known to decrease the risk of CVD [51]. Exercise also increases the insulin sensitivity which enables the body to store blood glucose energy more effectively [63]. This leads to more healthy blood glucose profiles and is one of the reasons for reduction in the risk of CVD.

The following statistics were obtained from the American Heart Association. Estimates for the year 2001 are that 64,400,000 Americans have one or more forms of CVD [1]. These forms are:

- High blood pressure: 50,000,000
- Coronary heart disease: 13,200,000
- Stroke: 4,800,000

CVD claimed 931,108 lives in 2001 (38.5% of all deaths in the United States of America). Most of the CVD mortalities are caused by CHD. Other mortalities were cancer claiming 553768 lives, accidents claiming 101,537 lives and HIV (Aids) claiming 14,175 lives [1].

In 1998 CVD cost the USA $274 billion, and the financial implications are increasing every year. It is clear that CVD is a major problem affecting millions of people in the Western world.

If blood glucose energy can be controlled the various risk factors associated with

CVD can be kept at healthy levels. This will reduce the risk of CVD. A great need exists for any method which can be used to help reduce the risk of CVD.

The staff at Human-Sim (Pty) Ltd have developed a concept that they believe can be used to decrease the risk of CVD. This concept is known as the Equivalent Teaspoon Sugar (*ets*). The *ets* concept is a universally applicable unit of measurement for foods with a known glycaemic index (GI). It will reflect blood glucose response and will also take food portion into account [7].

In other words, the *ets* concept can be used to quantify blood glucose energy. This makes it possible to express various factors (such as carbohydrate intake, exercise and stress), which can influence blood glucose levels, with *ets*. *Ets* values are easy to comprehend and can help to control blood glucose levels, thus reducing the risk of CVD.

1.2. The purpose of this study

The purpose of the study is to show that a link exists between blood glucose energy and CVD under various circumstances (carbohydrate intake, stress and exercise). If such a link can be demonstrated the *ets* method can be used as a predictive tool of CVD risk.

Two methods will be investigated to link *ets* with CVD. The first method is to link *ets* with mean blood glucose levels. A linear correlation exists between mean blood glucose and HbA_{1c}, as well as a significant correlation between HbA_{1c} and CVD. The second method is to express glycaemic load intake as *ets*. Glycaemic load correlates significantly with CVD. It is through this correlation that *ets* can be linked with CVD.

1.3. Hypothesis

A positive correlation exists between *blood glucose energy* and CVD. Since *ets* is a unit that is used to quantify blood glucose energy, *ets* can be linked with CVD. Conversely, CVD risk can be measured with *ets*.

1.4. Motivation for this study

The need exists for easy-to-use methods that can improve cardiovascular health. The *ets* concept is a simple and easy-to-use concept which can help people in general to improve their cardiovascular health by controlling their blood glucose energy.

Products that can be used to calculate the relative risk of CVD can be created. Such products will typically be a palm and software related. This software will typically be able to predict CVD risk factors for an individual person through using the *ets* concept to quantify carbohydrate intake, stress, and exercise. Such product can have financial benefits for Human-Sim (Pty) Ltd.

1.5. Beneficiaries of this study

People in general can benefit from this study. This study indicates that by restricting carbohydrate intake the cardiovascular health of a person can be improved. The *ets* concept can improve diet techniques, making it easier for people to keep track of their carbohydrate energy intake.

CVD costs most industrialised countries billions of dollars. By improving nutritional awareness amongst people, their general health can be improved. This can save a country a tremendous amount of money.

1.6. *Brief overview of this study*

The remainder of the chapters of the dissertation will consist of the following sections:

- Chapter 2 discusses the methodology of the study.
- Chapter 3 will discuss CVD formation and risk factors.
- Chapter 4 discusses the correlation between blood glucose and CVD risk factors.
- Chapter 5 discusses the link between blood glucose and the risk factor associated with CVD.
- Chapter 6 discusses the *ets* concept and the simulation model.
- Chapter 7 discusses the method used to link *ets* intake with CVD risk factors associated with HbA_{1c} percentages by determining the effect of *ets* intake on HbA_{1c} percentages using the Diabetic Toolbox.
- Chapter 8 discusses the effect of glycaemic intake on CVD risk factors. *Ets* intake is linked with glycaemic load intake. *Ets* was linked with CVD risk.
- Chapter 9 discusses the correlation between stress, *ets*, and CVD.
- Chapter 10 discusses the correlation between *ets* expended in exercise and CVD.
- Chapter 11 discusses the conclusions, contributions to the field and recommendations.

2. THE METHODOLOGY OF THE STUDY

2.1. Introduction

In this chapter the methodology of the study is discussed. This study differs from others in that no experiments were done. The data obtained to prove the existing correlations were obtained by means of a literature search on the Internet. The articles were examined and the necessary conclusions were drawn.

The simulation model Diabetic Toolbox was used to determine some of the correlations not found in the literature.

2.2. The research study

To determine the effect that blood glucose has on CVD, the following correlations were investigated:

A literature study was done on the various hypotheses postulated on the formation of CVD. Most of the data was obtained by doing a literature search on the Internet using various search engines. The search engines used are Google, Science Direct, Pubmed and Netscape.

The risk factors most relevant to these hypotheses were investigated. These factors were blood viscosity and blood lipids. To indicate the relevance of these factors to CVD risk, cohort studies were investigated to illustrate the effect of these factors on the risk factor of CVD.

A cohort study (or prospective study) is defined as an epidemiological study comparing a certain entity with an exposure of interest, to those without the exposure. These two cohorts are then followed in time to determine the differences in the rates of disease between the exposed subjects [63]. Blood

viscosity and blood lipids proved to be associated with CVD risk [17] [56] [62].

Relative risk can be explained as follows. If X% of people exposed to a putative cause suffer a certain effect, and Y% not exposed to the cause suffer the same effect, the relative risk factor is X/Y. If the effect is negative (for example death or illness), then a relative risk greater than unity denotes a bad cause, while a relative risk less than unity suggest a beneficial cause. A relative risk of unity suggests that there is no correlation.

To determine the importance of blood glucose in the formation of CVD, the effect that blood glucose has on blood viscosity and blood lipids was investigated. Measured data showing the effect that mean blood glucose levels and carbohydrate intake has on blood lipids and blood viscosity, were obtained by means of a literature search on the Internet. The search engines used were Google, Science Direct, Pubmed and Netscape. Articles reviewing clinical tests conducted to determine the effect of blood glucose on blood viscosity and blood lipids were researched.

To link *ets* intake (blood glucose energy) with CVD risk, two studies were conducted. Study 1 used data obtained from cohort studies conducted by Kay Thee Khaw *et al* [10]. Relative risk factors linking HbA_{1c} percentages with CVD were obtained from that study. No data showing the correlation between carbohydrate intake and HbA_{1c} could be obtained. Diabetic Toolbox was used to predict blood glucose responses to *ets* intake. The results obtained from Diabetic Toolbox were used to determine the HbA_{1c} percentage with *ets* intake. This method was then used to determine a link between *ets* intake and CVD risk.

The results discussed in chapter 8 show that the method used in study 1 proved to be unsuccessful. This led to a new approach to the problem and a second study was conducted.

The method used in study 2 was to obtain measured data linking glycaemic load intake with CVD. This was done by a literature search using the search engines previously mentioned. Measured data was obtained from a study conducted by

Simin Liu *et al* [15] linking glycaemic intake with coronary heart disease (CHD). CHD is the most common form of CVD and is responsible for most of the deaths caused by cardiovascular disease [15].

2.3. *Study 1: Determining the link between ets intake and CVD risk using Diabetic Toolbox*

To obtain the relative risk factors associated with blood glucose levels, a thorough literature search on the Internet was done. Most of the literature indicated that diabetics with poor glycaemic control have a higher risk of CVD. Diabetics with poor blood glucose control showed an increase in HbA_{1c} percentages.

A cohort study conducted by Kay Thee Khaw *et al* [10] was found during a literature search on the Internet. The study was investigated to find measured data giving risk factors associated with HbA_{1c} percentage.

Data linking dietary intake with an increase in the HbA_{1c} percentage was obtained. The data suggested that an increase in carbohydrate intake resulted in higher HbA_{1c} percentages. However, the data could not be used to link *ets* intake with HbA_{1c} percentages in order to calculate the risk factors associated with *ets* intake. Therefore simulations had to be done in Diabetic Toolbox to determine the effect of *ets* intake on the HbA_{1c} percentage.

Diabetic Toolbox was used to simulate the increase in mean blood glucose levels due to *ets* intake of a typical Type 2 diabetic. The data obtained from the simulation model was used to determine the correlation between *ets* intake and the risk of CVD.

Diabetic Toolbox is a dynamic blood glucose simulation model, incorporating the effects of the glycaemic index (GI) of carbohydrate food, energy utilisation and the principles of regulatory and counter regulatory mechanisms.

The Diabetic Toolbox output is a daily blood glucose simulation. From this the

mean blood glucose levels are calculated. Food input is based on the carbohydrate amount in the food. The GI of the food is also taken into account as this will definitely influence the accuracy of the simulation.

Each human has a different blood glucose response to food and exercise. Thus characterisation is necessary to obtain accurate results. The glucose response is determined by the person's age, gender, body mass index and diabetic status.

A normal person will show the lowest increase in blood glucose levels due to food intake, a Type 2 diabetic will have a higher blood glucose level and a Type 1 diabetic the highest if he does not inject insulin to lower his blood glucose level.

The insulin sensitivity of a person is also taken into account during the characterisation process to increase the accuracy of the results.

The Diabetic Toolbox was verified by Human Sim (Pty) Ltd. The verification of The Diabetic Toolbox is documented [7].

2.4. *Study 2: Determining the link between ets intake and CVD risk using measured data*

In this study literature was researched on the effect of dietary carbohydrate intake on the risk of CVD. A study conducted by Simin Liu *et al* [15] was found by doing a search on the Internet. The study determined risk factors of CVD with glycaemic load intake. Measured data obtained from the study was used to determine the equivalent *ets* intake.

The measured data obtained from the study conducted by Simin Liu *et al* made it possible to link the amount of blood glucose energy with the risk of CVD. This made it possible to verify *ets-stressed* with CVD and *ets-exercised* with CVD.

2.5. The link between ets (exercise) and CVD

In order to link *ets* expended in exercise with CVD risk, risk factors associated with KCal expended during exercise were obtained through a literature study on the Internet. *Ets* was linked with KCal expended during exercise.

The results obtained were verified with the data obtained from Simin Liu *et al* [15]. The effect of excess *ets* intake on CHD risk was compared to the effect of *ets* expended during exercise.

2.6. The link between ets (stressed) and CVD risk

To determine the link between *ets-stressed* and CVD, a literature search on the Internet was done to obtain the risk factors associated with long term stress. By using data obtained form empirical measurements and simulation, the effect of *ets-stressed* on CVD risk was determined. The two studies were compared to each other and a remarkable correlation was found.

3. LITERATURE STUDY OF CVD FORMATION

3.1. Introduction

As previously discussed, arteriosclerosis is a multi-factorial process associated with genetic, environmental and lifestyle factors. Arterial wall damage results from the many complex interactions between noxious stimuli and the healing responses of the arterial wall [34]. Arteriosclerosis ultimately leads to CVD and CVD related illnesses [3].

Coronary Heart Disease (CHD) and stroke cause most mortality cases of CVD. CHD claims more than 60% of CVD mortalities [1].

3.2. Hypotheses of the pathogenesis of arteriosclerosis

It is clear that the process of arteriosclerosis is very complex. Over the years a couple of hypotheses have been formed, none of them being universally accepted. The number of hypothesises gives an idea of the complexity of the disease [5]. Two of the hypotheses that seem to be the most accurate are the hemodynamic and lipid irritation hypotheses [3] [4].

3.3. The hemodynamic hypothesis and the role of blood viscosity

The viscosity of a fluid is a measure of how resistive the fluid is to flow. The mechanical forces exerted on the vessel walls are determined by three factors: the pumping pressure, vessel geometry and blood viscosity [12].

The shear stress of the arterial wall is directly proportional to the viscosity. This means that the higher the viscosity of the blood the higher the shear stress on the

arterial wall. However, exceptions do exist. Higher blood viscosity increases the resistance to blood flow and amplifies the tendency for eddy currents and therefore lowers shear stress. These areas, like the coronary artery, are likely to form arteriosclerotic lesions [12].

The hypothesis suggests that the mechanical forces applied to the arterial wall due to blood flow through the arteries mediate arteriosclerosis. Arteriosclerosis has been demonstrated to occur with the widely identified risk factors. Factors such as smoking, hypertension, high cholesterol levels and diabetes aggravate the natural history of arteriosclerosis [3] [25] [26].

Investigations of the cellular mechanisms of arteriosclerosis initiation and progression have contributed to a consistent model involving immune and inflammatory responses perpetuated by a self-reinforcing cycle of monocytes recruitment, lipid accumulation by macrophages, increased smooth muscle cell proliferation, increased oxidant activity and eventual plaque rapture and thromboembolic complications. The regulation of the endothelium by shear stress can explain the focal propensity of arteriosclerotic response to intimal injury [12] [14] [27].

It appears that a certain shear stress (above 15 dyne/cm^2) has a protective effect on the endothelium. This protective effect consists of decreased expression of vasoconstrictors, paracrine growth, inflammatory mediators, adhesion molecules, oxidants, and elevated production of vasodilators, nitric oxide (NO), growth inhibitors, fibrinolytics, antiplatelet factors and antioxidants [12] [27] [29].

Thus, the right amount of shear stress on the endothelium stimulates the endothelium in such a way that is it less susceptible to pathogenic stimuli of injury, cell adhesion, cell proliferation and lipid uptake [12] [28].

In contrast, the outer wall bifurcations are characterised by a low shear stress region. The shear stress in this region is of the order of 4 dyne/cm^2. These areas seem to be especially susceptible to arteriosclerosis formation. These areas have

greater endothelial cell cycling and are more vulnerable to the uptake of LDL cholesterol, especially oxidised LDL cholesterol.

The low antioxidant levels are likely to act in synergy with reduced production of nitric oxide to increase the production of vasoconstrictors and mitogenic substances such as endothelin I, angiotensin II and platelet derived growth factor B [12] [27] [30] [31].

These substances act to perpetuate underlying smooth muscle and fibroblast proliferation. In addition they reduce production of fibrinolytic tissue-type plasminogen activator, coupled with low production of nitric oxide and prostacyclin, cause focal platelet aggregation and fibrin deposition. This accelerates platelet plaque formation and increases the risk of thromboembolic events. This hypothesis is compatible with the effects of hyperglycaemia, hyperlipidemia and blood viscosity [12] [27] [30] [31].

3.4. Blood viscosity as risk factor of CVD

A cohort study is defined as an epidemiological study comparing a certain entity with an exposure of interest, to those without the exposure. These two cohorts are then followed in time to determine the differences in the rates of disease between the exposure subjects [20]. Blood viscosity and blood lipids proved to be associated with CVD risk [4] [21] [22] [23].

Danesh *et al* researched prospective studies published before mid 1998 that reported on correlations between coronary heart disease death or non-fatal myocardial infarction, haematocrit, viscosity, and erythrocytes sedimentation rate [21]. Most of their research was done through Medline searches, scanning of relevant references lists, hand searching of cardiology, epidemiology, and other relevant journals, and by correspondence with the authors of such reports.

Six prospective studies of plasma viscosity and coronary heart disease were identified, involving a total of 1,629 cases with a weighted mean age of 58 years

and a weighted mean follow up of six years. The studies were done in Germany and the United Kingdom. Most of the studies used capillary viscometers to measure the viscosity [21].

There was a correlation between blood viscosity and the risk factor of CVD. The R^2 value of 0.6 was obtained. High blood viscosity was related to smoking, blood pressure, high LDL cholesterol level, low HDL cholesterol level, blood triglycerides, obesity, diabetes and physical inactivity. Most of these factors, except smoking, can also be linked to high blood glucose levels [21].

In a study conducted by J W G Yarnell, the predictive values of three haemostatic/inflammatory risk markers for subsequent coronary heart disease (CHD) was investigated [22]. Two UK populations, totalling 4,860 men, were screened for evidence of CHD between 1979 and 1983. Men were followed over 10 years and validated coronary events were recorded. Risk estimates were made using relative odds, receiver operator characteristics (ROC) curves and deciles of risk. The relative odds of major CHD events, by fifths of the distribution of plasma viscosity for all men, and men free of CHD at baseline examinations is represented in figure 3.1 [22].

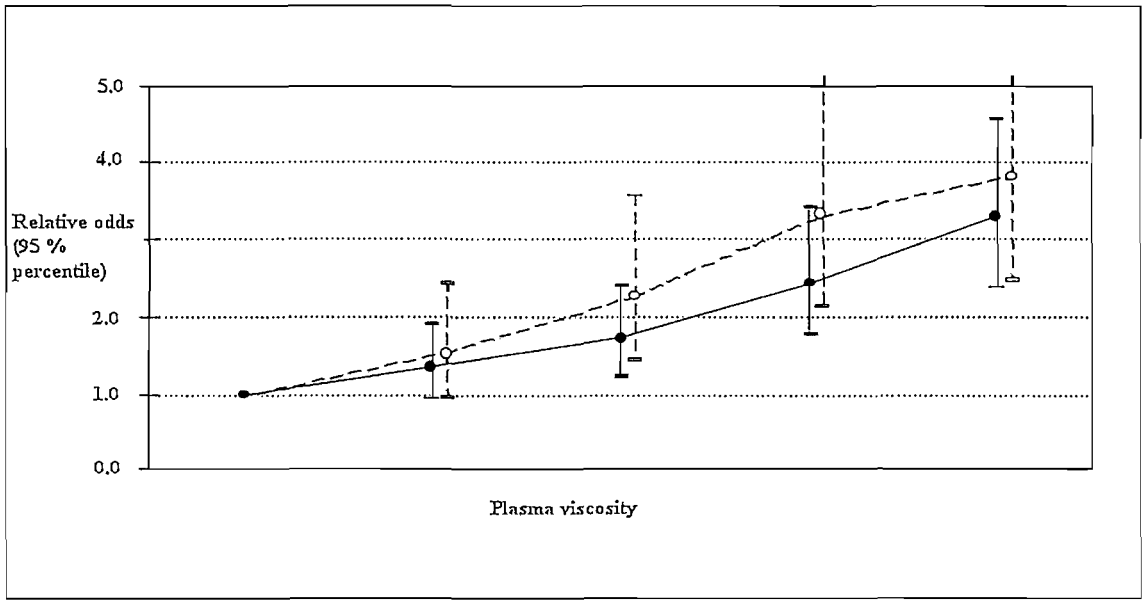

Figure 3.1: The relative odds of major CHD events associated with increase in plasma viscosity.

Figure 3.1 shows the relative odds of a major incident of CHD in correlation with plasma viscosity. The odds rise steadily as plasma viscosity increases. The corresponding relative odds of the fifth quintile are 3.3 (95% CI 2.40, 4.54). The relative odds associated with the fifth quintile of total cholesterol were 2.07 (95% CI 1.55, 2.78).

This indicates that plasma viscosity is not only a more accurate predictor of CHD but a high plasma viscosity is associated with a higher level of risk in comparison with cholesterol.

Cholesterol is viewed as one of the most accurate predictors of CHD. Yarnell's results indicate that plasma viscosity is a more accurate predictor.

Each 0.01 mPa*s (dynamic viscosity where m = length, Pa = stress, s = seconds) increase in plasma viscosity can be associated with a 4% increase in coronary heart disease risk. This result indicated that blood viscosity is one of the most accurate predictors of CHD [22].

The results found in these studies indicate that there is truth in the hemodynamic arteriosclerosis model [14] [22]. The results show that an increase in blood and plasma viscosity does increase the risk of arteriosclerosis and can possibly be the initiating factor [12] [31].

3.5. Lipid-Insudation-Irritation Hypothesis and the role of blood lipids

Most of the fats in a person's diet are neutral fats, also known as triglycerides. Triglycerides consist of one glycerol nucleus and three fatty acids. There are also small quantities of phospholipids, cholesterol and cholesterol esters [33].

Phospholipids and cholesterol esters contain fatty acids themselves and are therefore considered to be fats themselves. Cholesterol on the other hand contains no fatty acids. Cholesterol has physical properties similar to those of fats

and is therefore considered from a dietary point of view as a fat [33].

Cholesterol is a lipoprotein. Unlike fatty acids and triglycerols, cholesterol serves not as a metabolic fuel but as a precursor for plasma membranes, bile salts, steroid hormones and other specialised molecules [8].

Cholesterol can be obtained by dietary intake or the body can synthesize it. All dietary cholesterol intakes come from animal products like cheese and egg yolk. Not all ingested cholesterol is absorbed into the bloodstream and much of it passes through the intestinal tract without being absorbed [8].

Almost all cells can synthesize their own cholesterol required for their plasma membranes, but cannot do so adequately. The liver and cells lining the intestinal tract can produce large amounts of cholesterol, which is secreted into the bloodstream and used by most of the other cells [8] [33].

The synthesis of cholesterol by the liver is inhibited whenever dietary cholesterol is increased. The reason for this is that cholesterol inhibits the enzyme needed for cholesterol synthesis. This means that the plasma cholesterol will stay the same when dietary cholesterol is absorbed into the bloodstream because the liver compensates for the increase in cholesterol and produces less cholesterol [8] [33].

But if dietary cholesterol is reduced and plasma cholesterol begins to fall, hepatic synthesis is stimulated and there is an increased production of cholesterol by the body. This is the main reason why it is so difficult to alter a person's cholesterol level just by changing their dietary intake of cholesterol [33].

Like most lipids, cholesterol circulates the plasma as part of various lipoprotein complexes. These include chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). LDL are the main cholesterol carriers and they deliver cholesterol to the cells. HDL serve as acceptors for cholesterol from the tissue and transport the cholesterol back to the

liver [33].

LDL is widely known as "bad" cholesterol. Elevated levels of LDL are associated with cardiovascular disease because of an increased deposition of cholesterol on the arterial walls. An increase in LDL is associated with an increase in plasma viscosity [37]. HDL is widely known as good cholesterol and is associated with the removal of excess LDL. An increase in HDL is associated with a decrease in plasma viscosity [33] [35].

A risk factor for the development of arteriosclerosis is not the total amount of cholesterol but the ratio between LDL and HDL. The lower the ratio the lower the risk [34].

3.6. Blood lipids and cardiovascular disease

The hypothesis that triglycerides (TG) elevations are associated with arteriosclerosis was proposed in the early 1960's by Albrink *et al* [16] based on observations of non-diabetic and diabetic cohorts of industrial employees.

Subsequently the Paris Prospective Study [4] showed that TG elevations in diabetes were a stronger predictor of coronary death than were cholesterol concentrations. In multivariate analysis it was the only predictor [4].

The Helsinki Heart Study and the Physicians' Health Study found that TG concentrations larger than 200 mg/dL, even in the absence of diabetes, were associated with an increase in the risk of CVD [23].

The hypothesis focuses on the relation between fatty materials circulating in the blood, which infiltrate the arterial walls. These deposits cause inflammation and proliferation of cells which can lead to arteriosclerosis.

Research shows that TG-rich lipoproteins produce typical arteriosclerotic changes. TG-rich lipoproteins show an increased movement into the intima. The

result is the formation of fatty streaks, which are a key factor in the formation of arteriosclerosis. There is thus reason to believe that TG-rich lipoproteins have an initiating effect on arteriosclerosis.

Low levels of HDL cholesterol are also viewed as a risk factor of CVD. Studies show that each 1% increase in HDL cholesterol was associated with a 2 to 3% reduction in CVD risk. Diabetic patients are also known to have a lower HDL cholesterol level. The ratio between LDL cholesterol and HDL cholesterol is viewed as an accurate predictor of CVD.

3.7. Summary

Modern day technology and research have gathered enough information to put together theories on the formation of arteriosclerosis. This formation process is linked with certain risk factors.

With the aid of computers the hemodynamic profiles in the body's main arteries can be calculated. This gave rise to a new hypothesis, namely the hemodynamic hypothesis. Blood viscosity plays an important part in this hypothesis [3] [12] [13] [14] [22].

The mechanism by which arteriosclerosis grows has been established. Blood lipids, especially triglyceride-rich lipoproteins such as LDL and VLDL cholesterol, are associated with the formation of fatty streaks which ultimately lead to arteriosclerotic lesions and CVD [3] [4] [23].

Research shows that there is a correlation between blood glucose and the above named risk factors. Diabetics are known for their high mean blood glucose levels and high rate of CVD mortality. Blood glucose has a drastic effect on the blood lipids and blood viscosity and can thus possibly be one of the main causes of CVD. In the next chapter the link between blood glucose and the risk factors are investigated.

4. THE CORRELATION BETWEEN BLOOD GLUCOSE, BLOOD LIPIDS AND BLOOD VISCOSITY

4.1. Introduction

As discussed in the previous section, blood viscosity and blood lipids are viewed as having an initiation effect on the formation of arteriosclerosis. In this section the link between blood glucose and these risk factors is investigated.

4.2. Blood glucose

Most of the blood sugar in the human body is obtained from the intake of carbohydrates. Carbohydrates consist of sucrose, popularly known as cane sugar, lactose which is obtained from milk, and starches which are mostly obtained from grains. Other carbohydrates ingested to a slight extent are amylose glycogen, alcohol, lactic acid, pectins, dextrins and minor quantities of carbohydrate derivatives in meat [33].

In an ordinary carbohydrate diet more than 80% of the carbohydrate digestion is represented by glucose. The glucose is absorbed into the portal blood [33]. Much of the absorbed carbohydrates enter various cells where they are catabolised to carbon dioxide and water, providing the energy for adenosine triphosphate (ATP) formation. The other 20%, which consist of galactose and fructose, are converted into glucose in the liver [34].

Most of the glucose enters various cells where it is catabolised to carbon dioxide and water, providing the energy for ATP formation. Glucose is the body's main form of energy. The skeletal muscle consumes most of the glucose even at rest.

Skeletal muscle not only catabolises most of the glucose during the absorptive

phase but also converts some of the glucose into glycogen which can be stored in the muscle. A large percentage (±20%) of the glucose is stored in the liver where it can be released to serve as an extra energy source [34].

An increase in blood glucose concentration stimulates the secretion of insulin. The insulin stimulates the entry of glucose into the muscle and adipose tissue as well as the net uptake of glucose in the liver. This reduces the blood glucose level, thereby removing the stimulus for insulin secretion, which returns to its previous level [34].

The progression from normal glucose tolerance to Type 2-diabetes is characterised by dual defects that include insulin resistance and an insulin secretion defect caused by beta-cell dysfunction. Insulin resistance is characterised by decreased tissue sensitivity to insulin and marked compensatory hyperinsulinemia [19].

Initially plasma glucose levels are maintained in the normal range. In patients who will eventually develop diabetes, there is a decline in the insulin secretion capacity of the beta cells [19]. The first glucose abnormality that is detected is a rise in the postprandial glucose levels because of reduced insulin secretion. With time the beta cells secrete less insulin causing a rise in fasting plasma glucose levels. Eventually diabetes occurs with even less insulin secretion [19].

The Oral Glucose Tolerance Test (OGTT) has traditionally been used to classify the status of glucose tolerance for diagnostic purposes: Normal Glucose Tolerance (NGT) versus Impaired Glucose Tolerance (IGT) versus diabetes [36]. The glucose tolerance test is used to estimate insulin sensitivity and β-cell function.

4.3. Hemoglobin A_{1c}

Hemoglobin A_{1c} (HbA_{1c}) is an important product of blood glucose. It is formed when glucose "sticks" to haemoglobin to make glycosylated haemoglobin. A

higher level of glucose in the blood will result in more HbA_{1c} in the blood [24].

Red blood cells live for 8-12 weeks before they are replaced. HbA_{1c} levels stay almost constant after a four-week period. In spite of this, it is possible to tell what the mean blood glucose level of a person was over the previous period of 8-12 weeks by measuring the HbA_{1c} levels. The HbA_{1c} test is currently one of the best ways to verify that a person's diabetes is under control [24].

HbA_{1c} is a very accurate method of predicting a person's mean blood glucose level. In most cases a person's HbA_{1c} percentage gives a much better correlation between total cholesterol and triglycerides than a person's basal blood glucose level [10].

In data obtained from the research studies conducted by Curt L Rohlfing *et al* [24] the correlation between mean blood glucose level and HbA_{1c} percentage was calculated.

Mean blood glucose (mmol/l)	**HbA_{1c} %**
3.6	4
5.6	5
7.6	6
9.6	7
11.5	8
13.5	9
15.5	10
17.5	11
19.5	12

Table 4.1: Correlation between mean plasma glucose and HbA_{1c} percentage.

The relationship between mean blood glucose and HbA_{1c} can be taken as linear. The R^2 value is 0.82. These values can by used to create a link between *ets* and HbA_{1c}. The equation representing the state line is as follows:

$$MBG = 1.98 * HbA1c - 4.29 \quad (4.1)$$

Where MBG represents the mean blood glucose level [24].

In research done by Otto Tshritter *et al,* a statistically significant correlation was found between the area under the curve (AUC) of the oral glucose tolerance test (OGTT) and the HbA_{1c} percentage [38]. This indicates that if the insulin resistance of a person increases the mean blood glucose level of a person can increase with the intake of carbohydrates [38].

4.4. Link between blood glucose and blood lipids

In this section the link between blood glucose and blood lipid levels is illustrated. As discussed, blood lipids play an important role in the mechanism of arteriosclerosis. High levels of triglycerides and LDL cholesterol and low levels of HDL cholesterol are associated with CVD.

A number of studies link dietary sugar with adverse changes in lipoprotein. Several studies have shown an inverse association between dietary sucrose and HDL. Data from the Coronary Artery Risk Development in Young Adults (CARDIA) study show a constant inverse association between dietary sugar intake and HDL cholesterol levels. The study was done on black and white, males and females [5] [32].

An influx of sugar into the bloodstream upsets the body's blood sugar balance, triggering the release of insulin which the body uses to keep blood glucose at a constant and safe level.

Insulin also promotes the storage of fat, so that when sweets high in sugar are eaten, an increase in body weight and triglyceride levels, both of which have been linked to cardiovascular disease, can result. Complex carbohydrates tend to be absorbed more slowly, lessening the impact on blood-sugar levels [32] [33] [34].

In a study conducted by Kay-Tee Khaw *et al* [10] the following statistical data was obtained. The study investigated the relation between HbA_{1c}, diabetes and mortality in men. There is a significant correlation between HbA_{1c} and blood lipids. The correlation between blood glucose and blood lipids improves when the mean blood glucose is considered and not the resting or basal blood glucose level.

The study looked at 4,226 men aged between 45 to 79 years. The men's HbA_{1c} levels were measured at the baseline survey in July 1995 and were followed up to December 1999. The results are shown in the following table:

Factor	Quartile 1	Quartile 2	Quartile 3	Quartile 4
HbA_{1c} %	4.57	5.20	5.82	8.35
Cholesterol (mmol/l)	5.88	6.01	6.11	6.22
LDL (mmol/l)	3.81	3.89	3.95	3.90
HDL (mmol/l)	1.26	1.26	1.24	1.10
Triglycerides (mmol/l)	1.91	2.00	2.14	2.80
No. (%) with history heart attack or stroke	4.2	5.5	8.8	18.5

Table 4.2: Results obtained from Kay Tee Khaw, which show the correlation between HbA_{1c} percentages and blood lipids.

In table 4.2 the correlation between HbA_{1c} percentages and blood lipids is given. The data from the table is used to plot the following graphs. The standard deviation is not included in the graphs. Data from the 4,664 men is divided into four quartiles of HbA_{1c} percentage. The average of each quintile of HbA_{1c} percentage with the corresponding average values of total cholesterol, LDL, HDL and triglycerides is plotted. The figures illustrate the change in the various factors due to the change in HbA_{1c} percentage.

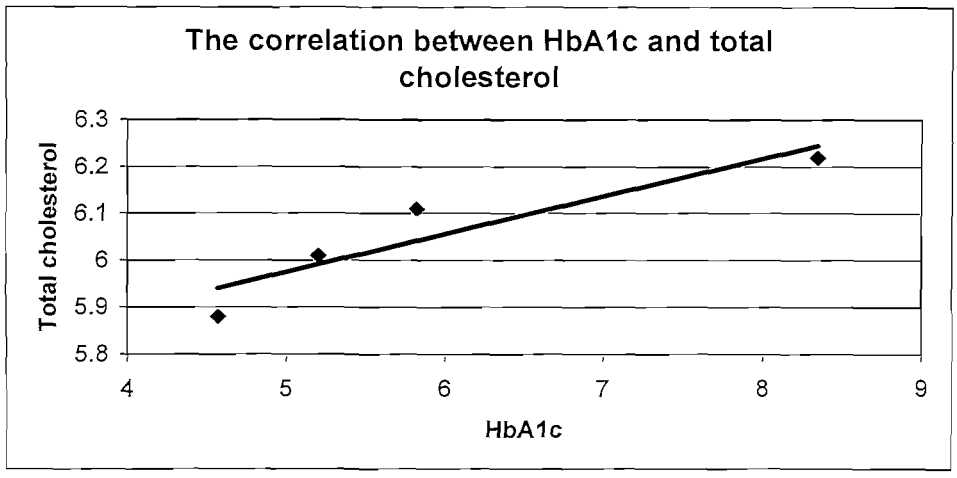

Figure 4.1: The correlation between HbA_{1c} and total cholesterol.

The average values of the four quartiles of HbA_{1c} values are plotted against the average values of the four quartiles of total cholesterol. There is a positive correlation between total cholesterol and HbA_{1c} percentage. This means that if the HbA_{1c} percentage increases, it can cause an increase in total cholesterol.

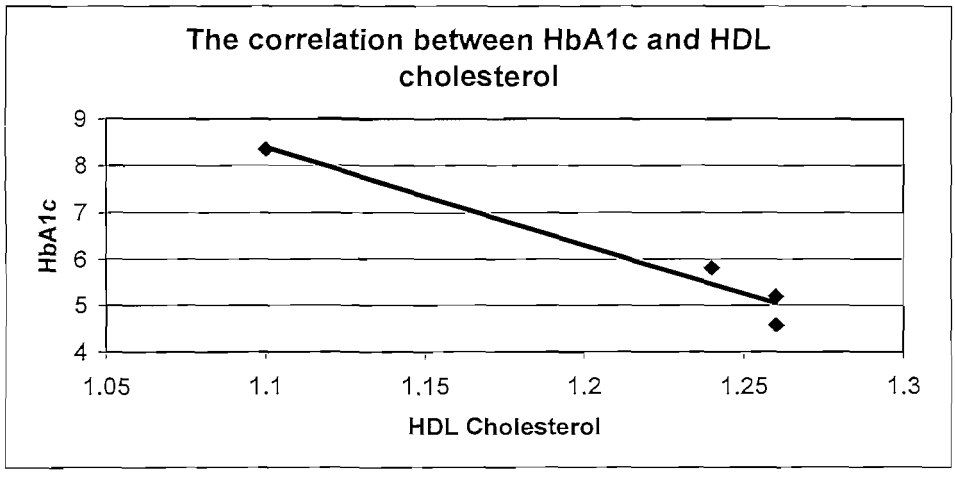

Figure 4.2: The correlation between HbA_{1c} and HDL cholesterol.

In figure 4.2 the average values of the four quintiles of HbA_{1c} are plotted against the corresponding values of HDL cholesterol. Note that there is an inverse correlation between HbA_{1c} and HDL cholesterol.

Therefore a higher percentage of HbA_{1c} will indicate lower levels of HDL, which is known as "good cholesterol" and a high value of HDL cholesterol is associated with a low risk of CVD [10].

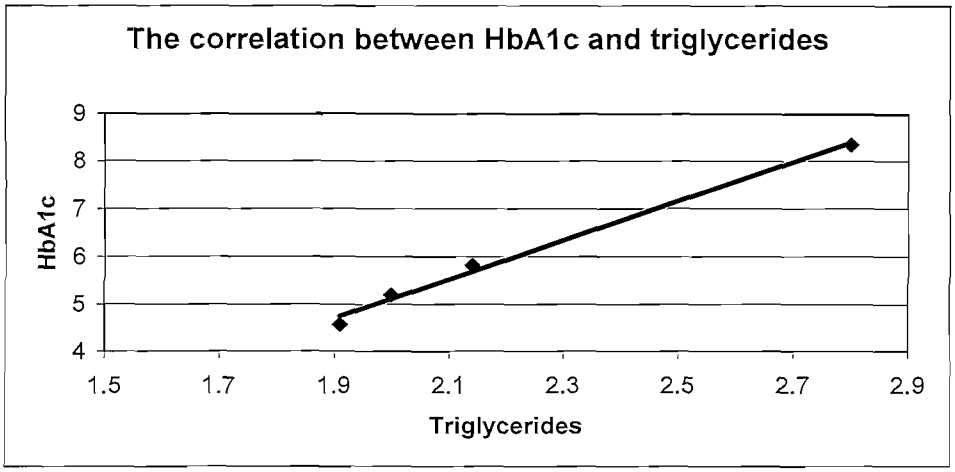

Figure 4.3: The correlation between HbA_{1c} and triglycerides.

In figure 4.3 the average values of the four quartiles of HbA_{1c} are plotted against the average values of the four quartiles of triglyceride levels. HbA_{1c} and triglyceride correlates positively [14]. A high mean blood glucose level makes it easier for the human body to synthesize triglycerides from glucose [33]. Thus a high mean blood glucose level increases a person's triglyceride level.

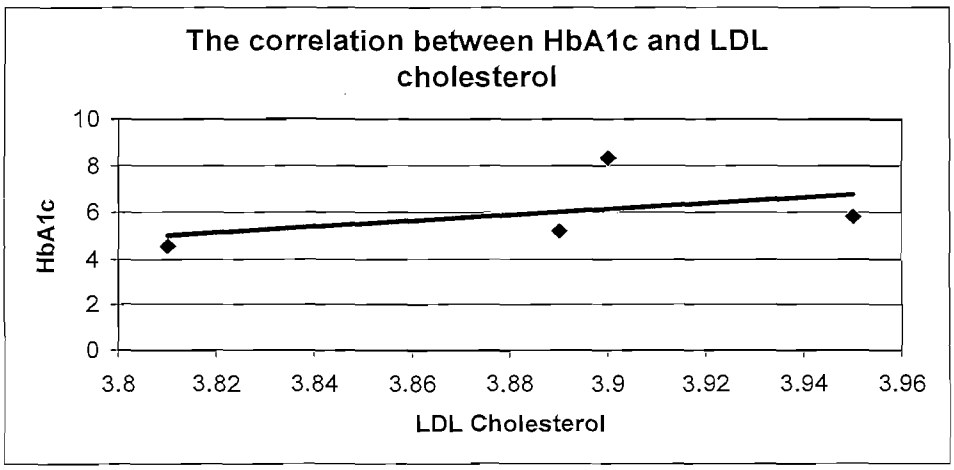

Figure 4.4: The correlation between HbA_{1c} and LDL cholesterol.

In figure 4.4 the average values of the four quartiles of HbA_{1c} are plotted against the average values of the four quartiles of LDL cholesterol. LDL cholesterol correlates positively with HbA_{1c}, however the correlation is not significant.

In a study done by Fahim Abbasi *et al* on the effect of high carbohydrate diet on triglyceride rich lipoproteins, no correlation could be found with carbohydrate intake and LDL cholesterol level [17]. It appears that a high blood glucose level doesn't affect LDL cholesterol significantly.

The results of this study show that there is a positive correlation between a person's mean blood glucose level and blood lipids especially triglycerides. As previously discussed, blood lipids is a risk factor of CVD.

In the same study the effect of a high carbohydrate diet on triglyceride-rich lipoproteins and coronary heart disease risk was researched. The test was conducted on eight healthy non-diabetic volunteers [17].

The diets contained as a percentage of total calories either 60% carbohydrate, 25% fat and 15% protein, or 40% carbohydrate, 45% fat, and 15% protein. They were consumed in random order for two weeks, with a two-week washout period in between [17].

Measurements were obtained at the end of each dietary period of plasma triglycerides, cholesterol, LDL cholesterol, HDL cholesterol, remnant lipoprotein (RLP) cholesterol and RLP triglycerides concentrations, both after an overnight fast and throughout an eight hour period (8 am to 4 pm) in response to breakfast and lunch.

Fasting plasma triglycerides, cholesterol, LDL cholesterol, RLP cholesterol and RLP triglyceride concentration with the 40% and 60% carbohydrate diets are given in table 4.3 [17].

Variable	40% CHO	60% CHO	P value
Triglyceride (mg/dl)	113 +/- 19	206 +/- 50	0.03
Total cholesterol (mg/dl)	191 +/- 12	198 +/- 9	0.27
LDL cholesterol (mg/dl)	124 +/- 11	123 +/- 11	0.95
HDL cholesterol (mg/dl)	44 +/- 3	39 +/- 3	0.003
RLP cholesterol (mg/dl)	6 +/- 1	15 +/- 6	0.005
RLP triglycerides (mg/dl)	16 +/- 3	56 +/- 25	0.003

Table 4.3: Fasting plasma cholesterol, triglyceride, remnant lipoprotein cholesterol, and triglyceride concentration with diets containing different amounts of carbohydrates.

The results show that the 60% carbohydrate diet is associated with a significant rise in plasma triglyceride, RLP cholesterol and RLP triglyceride concentration. In addition HDL cholesterol concentrations were significantly lower with the 60% carbohydrates diet. Plasma cholesterol and LDL cholesterol concentration were essentially identical for the two diets [17].

An interesting result is that in the low carbohydrate diet the replacement of carbohydrates with monounsaturated and polyunsaturated fats does not increase total and LDL cholesterol, despite the higher fat content. The results showed that elevated fasting triglyceride concentrations, induced by high carbohydrate diets, persist throughout the day in response to meals, despite the decrease in the fat content of the meals [17].

The research studies show that there are correlations between blood glucose (especially mean blood glucose levels) and blood lipid levels. High mean blood glucose levels are associated with an increase in triglyceride levels and decrease the HDL cholesterol level. Carbohydrate intake also correlates positively with

blood lipid levels. An increase in carbohydrate intake increases blood lipid levels.

These changes in blood lipid levels can lead to the formation of arteriosclerosis. This is one of the links through which blood glucose can initiate the formation of arteriosclerosis that can lead to CVD mortality.

4.5. Link between blood glucose and blood viscosity

The conclusion can be drawn that because of the increase of large triglyceride molecules, there is an increase in the plasma viscosity. This affects the blood flow in such a way that arteriosclerotic lesions can form, leading to CVD [39].

People with hyperglycemia are likely to have higher blood viscosity than normal people. It is also known that diabetics with poor glycaemic control have a higher blood viscosity than diabetics with good glycaemic control.

Yildirim Cinar [40] investigated the correlation between blood viscosity and hyperglycemia. The results were as follows: Yildirim found a positive correlation between plasma viscosity and blood glucose levels. The correlation coefficient of blood glucose versus blood and plasma viscosity levels ranged from 0.59 to 0.49 ($P = 0.002$) and from 0.55 to 0.53 ($P = 0.0007$). Thus with an increase in the blood glucose level there is an increase in blood viscosity. However, this is a basal blood glucose level and is not an indication of a person's average blood glucose level, which is a more accurate representation of a person's glycaemic control [40].

A C Mellinghoff [41] investigated the influence of glycaemic control on viscosity and density of plasma and whole blood in Type 1 diabetic patients. The results showed a significant correlation between glycaemic control and blood viscosity.

Diabetic patients were divided into two groups, a group with good glycaemic control (HbA_{1c} = 7.1 +/- 0.6%) and a group with poor glycaemic control (HbA_{1c} = 8.7 +/- 0.7%). A positive correlation between the HbA_{1c} percentage and plasma

viscosity was found. A correlation coefficient r = 0.51 with a standard deviation P < 0.01 was calculated. An increase in plasma and whole blood viscosity as well as plasma density was found in the diabetic patient with poor glycaemic control as compared to well-controlled patients [41].

The effectiveness of a person's glycaemic control is represented by that person's HbA_{1c} percentage. The higher the HbA_{1c} percentage, the poorer was the glycaemic control - and the poorer the glycaemic control, the higher the plasma viscosity level [41].

Diabetics with poor glycaemic control had higher blood lipid levels compared to diabetics with good glycaemic control. The study illustrates that good glycaemic control can decrease a person's blood viscosity [41].

Blood lipids, especially triglycerides and HDL cholesterol, are known to have an effect on blood viscosity [39] [42] [43]. Triglycerides increase blood viscosity and HDL cholesterol decreases blood viscosity. In a study conducted by James H Stein *et al* [39], treatment of severe hypertriglyceridemia was accompanied by reductions in plasma and serum viscosity without changes in fibrinogen levels. Fibrinogen is a protein and a major determinant of plasma viscosity [39].

In the study, 26 patients with severe hypertriglyceridemia (> 5.66 mmol/l) were used. Fasting lipid, total serum protein, fibrinogen, plasma viscosity and serum viscosity levels were measured before and after therapy with 1200 mg/d of gemfibrozil a lipid-lowering drug.

Triglyceride levels decreased by 70% (P < 001). Mean plasma viscosity levels decreased by 5.2% (0.082 mPa/s P=0.003) and 6.1 % (0.086 mPa/s p = 0.013) respectively [39].

The data available did indicate that an increase in HbA_{1c} percentage increased the blood viscosity. Most of the data also indicated that diabetics with poor glycaemic control have high plasma viscosity levels [40] [41].

An increase in mean blood glucose causes the blood rheology to change. This effect is mostly indirect. An increase in mean blood glucose increases LDL cholesterol levels and decreases HDL cholesterol. This change in blood lipids increases the blood viscosity. An increase in blood viscosity changes the hemodynamic stresses on the arteries. This can cause arteriosclerotic lesion formation and ultimately CVD mortality [39] [40] [41].

5. THE CORRELATION BETWEEN BLOOD GLUCOSE AND THE CVD RISK FACTOR

5.1. Introduction

As previously discussed, blood glucose has numerous effects on blood lipids and blood viscosity. Blood lipids and blood viscosity play a big part in the initiation and formation of arteriosclerosis [10] [11]. Cohort studies, where the high mean blood glucose levels and high glycaemic load intake were compared to CVD mortality, show that there is an increased risk in CVD [10] [11] [15].

The epidemiologist studies populations to determine the relationships between behaviors and certain diseases. In this chapter the effect that blood glucose, especially mean blood glucose levels represented by HbA_{1c}, and glycaemic load intake has on CVD, was investigated.

5.2. Cohort studies of the relation between HbA_{1c} and CVD

In a study conducted by Irene Stratton *et al.* [9] the association of glycaemia with macro- and micro-vascular disease complications of Type 2 diabetes (UKPDS 35) was studied.

To assess the potential associations between updated mean HbA_{1c} and complications, the Proportional Hazard Regression (Cox) model was used. The Cox regression is used to model survival times. It is also called the Proportional Hazard model because it estimates the ratio of the risk (hazard ratio).

As in any regression model there are multiple predictor variables, and the outcome variable. The model assumes that the underlying hazard rate is a function of the independent variables and constant over time. There is no assumption of the shape

and nature of the underlying survival function.

Potential confounding risk factors included in the Cox model were gender, age, ethnic group, smoking at time of diagnosis of diabetes, and baseline high and low density lipoprotein cholesterol, triglyceride presence, and albuminuria measured after three months dietary treatment, and systolic blood pressure represented by the mean of measures at two and nine months after diagnosis [9].

The hazard ratio was used to estimate the relative risk. At each time the updated mean HbA_{1c} value for individuals with an event was compared with the updated value of those who had not had an event by that time [9].

The observational analysis showed highly significant associations between the developments of each of the complications of diabetes, including mortality, across the wide range of exposure to glycaemia that occurs in patients with Type 2 diabetes.

Each 1% reduction in HbA_{1c} percentage was associated with a 37% decrease in the risk of micro-vascular complications and a 21% decrease in any end point of death related to diabetes. The relation to macro-vascular disease was less steep. The relative risk for myocardial infarction, stroke and heart failure was reduced by 14%, 12% and 16%. All of the statistical findings are statistically significant [9].

The study indicated the following:

1. There is a direct relationship between the risk of complications of diabetes and glycaemia over time.

2. The lower the glycaemia, the lower the risk of complications.

The results indicate that the risk of CVD could be lowered with better blood glucose control.

In a study conducted by Beverly Balkau *et al* [18] the effect that high blood glucose concentration has on the risk factor for Coronary Heart disease (CHD) was investigated. They studied the 20-year mortality of non-diabetic working men, aged 44 to 45 years, in three European cohorts. These cohorts are the Whitehall Study in which 10,025 (n = 10,025) men participated, the Paris Prospective Study (n = 6,629) and the Helsinki Policemen Study (n = 631) [18].

These men were identified by their two-hour glucose levels following an oral glucose tolerance test and by the absence of a prior diagnosis of diabetes. Mortality was analysed according to the percentiles of the two-hour and fasting glucose distributions, using the Cox Proportional Hazard Model. In all these studies CHD was the major cause of death [18].

They found that the middle-aged non-diabetic men whose blood glucose distribution was in the upper 20% of the of the glucose distribution were at a significantly higher risk of early death in comparison to the lower 80%, with hazard ratios increasing with the glucose levels, reaching 1.4 (95% CI 1.1-1.6) for men in the upper 2.5% in this distribution after adjustment for risk factors [18]. The men in the upper 20% are associated with glucose intolerance and insulin resistance, the first signs of the onset of diabetes.

In a study conducted by Kay-Tee Khaw *et al* [10] the value of HbA_{1c} concentrations, a marker of blood glucose concentrations, as a predictor of death from cardiovascular disease and all causes in men was examined. The results clearly indicate that high levels of HbA_{1c} increase a person's risk factor of CVD. The results of the study are as follows:

In the study 4,662 men aged 45-79 years who had had HbA_{1c} measured at a baseline survey in 1995-7, were followed up to December 1999. Mortality from all causes was documented including CVD, ischaemic heart disease and other causes of death [10].

Figure 6.1 shows age-adjusted mortality by concentration of HbA_{1c} and self reported diabetes. Men with established or undiagnosed diabetes were at greater risk of

dying from all causes, cardiovascular disease or ischaemic heart disease compared with men without diabetes. Risk of death increased through the range of HbA_{1c} concentrations, with lowest rates in those with HbA_{1c} concentrations less than 5% and a gradient of increasing rates through the whole distribution [10].

In separate models, diabetes status significantly predicted death from all causes, cardiovascular disease and ischaemic heart disease, and HbA_{1c} concentrations predicted all causes, cardiovascular, ischaemic heart disease and non-cardiovascular mortality independently of age and known risk factors.

When diabetes status and HbA_{1c} concentrations were both included in the same model, diabetes no longer significantly independently predicted mortality. The increased risk of mortality in men with diabetes was largely mediated through HbA_{1c} concentration. An increase of 1% in HbA_{1c} percentage was associated with a 30% increase of all causes and a 40% increase of cardiovascular or ischaemic heart disease mortality [10].

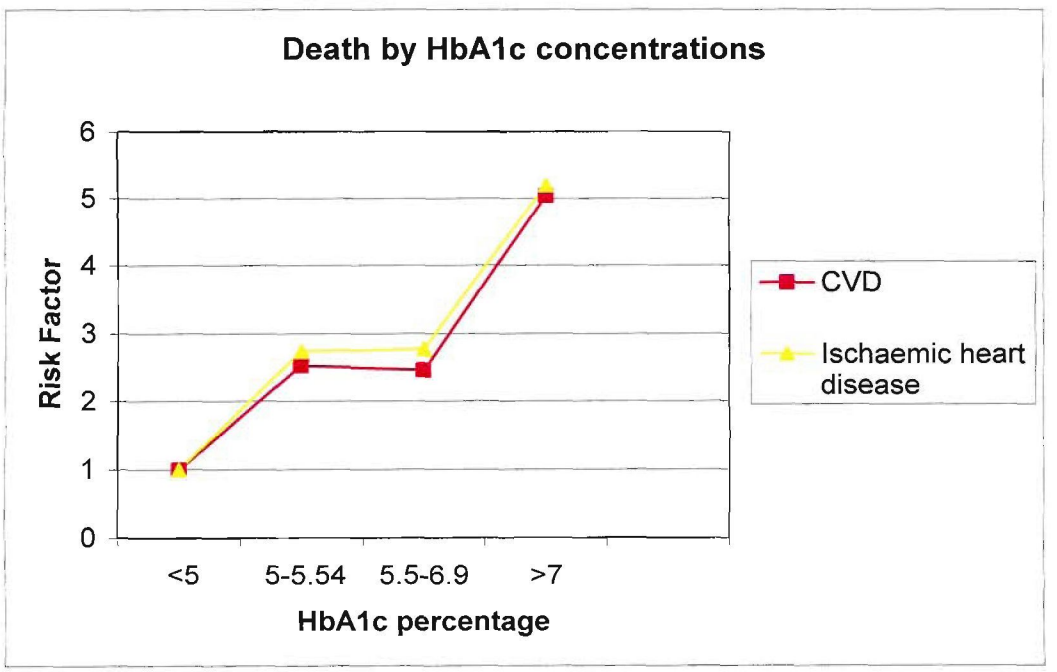

Figure 5.1: The relative risk for mortality associated with HbA_{1c} percentage.

Kay-Tee Khaw *et al* [10] findings indicate that HbA_{1c} concentration significantly predicted mortality, with increasing risk throughout the whole range of concentrations, even below the threshold commonly accepted for diagnosis of diabetes.

This effect was independent of known risk factors and consistent, after men with existing diabetes, heart disease and stroke were excluded. The HbA_{1c} percentage proves to be a stronger predictor of CVD and ischaemic heart disease than cholesterol, body mass index and blood pressure [10].

An increase of 40% in CVD and CHD risk is associated with a 1% increase in the HbA_{1c} percentage. Firstly, a blood glucose level must be obtained that is associated with a risk factor of unity. This means that a person's HbA_{1c} percentage has no effect on his risk factor of CVD. Kay Tee Khaw found that a value of 5% or less is associated with a risk factor of one. Thus, people who are able to keep their HbA_{1c} percentage lower or equal to 5%, have the lowest risk of dying of CVD according to their mean blood glucose level.

5.3. Cohort study investigating the effect of glycaemic load on CVD

In a study done by Simin Liu *et al* [15] the effect of dietary glycaemic load intake on coronary heart disease (CHD) was investigated. CHD is a macro-vascular disease and is responsible for most CVD deaths. In this study 75,521 women aged between 38 and 63 years with no previous diagnosis of diabetes mellitus, myocardial infarction, angina, stroke, or other cardiovascular diseases in 1984, were followed for 10 years [15].

Each participant's dietary glycaemic load was calculated as function of glycaemic index, carbohydrate content and frequency of intake of individual foods reported on a validated food frequency questionnaire at baseline. All dietary variables were updated in 1986 and 1990 [15].

The group was divided into five quintiles of increasing glycaemic load intake. The glycaemic load was calculated by using the GI value with white bread as reference source. During the 10 year follow up, 761 cases of CHD (208 fatal and 553 nonfatal) were documented. Dietary glycaemic load were directly associated with the risk of CHD after adjustment for age, smoking status, total energy intake and other CHD risk factors. The relative risk from the lowest to the highest quintiles of glycaemic load were 1.00, 1.01, 1.25, 1.51, and 1.98 (P-value < 0.0001). Carbohydrates classified by glycaemic index as opposed to their traditional classification as ether simple or complex, was a better predictor of CHD risk. The association of dietary glycaemic load and CHD risk was most evident among women with body weights above average.

These epidemiological data suggest that a high dietary glycaemic load from refined carbohydrates increases the risk of CHD, independent of known coronary disease risk factors.

5.4. Summary

Research indicates that the risk of CHD increases with high glycaemic index diets. These are associated with high blood glucose spikes and insulin levels and also increase triglyceride concentrations and decrease HDL cholesterol, both of which are associated with CVD risk.

A strong correlation also exists between a person's average blood glucose level, (which is represented by the HbA_{1c} percentage) and the risk of CVD. Some of these studies indicate that by reducing the mean blood glucose level, the risk factor of CVD can be reduced.

6. EQUIVALENT TEASPOON SUGAR (*ets*)

6.1. New concept Equivalent Teaspoon Sugar (ets)

Literature research shows that blood glucose control plays an important part in the fight against CVD [9] [44] [18]. Researchers at Human Sim (Pty) Ltd have introduced the Equivalent Teaspoon Sugar (*ets*) concept [61]. This concept can help people in general (healthy people and diabetics) to control their blood glucose levels.

Research shows that the risk of CVD can be reduced if carbohydrate intake is controlled and mean blood glucose levels are reduced [9] [10] [18] [15]. The reason for the development of the *ets* concept is simple. People interested in glycaemic response predictions require a means to compare any food, regardless of digestibility and portion size.

The *ets* concept is a universally applicable unit of measure for foods with a known glycaemic index (GI). It will not only reflect blood glucose response but will also take food portion into account. This means that quite literally apples can now be compared with pears, or cola with cranberry juice, both qualitatively and quantitatively [7].

6.2. Glycaemic Index

In essence the GI of a particular foodstuff relates to the glycaemic response (or rise and fall of blood sugar level) which is ingestion induced. Only foods that contain carbohydrates result in a significant rise in blood sugar levels in human beings. Neither pure protein nor pure fat has any substantial impact on blood glucose levels [45].

The glycaemic index of foods is therefore a ranking of foods based upon their short-term effect on blood sugar levels. To make a fair comparison, all foods are

compared with a reference food and are tested in equal carbohydrate amounts. The standard against which GI is measured is 50g of carbohydrate in the form of pure glucose. This "reference" amount is assigned the relative value of 100 [46].

The measurement procedure for GI is as follows: A healthy person is required to fast for at least six to ten hours prior to performing the test. This fasting ensures that any traces of glucose, and the effects of previous meals, are negligible.

The next step is to ingest the reference food (in this case glucose). 50g of pure glucose (usually diluted in water for easier consumption) is used. Over the next two hours, blood samples are taken at 15-minute intervals during the first hour, followed by two 30-minute intervals for the remaining hour. Blood sugar levels of the samples are measured in the laboratory and recorded. The result is a graph of blood sugar level plotted against elapsed time.

After a similar fasting period the procedure as described above is repeated. But, instead of ingesting pure glucose, the food, for which the GI is to be calculated, is eaten. The amount of food that has to be taken has to be the amount that contains exactly 50g of carbohydrate. (In the case of potatoes, for example, 250g of potatoes are required because that portion will yield 50g of carbohydrate). Again the blood sugar measurements are taken as described for the reference food.

GI is henceforth defined as the fractional relationship (percentage) between the glycaemic responses of the measured food and the reference food. To relate the responses the area under the curves (AUC) are calculated for each test and compared by dividing the AUC of the test food by the AUC of the reference food.

$$GI = \frac{AUC_{Food}}{AUC_{Reference}} \qquad (6.1)$$

The GI factors determined for different foods have been found to mostly yield repeatable values per individual and as such are useful indicators when selecting carbohydrate food for glycaemic control by people with blood glucose disorders such as diabetes.

The application of GI unfortunately presents a few problems. These include the following:

- GI alone does not provide a practical application platform for its use due to the fact that GI values in themselves cannot easily be quantitatively applied to meal planning. This problem persists because GI values are not related to food portion sizes. It is a property of the food, but not of the amount of the food.

- Many food manufacturers and producers oppose GI labelling of foods because many consumers perceive high GI values as negative and therefore undesirable. This fact creates a skewed image of certain foodstuffs because GI is not the only determining factor concerning blood sugar response due to the food. In many cases the amount of food consumed affects the glycaemic response more than the type of carbohydrate that is ingested.

  For example, a massive 1.3 kg of watermelon (containing only 8g of carbohydrate per 150g serving) has to be ingested to produce the same glycaemic response as 50g of glucose powder. Because of its relatively high GI value of 72, it can be perceived by some people that watermelon is "bad" to eat. But, since the carbohydrate content of watermelon is relatively small, a normal sized portion would produce totally acceptable blood sugar levels [46].

- GI values are based on average glycaemic responses measured in a number of different individuals. The problem is that there is often a significant variation

in the measurements between individuals. Average GI values calculated are regarded by many as unscientific and therefore have little to contribute to general dietary planning and management. The reasons for the variances are not yet described to scientific satisfaction and may be attributable to a host of metabolic and biochemical factors. However, the glycaemic response to GI-measured food yields acceptably repeatable results for individual test subjects.

Although generalised, GI values do provide some indication of relative variances to be expected when determining glycaemic response or energy utilisation in the human body. GI values therefore have a valid role to play in nutritional management. In the following sections, the specific role that GI can play will be discussed in more detail.

6.3. Glycaemic load

The glycaemic index received much criticism in the literature because of the limitations mentioned in section 6.2. In response to these negative comments, Brand Miller published an article to highlight the advantages of the index in an attempt to counter some of the criticism [47]. In her article she stated that: "It (GI) was never intended to be used in isolation". This comment was in response to a statement that GI should not be used due to the negative connotations linked to certain foodstuffs [47].

The amount of carbohydrate that was associated with those foods was not considered. For example, it might be perceived that cola, with a GI of 64, is "better" for human consumption (will induce a lower glycaemic response) than cranberry juice, with a GI of 75, because of the lower GI. Similarly people might want to eliminate carrots from their diets because of the extremely high GI of 93 [46].

However, common sense would argue that cranberry juice should be "healthier" than cola and that carrots cannot be "unhealthy" as the GI value indicates. The reason for this common misconception is that the amount of carbohydrates that are consumed in normal portions of the food is not taken into account when comparing the foods

[48]. GI is only applicable if foods are compared that contain equal amounts of carbohydrate.

Therefore, to relate foods with varying amounts of carbohydrate, Salmerón *et al* introduced a novel dietary variable termed "glycaemic load" [49]. The glycaemic load (GL) of a food is simply defined as the product of the glycaemic index (GI) of the food and the carbohydrate content of the portion that is considered (m_{CHO}). This calculation is shown in equation (6.2).

$$GL = GI.m_{CHO} \tag{6.2}$$

Consider a normal portion of carrots containing 5g of carbohydrate. The glycaemic load of the portion of carrots can be calculated with equation (6.2)

$$GL = GI.m_{CHO} = (93\%)(5) = 4.7\,.$$

Since the introduction of the glycaemic load concept many studies have been conducted to establish links between GL and diseases, abnormalities and health risks [50]. However, the concept has not yet publicly been accepted as the general criterion for ranking the "healthiness" of different foods. This might be due to the difficulty of having to memorise both GI values and carbohydrate content of foods.

In the next section a new approach is presented that is based on a similar argument as the glycaemic load. However, the new approach is aimed at ease-of-use, as well as accuracy of glycaemic prediction.

6.4. Energy extracted from ingested carbohydrates

Measurements with a bomb calorimeter suggest that energy of approximately 4 kCal/g can be released from carbohydrate when it is oxidised in pure oxygen. Obviously, the human energy system does not use the same process for energy

conversion as a bomb calorimeter. Intuitively it can be suspected that the body converts less energy from ingested carbohydrates than the optimum process.

However, a Type 1 diabetic has no insulin secretion and therefore must inject his insulin. If the diabetic does not inject insulin, his blood glucose level will rise until all the glucose energy has been converted into blood glucose energy. The level with which the diabetic's blood sugar will rise, will give a good measure of the amount of blood sugar energy that has been converted from ingested carbohydrates.

However, a series of empirical measurements, shown schematically in figure 6.1, illustrate a trend that is different from this expected result. Blood sugar response to glucose (and thus the conversion of glucose into blood sugar energy) is approximately four times more efficient than the response to fructose. The subsequent question is: How can the energy available after conversion for any other type of carbohydrate be calculated?

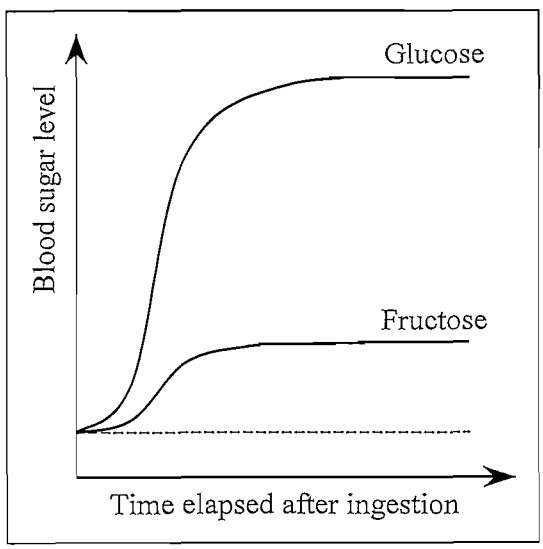

Figure 6.1: Schematic representation of actual measurements of blood sugar response when a Type 1 diabetic eats equal amounts of carbohydrate contained in glucose and fructose.

The Glycaemic Index (GI) of glucose, which is the reference food, is 100. This is approximately four times greater than that of fructose, which is only 23. Therefore GI

actually gives an indication of the energy conversion potential of the carbohydrates under investigation.

However, according to researchers [46] the definition of GI states that GI is the "rate of absorption" for a carbohydrate into the bloodstream. If this definition is correct, then measurements shown schematically in figure 6.2 would be expected. However, true empirical measurements (figure 6.1) contradict figure 6.2. Therefore a new definition of GI is proposed, namely that GI provides the "energy conversion potential" of carbohydrates.

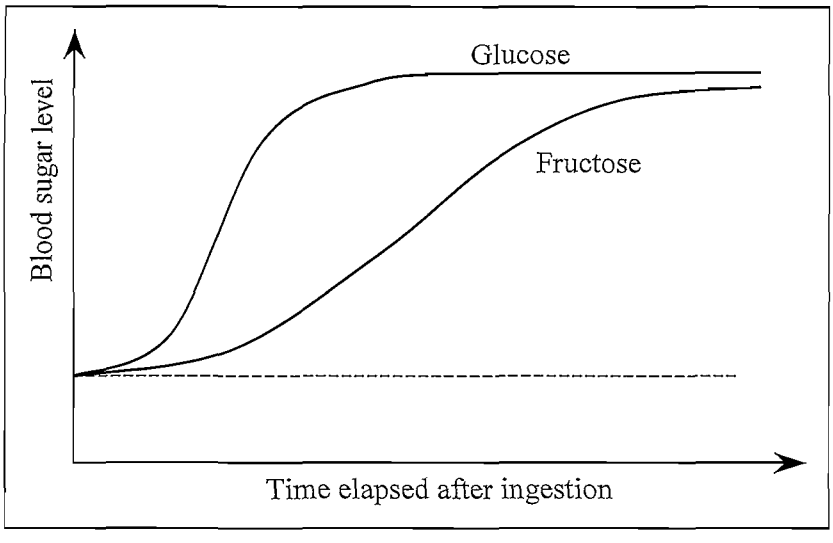

Figure 6.2: Schematic representation of expected blood glucose response if the correct definition of GI is "rate of digestion": Type 1 diabetic ingesting the same mass of carbohydrate through glucose and fructose.

6.5. *Important ets formulas*

In the *ets* concept, the amount of available blood sugar energy contained in a meal, is considered. It is assumed that only carbohydrates in a meal can provide blood sugar energy. This energy is then equal to the total amount of energy contained in the carbohydrates present in the meal (m_{CHO}) [7].

When measured in a laboratory with processes such as bomb calorimeters,

carbohydrates are found to release a certain maximum amount of energy per mass. This absolute amount of available energy is denoted as k_{CHO}. This is the same for all carbohydrates. k_{CHO} is 4 kCal/g. The total amount of available blood sugar energy from any meal (E_{CHO}) is then the total energy ($m_{CHO}\,k_{CHO}$) multiplied with the conversion potential (GI_{CHO}). This product is shown in equation (6.3):

$$E_{CHO} = GI_{CHO} m_{CHO} k_{CHO} \tag{6.3}$$

The next step is to relate the amount of energy from carbohydrates in a meal to equivalent teaspoon sugar (*ets*). One *ets* (one teaspoonful of cane sugar) contains 5 g of carbohydrates. In other words, the total amount of available energy from one *ets* is $5k_{CHO}$ kCal. Since the GI of sugar is 65, it follows from equation (6.3) that the energy that can be extracted from one teaspoon of cane sugar is [7]

$$E_{teaspoon\ \ sugar} = GI_{sugar} m_{teaspoon\ \ sugar} k_{CHO} = (65)(5)k_{CHO} = 325k_{CHO}\,. \tag{6.4}$$

Equivalent teaspoon sugar, or *ets*, is now defined as the fractional amount of blood sugar energy that can be extracted from any foodstuff, in relation to one teaspoonful of cane sugar, expressed in *ets*. This means that 1 teaspoon of sugar has 13 kCal available for the body to use. The equation for calculating the *ets* of any meal is

$$ets = \frac{E_{CHO}}{E_{teaspoon\ \ sugar}} = \frac{GI_{CHO} m_{CHO} k_{CHO}}{325k_{CHO}} = \frac{GI_{CHO} m_{CHO}}{325}\,. \tag{6.5}$$

Equation (6.5) can now be used to calculate the *ets* value for any food with a known GI value according to the portion size [7].

The reasoning behind the formulation of *ets* as a measure of carbohydrate intake is simple. People interested in glycaemic response prediction require a measure with which to relate any food, regardless of digestibility and portion size. By comparing foods with respect to the blood sugar energy they have available per portion, provides a practical and easy-to-use measure for any food containing carbohydrates

[7].

6.6. *The simulation model*

A simulation model was developed by Human-Sim (Pty) Ltd to simulate the body's blood glucose response. This model is known as the Diabetic Toolbox and is verified [7]. Verification of the Diabetic Toolbox was done by Human Sim (Pty) Ltd [7]. The following is a short description of how the existing simulation works and what alterations were made to calculate the mean blood glucose level of a person.

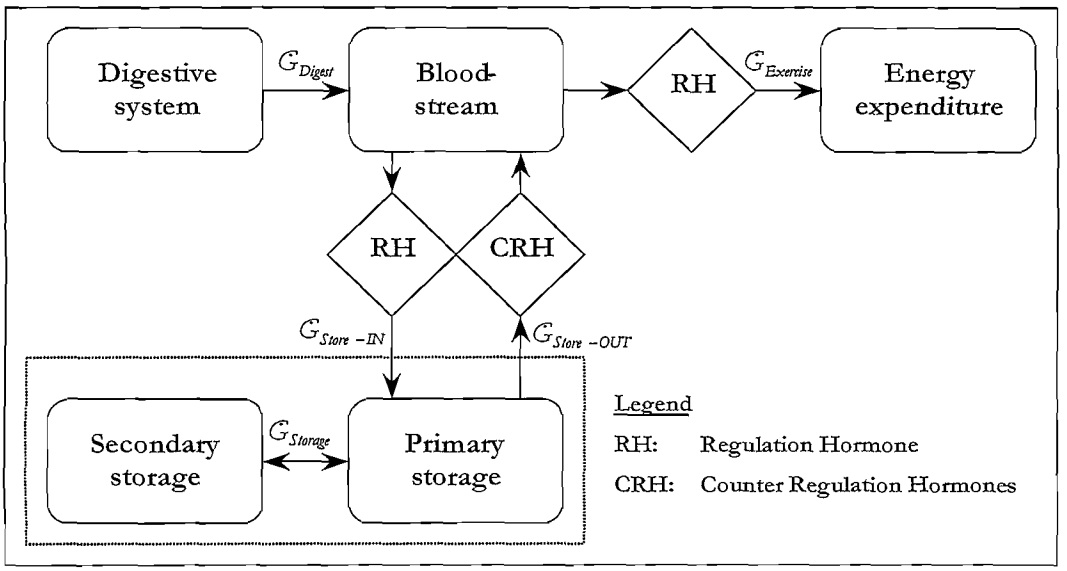

Figure 6.3: Schematic layout of the integrated human energy simulation model.

The simulation model is based on the flow of energy to and from the different components. As can be seen from the figure, glucose flows from the digestive system into the bloodstream ($\dot{G}_{Digest}$). From there it is either utilised in the energy expenditure component ($\dot{G}_{Exercise}$) or it is stored in the storage component ($\dot{G}_{Store-IN}$). This is a brief description of how the simulation model works [7].

However, the simulation model could not calculate the mean blood glucose levels needed to determine the HbA_{1c} percentage of a person. In order to do this minor

alterations had to be made.

6.7. Adapting the simulation model to calculate mean blood glucose

In order to determine the mean blood glucose levels through simulation, alterations had to be made to the bloodstream component. The bloodstream component model is a standard linear storage tank model with two energy in-flow and two energy out-flow connections.

It also makes provision for controller feedback connections. These feedback connections are necessary for the control system to determine what the current blood glucose concentration is at any given time step ($G_{Blood(t)}$). The bloodstream component is the model that contains the set point variable to which the main control system can then act and react.

To dynamically solve the amount of blood glucose energy in the bloodstream component at any given time step ($G_{Blood(t)}$), the total flow of glucose energy from the in- and out-flow connections are linearly added to the glucose amount of the previous time step ($G_{Blood(t-1)}$).

$$G_{Blood(t)} = G_{Blood(t-1)} + \left(\dot{G}_{Digest} + \dot{G}_{Store-Out} - \dot{G}_{Store-In} - \dot{G}_{Exercise}\right)_{(t)} \qquad (6.7)$$

In the equation the connections that add glucose to the bloodstream component are denoted as positive, while the connections that subtract glucose are marked as negative. Since *ets* is a good quantity for measuring energy, $G_{Blood(t)}$ is measured in *ets*. Similarly, *ets* is also used to quantify the flow of glucose energy ($\dot{G}$), and therefore the unit for measuring all the flows in Equation 6.7 is the time derivative of *ets*, i.e. *ets* /time.

To determine the mean blood glucose level, all the blood glucose values are counted

together. The total is then divided through the number of time steps thus giving the mean blood glucose level over a specific time. The mean blood glucose level is represented by equation 6.8.

$$G_{Blood(Average)} = G_{Blood(t=0)} + \sum_{time=0}^{time=t} \left(\dot{G}_{Digest} + \dot{G}_{Store-Out} - \dot{G}_{Store-In} - \dot{G}_{Exercise} \right) \qquad (6.8)$$

The average blood glucose level can be linked with HbA_{1c} percentage. In the literature study the mathematical correlation between HbA_{1c} percentages and mean blood glucose levels was established. Equation 4.1 on page 24 can be used to calculate the HbA_{1c} percentage if the mean blood glucose level is known.

The simulation model makes it possible to simulate the mean blood glucose level of a person. A large number of simulations can be run in succession, eliminating the need to do clinical tests on the blood glucose response of a person. This saves a lot of time and money.

6.8. *Ets and Kilocalories*

During exercise the muscles and brain need energy. Most of this energy comes from muscle glycogen and fat stores. This energy is not used in the blood glucose control process by the brain. Other sources of energy are liver glycogen or ingested food. This is the energy that is used to control your blood glucose level, supplying energy to the brain and restoring energy to the muscles.

Depending on the intensity and duration of the exercise, the required amount of energy needed for blood glucose control will vary. Thus, if a person does not eat during exercise, the liver alone will supply the needed blood glucose to control the blood glucose level.

As discussed in the previous section, the *ets* concept was originally based on the amount of energy that is available from ingested carbohydrates. This logic can now be extended further in order to express energy utilisation by the human energy

system in terms of *ets*. The conclusion is that the energy expenditure a person experiences during exercise can be directly related to the required amount of *ets* that has to be consumed.

The derivation of the equations leads to Equation 6.9

$$E_{Expended} = f_{Expended} ets \tag{6.9}$$

$E_{Expended}$ in the above equation is the total amount of energy expended during the endurance event and it is measured in KCal. It can be measured for any specific person participating in any specific event or an approximated value can be found from published exercise tables [61]. (Importantly, these tables are developed for the "average" athlete and do not account for the event fitness level of the specific person performing the exercise)

6.9. Summary

The *ets* concept is a new and novel concept developed by Human-Sim (Pty) Ltd. It provides a measure of the amount of glucose energy that can be extracted from ingested food. It differs from current methods of evaluating foods in that the *ets* concept is a function of both the amount of carbohydrate in the food (mass) as well as the coefficient of the absorption of the carbohydrate in the food. The simulation model proved to be useful for the simulation of blood glucose levels.

7. STUDY 1: DETERMINING THE LINK BETWEEN *ets* INTAKE AND CVD RISK FACTOR BY MEANS OF THE DIABETIC TOOLBOX

The cohort study done by Kay-Tee Khaw *et al* [10] indicates that a correlation exists between the HbA_{1c} percentage and CVD risk in diabetic patients. An increase in the HbA_{1c} percentage is a phenomenon which mostly occurs in diabetic patients. As mentioned, the HbA1c percentage resembles the mean blood glucose level of the last 8 to 12 weeks.

In order to create a link between *ets* intake and CVD, the simulation program Diabetic Toolbox, was used. The program was modified in order to calculate mean blood glucose levels with *ets* ingested. The mean blood glucose levels could be linked with the HbA_{1c} percentage. This made it possible to link *ets* intake with CVD risk.

7.1. Correlation between HbA_{1c} and CVD risk

Measured data obtained from Kay Thee Khaw *et al* [10] shows that there is an increase in CVD risk due an increase in HbA_{1c}. Figure 7.1 shows a 40% increase in CVD risk for every 1% increase in HbA_{1c} percentage.

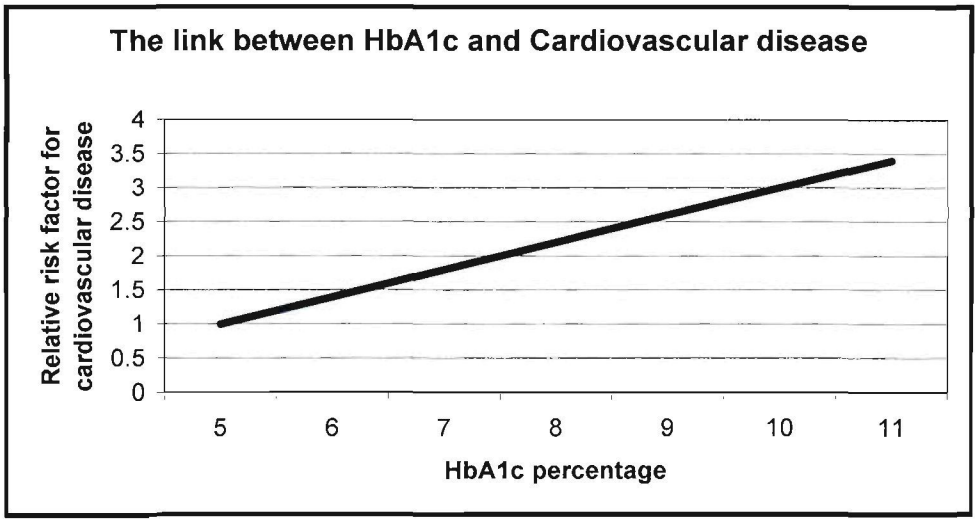

Figure 7.1: The link between HbA_{1c} percentage and CVD risk.

7.2. Correlation between mean blood glucose and HbA_{1c}

The literature study shows that a linear correlation exists between mean blood glucose levels and the HbA_{1c} percentage. Equation 4.1 is used to calculate the HbA_{1c} percentage from the mean blood glucose levels obtained by simulating the effect of *ets* intake.

7.3. Constraints used in simulation

To simulate the blood glucose response, a virtual character was created. The virtual character is characterised as a typical non-insulin dependent Type 2 diabetic. The characteristics of the character are represented in table 7.1.

Person	Typical Type 2 diabetic person
Age	40-50
Height	1.6-1.7
Weight	60-75
Normal activity	Low
Typical daily routine	Office
Diabetic status	Typical Type 2 Diabetic
Typical blood sugar distribution	Irregular
Recommended daily allowance (RDA)	1500 Kcal
RDA carbohydrates	50%
RDA protein	30%
RDA fat	20%
Exercise sessions	0
Number of full meals	3
Number of snacks taken	3
Blood glucose response	Scattered
Basal blood glucose level	7 mmol/l

Table 7.1: Characteristics of person used in simulation model

The energy intake of the person was based on an *ets* intake of 25 *ets* to 45 *ets*. The effect that *ets* intake has on the mean blood glucose levels was simulated. The reason for simulating an average Type 2 diabetic is:

1. The measured data obtained from Kay Thee Khaw represented the CVD risk factors for Type 2 diabetics with the HbA_{1c} percentage.

2. Healthy people do not have a significantly increased HbA_{1c} percentage because of their ability to store glucose more effectively than diabetics.

In the simulation a subject was given six evenly spaced meals per day; each containing approximately the same amount of *ets*. In order to keep the simulation as simple as possible, only the effect of pure sugar intake on the mean blood glucose level is simulated. This cancels out the effect any other foodstuff can have on the blood glucose level. Detailed results obtained from the simulations are given in

Appendix A.

7.4. Results obtained from the Diabetic Toolbox

An attempt was made to link *ets* intake with mean blood glucose levels in order to calculate the relative risk of CVD. The results obtained are discussed below.

The effect of different amounts of *ets,* ranging from 25 *ets* to 45 *ets,* was used to calculate the mean blood glucose levels. The reason for this range is that 25 *ets* represents a healthy amount of carbohydrate intake for such a person (60 kg). 42 *ets* represents the average American intake of *ets* for a person of average size. The amount of 45 *ets* is a realistic amount associated with a relatively high carbohydrate intake.

Figure 6.2 shows the increase in mean blood glucose with increasing *ets* consumption. The mean blood glucose of a Type 2 diabetic will increase because of their body's inability to effectively remove the blood glucose from the blood.

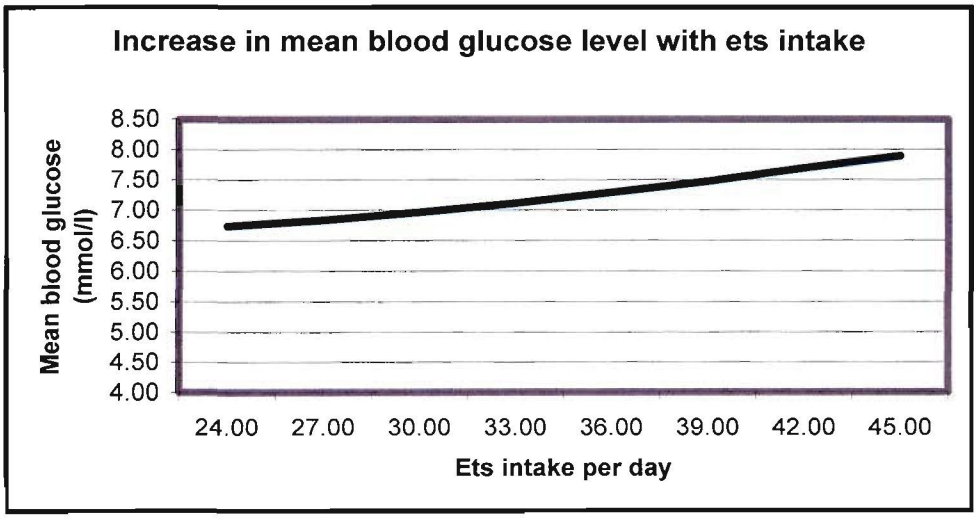

Figure 6.2: The effect of *ets* intake on mean blood glucose levels of a Type 2 diabetic as simulated by Diabetic Toolbox

The results indicate that there is an increase of 1.2 mmol in the mean blood glucose level with an intake of 21 *ets*. To place the amount of *ets* into context, 21 *ets* is equal to 2 soft drinks.

The Diabetic Toolbox can only calculate the mean average blood glucose for one day. To determine the HbA_{1c} percentage, the mean blood glucose level over a period of 8-12 weeks has to be calculated. To simplify this problem it is assumed that the same amount of *ets* will be consumed daily for a period of 8–12 weeks.

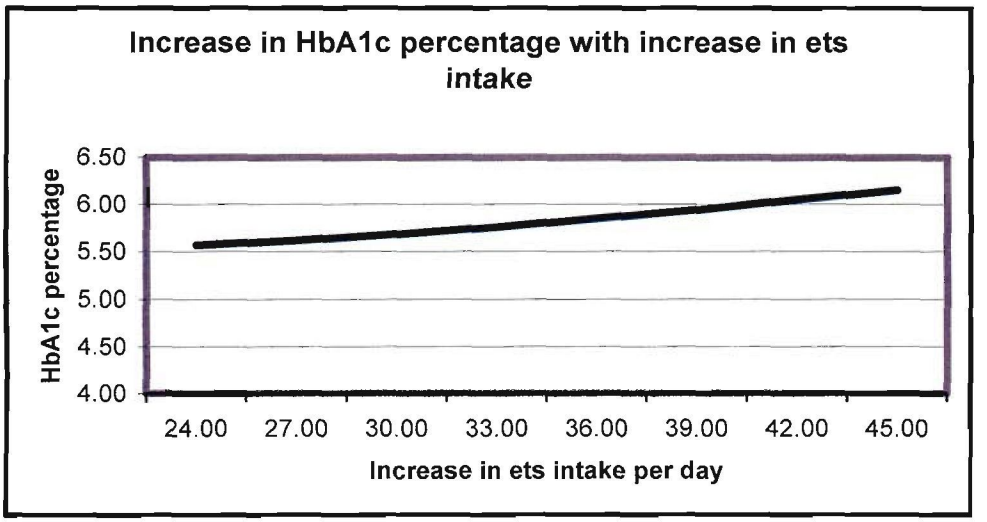

Figure 7.3: The effect of *ets* intake on HbA_{1c} levels of a Type 2 diabetic as simulated by Diabetic Toolbox

Figure 7.3 shows that the HbA_{1c} percentage increases 0.6 percent associated with an increased *ets* intake of 21 *ets*.

The relative risk factors associated with such an increase in the HbA_{1c} percentage show only a slight increase in the risk of CVD [10]. The increase in risk caused by increased *ets* intake is shown in figure 7.4. The results show an increase of 25 percent in the risk of CVD if the *ets* intake increases by 21 *ets*.

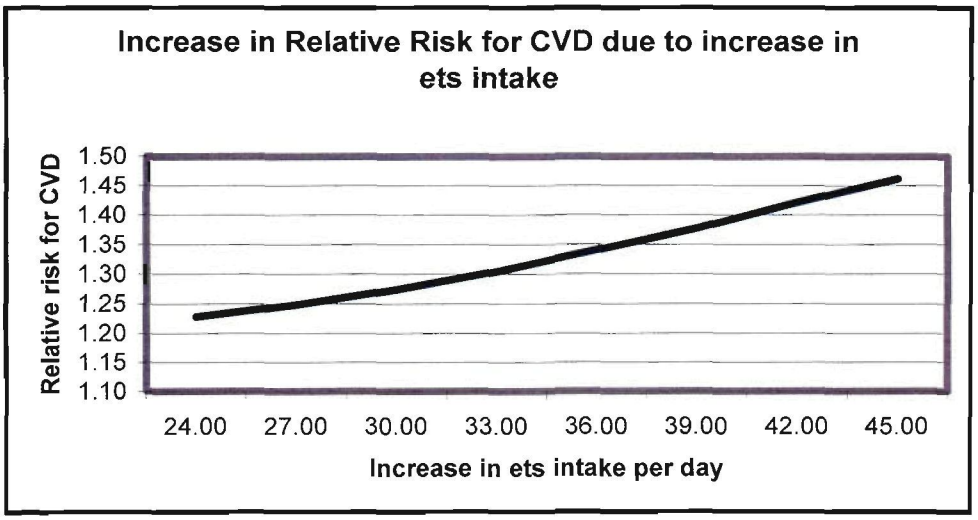

Figure 7.4: The link between *ets* intake and CVD for a person with Type 2 diabetes associated with HbA1c percentage.

The increase in the risk of CHD is far less than was expected. The amount of 21 *ets* for the size of the person simulated should have a greater effect on the risk of CVD. However, the simulation model showed a slight increase in the mean blood glucose level. The possible reasons for the low increase in the risk of CVD caused by increased *ets* intake are:

1. The CVD risk factors obtained from Kay Thee Khaw cohort study can be too conservative in the sense that the HbA_{1c} percentage can play a greater role in the risk factors of CVD.

2. Mean blood glucose levels are not affected in such a way as to increase the *risk of* CVD significantly due to *ets* intake.

3. Mean blood glucose levels are not accurate predictors of CVD risk. It is possible that the effect that mean blood glucose levels have on the risk factors, like blood lipids and blood viscosity, will be a better indication of the risk of CHD.

7.5. Summary

Ets intake correlates with mean blood glucose levels in that an increase in *ets* intake can increase the mean blood glucose levels of a person with diabetes. An increase in mean blood glucose levels does result in an increase in HbA_{1c} percentages. This increase in the HbA_{1c} percentage can be linked to an increase in the risk of CVD. The results show a slight increase in the risk of CVD. However, the increase is not significant enough to link *ets* intake with CVD risk factors.

Simulations were run to calculate the effect that stress and exercise have on mean blood glucose levels as well. The results obtained did show a change in mean blood glucose levels. However, this change in mean blood glucose levels was not significant enough to create a link between *ets* (blood glucose energy) and CVD. The results can be found in Appendices I.

The poor results obtained led to the formulation of study 2. Risk factors calculated from the effect that glycaemic load intake has on CHD risk for women, made it possible to link *ets* directly with CHD risk. The results showed a much better correlation between *ets* and CVD risk. This is discussed in Chapter 8.

8. STUDY 2: DETERMINING THE LINK BETWEEN *ets* INTAKE AND CVD RISK FACTORS, USING MEASURED RESULTS

In the study done by Simin Liu *et al* [15] the effect that glycaemic load intake has on CHD risk for women was investigated. A significant correlation exists between glycaemic load intake and CHD risk. The study is discussed in section 5.3.

Since glycemic load can be expressed by *ets*, the link between *ets* and CHD could be made. It is important to note that there is a difference between the definitions of the *ets* concept and glycaemic load as explained in section 6.4. Glycaemic load is derived from the glycemic index, which states that the glycaemic index is the rate of absorption of carbohydrates. The *ets* concept states the glycemic index is the conversion potential of carbohydrates.

This made it possible to create a link between the energy percentage obtained from carbohydrates compared to the total energy intake, and CHD risk. The methods used to create the link between *ets* and CHD are explained thoroughly in this chapter. Measured data obtained from Simin Liu *et al* was taken from healthy women, and not from diabetics. This made it possible to link *ets* with CVD in a much broader spectrum of people.

8.1. Energy intake from carbohydrates and CHD risk

Measured data obtained from Simin Liu *et al* is given in table 8.1 [15].

Quintile	1	2	3	4	5
Glycaemic load	117	145	161	177	206
Total energy intake (KJ)	7113	7453	7515	7386	7005
Glycaemic Index	72	75	77	78	80
Total carbohydrate (g)	161	191	207	222	249
Total fat (g)	67	64	61	56	50
Total protein (g)	79	75	72	68	62
Relative Risk of CHD	1	1	1.25	1.51	1.98

Table 8.1: Data from Simin Liu *et al* indicating the dietary data obtained from participants.

Table 8.1 is divided into 5 quintiles associated with increase in glycaemic load intake. The table shows the food intake (carbohydrates, fat and protein), energy intake (KJ) glycaemic load intake and GI associated with each quintile. The comparative risk factors of CHD are also given for each quintile.

Table 8.1 shows that the total energy intake per quintile does not increase significantly. It is also shown that the carbohydrate intake, glycaemic index, and glycaemic load increases per quintile. This means that the amount of energy obtained from carbohydrates increases per quintile, compared to the total energy intake. This increase in energy obtained from carbohydrates, increases the risk of CHD.

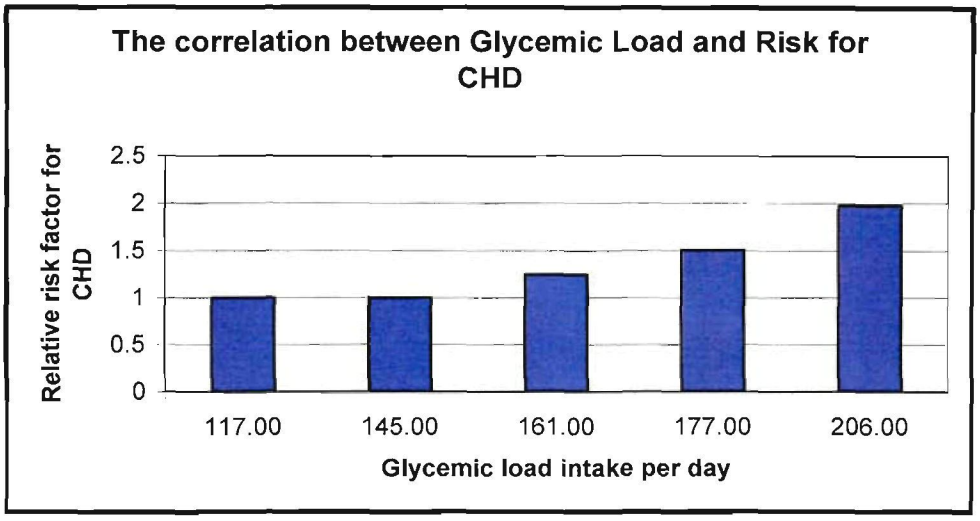

Figure 8.1: The correlation between glycaemic load intake and the risk of CHD.

Figure 8.1 illustrates a positive correlation between glycaemic load intake and the risk of CHD. The figure indicates that the risk of CHD increases if the glycaemic load exceeds an amount of 145. A glycaemic load intake of 206 could double the risk of CHD.

The data is obtained from measurements taken from 75,521 women. The measured data show the average values of each variable in each quintile. Therefore, it is assumed that in a woman of average size, the risk of CHD will increase if her glycaemic load intake exceeds an amount of 145. A larger than average woman will need more energy and will have a higher RDA. Such a woman will be able to ingest a higher glycaemic load in order to have the same relative risk of CHD.

Since the risk factors of CHD are calculated from measured data taken from 75,521 women, the calculations in this section will be based on women of average size.

8.2. Expressing glycaemic load as ets

To express glycaemic load as *ets* the following calculations had to be done. White

bread has a lower GI value than pure glucose. The *ets* concept is derived from GI, using pure glucose as reference source. The association between GI obtained from white bread and GI obtained from pure glucose is given by equation (8.1). Glucose has a GI value of 140 compared to white bread.

$$GI_{glucose} = \frac{GI_{whitebread}}{1.4} \qquad (8.1)$$

Equation (8.1) is used to determine the glycaemic load with pure glucose as reference source. Values obtained from the first quintile of table 8.1 are used to demonstrate the following calculations.

$$GI_{glucose} = \frac{72}{1.4} = 51.4$$

$$GL_{glucose} = \frac{117}{1.4} = 83.57$$

Now that the GI and GL with glucose as reference is available the amount of *ets* consumed daily can be calculated. In chapter 4 the *ets* concept was explained along with the derivation of important *ets* formulas. Equation (4.5) is used to calculate the amount of *ets* associated with glycaemic load.

$$ets = \frac{GI_{CHO} m_{CHO}}{325} = \frac{83.57 * 100}{325} = 25.71$$

The results of the calculation are given in table 8.2.

Quintiles	1	2	3	4	5
GI based on glucose as reference	51.4	53.6	55	55.71	57.17
GL based on glucose reference	83.57	103.57	115	126.43	147.14
Ets	25.71	31.87	35.38	38.90	45.27
Relative risk of CHD	1	1	1.25	1.51	1.98

Table 8.2: The converted glycaemic index and glycaemic load values with glucose as reference source.

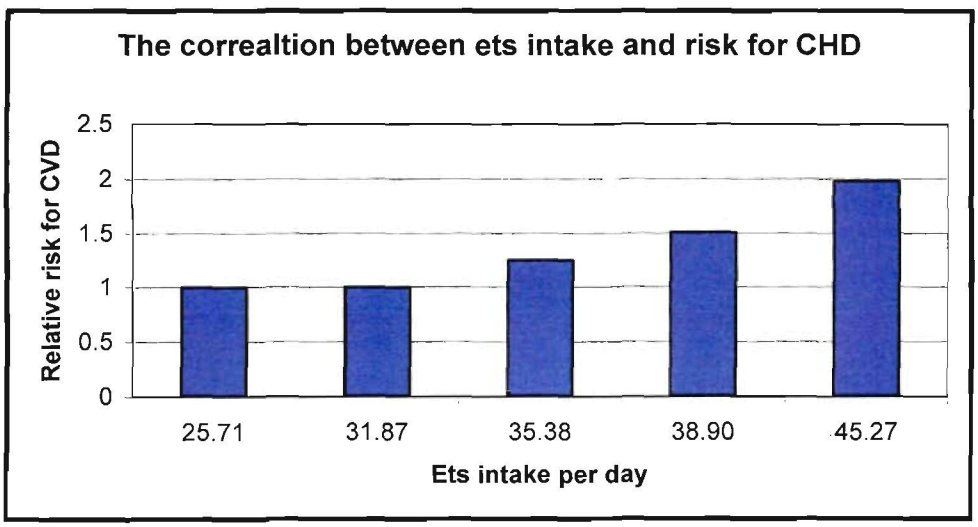

Figure 8.2: The correlation between *ets* intake and risk of CVD associated with glycaemic load intake.

Figure 8.2 shows that there is a positive correlation between the increase in *ets* intake and the risk of CHD, if the *ets* intake exceeds 31.87 *ets*. An *ets* intake of 45 *ets* is associated with a risk factor of 2. This is a significant increase in the risk of CHD. Thus the more energy consumed above a certain amount in carbohydrates (32 *ets*), the higher the risk of CVD will become.

Upon further investigation of the cohort study done by Simin Liu *et al* [15], the following correlations were discovered. In table 8.2 the total amount of energy consumed in each quintile is given. In order to determine the usable amount of energy obtained from carbohydrates compared to the total energy intake, the

following steps had to be followed:

The values from quintile 1 in table 8.2 are used to demonstrate the following calculations. The total energy intake in quintile 1 is 7113 KJ. If converted into KCal an amount of 1701 KCal is obtained. Measured data in quintile 1 show that an average amount of food equal to 1701 KCal is consumed per day.

If it is assumed that all the energy available in carbohydrates (4 KCal per g) can be absorbed by the human-body, then the following calculations show the amount of energy in carbohydrates. The amount of carbohydrate consumed can be obtained in table 8.1. Thus the KCal obtained from 161g of carbohydrate is

$$161gCHO = 644KCal$$

The energy percentage obtained from carbohydrates compared to the total amount of energy intake is:

$$\%CHO_{energy} = \frac{644KCal}{1701KCal}$$

$$\%CHO_{energy} = 38\%$$

However, true empirical measurements contradict this. The *ets* concept indicates that there is less available energy in carbohydrates than previously thought. *Ets* represents the energy conversion potential of carbohydrates. By using measured data obtained from Simin Liu *et al* [15] the amount of *ets* consumed per quintile was calculated as shown in table 8.2. Since one *ets* contains an amount of 13 KCal of blood glucose energy, the true amount of available energy associated with each quintile can now be calculated. Data obtained from the first quintile is used do demonstrate the calculations.

$$E_{CHO} = ets * 13KCal = 25.71 * 13KCal = 334KCal$$

It is now possible to calculate the correct percentage of energy obtained from

carbohydrates as shown in the next calculations:

$$\%CHO_{energy} = \frac{334KCal}{1701KCal}$$

$$\%CHO_{energy} = 19\%$$

If the same amount of carbohydrate is consumed but with different GI values, the carbohydrate with the lowest GI value will have a lower *ets* value, and thus a lower potential energy value compared to the carbohydrate with a high GI value. The results obtained from the calculations are given in table 8.3. The table also shows the relative risk factors of CHD associated with the amount of energy obtained from carbohydrates and the percentage of energy obtained from carbohydrates compared to total energy intake.

Quintile	1	2	3	4	5
Energy *ets (KCal)*	334.29	414.29	460.00	505.71	588.57
Percentage Carbohydrate composition	19.64	23.24	25.59	28.62	35.12
Relative Risk of CHD	1	1	1.25	1.51	1.98

Table 8.3: Results showing the usable carbohydrate energy intake calculated using the *ets* method, percentage energy obtained from carbohydrates and the relative risk factor of CVD associated with each quintile.

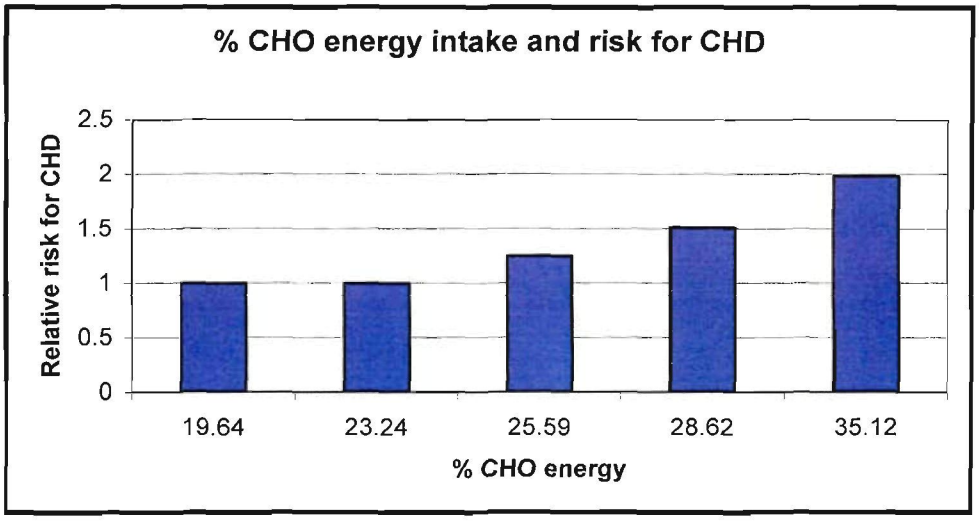

Figure 8.3: The correlation between percentage carbohydrate energy (obtained from total dietary intake) and risk for CHD.

The results shown in figure 8.3 indicate that as soon as the energy obtained from carbohydrates exceeds 23.24% of total energy intake, the risk of CHD increases.

Research shows that the brain needs approximately 20% of the total metabolism of the body [33]. The brain uses blood glucose as an energy source. As discussed in section 4.1, most carbohydrates are converted into blood glucose when digested.

If the percentage of energy obtained from carbohydrates is between 19% and 23% as calculated with the *ets* method, the relative risk of CHD is kept to a minimum. This is equal to the amount of energy needed by the brain. If the percentage of energy obtained from carbohydrates increases above 23% the risk of CHD increases. A percentage of energy intake from carbohydrates of 35% could double a person's risk of CHD as shown in figure 8.3. In other words, the energy obtained from carbohydrates needs only to supply the brain with energy. If the amount of energy obtained from carbohydrates supplies more energy than needed by the brain, a person can increase his/her risk of CHD.

However, it is important to note that if the carbohydrate intake is kept to a bare minimum, or completely removed from a person's diet, complications can occur.

Diets containing mostly proteins and fats can cause complications such as heart arrhythmias, cardiac contractile function impairment, sudden death, osteoporosis, kidney damage, increased cancer risk, impairment of physical activities and lipid abnormalities.

8.3. Determining the healthy ets intake for a specific person

Section 8.2 illustrates that the ideal carbohydrate energy makes up 20% of a person's total energy intake. The literature shows that a person's RDA is the ideal amount of energy intake for that person. One *ets* contains an amount of 13 KCal of useful energy. Using this information, the following algorithm can be constructed that will indicate the ideal *ets* intake for a specific person if that person's RDA is known.

$$ets_{\text{int ake}} = \frac{RDA * 0.2}{13} \qquad (8.2)$$

The RDA of a person is dependent on body mass and is easily obtainable in most diet-related literature.

8.4. Summary

The research study shows that a strong correlation exists between blood glucose levels and CVD. Some studies suggest that even a modest reduction in hyperglycaemia has the potential to prevent deaths from CVD [3] [52] [8]. A correlation exists between carbohydrate intake and CHD [15].

Measured data obtained from Simin Liu *et al* clearly shows that the CHD risk increases with an increase in glycaemic load intake. Through using measured data obtained from Simin Liu *et al* [15], the link between *ets* intake and CHD was made. The *ets* concept was used to calculate the percentage of energy obtained from carbohydrate intake, compared to total energy intake. The percentage of

energy consumed in carbohydrates also correlates with an increase in CHD. It seems that if the amount of glucose energy consumed exceeds the amount of energy needed by the brain the risk factor of CHD increases.

9. *ETS*-STRESSED AND CVD RISK

It is a well-known fact that long-term stress has a negative effect on a person's health, especially in their cardiovascular health. Numerous studies indicate the relationship between stress, depression and cardiovascular disease [52] [57]. The risk associated with an increase in blood glucose levels caused by stress was investigated. The results obtained are given in this section.

9.1. CVD and stress

In a prospective cohort study of industrial employees conducted by Mika Kivimaki *et al* [57] the relationship between work stress and cardiovascular mortality was established [57]. To determine the relative risk factors of CVD mortality the Cox Proportional Hazard Model was used.

The study showed that employees with high job stress had a twofold higher risk of CVD mortality than their colleagues scoring low in these dimensions. These stress situations stretch over a long period of time and are known as long-term stress situations. Table 9.1 shows the relative risk associated with work stress [57].

Characteristic	Hazard ratio (relative risk) of CVD mortality
Jobs stress: Low	1
Intermediate	1.53
High	2.2

Table 9.1: Hazard ratios for cardiovascular mortality by levels of work characteristics adjusted for age and sex.

The results in table 9.1 show that there is a drastic increase in CVD risk with an increase in stress. The results were adjusted for age and sex.

In a review article by David Eric *et al* [62] different prospective studies were investigated, showing the effect that depression has on the risk factors of numerous cardiovascular diseases. Their findings indicate very clearly that depression significantly increases the risk of cardiovascular diseases. Table 9.2 gives the calculated results obtained from the prospective studies, showing the relative risks associated with the cardiovascular diseases.

Authors	Year	No of Patients	Findings
Frasure-Smith *et al*	1993	222	Adjusted HR for death: 4.29
Anda *et al*	1993	2 832	Adjusted RR for cardiac death: 1.5
Ladwig *et al*	1994	377	Unadjusted RR for follow-up angina: 3.12
Aromaa *et al*	1994	5 355	RR for MI in men: 2.62, RR for MI in women 1.90
Ford *et al*	1998	1 190	RR of CHD: 2.12, RR for MI: 2.12
Ferketich *et al*	2000	7 893	Adjusted RR of CHD in women: 1.73, Adjusted RR *of CHD* in men: 1.71, Adjusted RR CHD death in men: 2.34
Penninx *et al*	2001	2 397	RR for cardiac death with major depression: 3.0, RR for cardiac death with minor depression: 1.6
HR = hazard ratio, RR = relative risk, CHD = coronary heart disease, MI = myocardial infarction			

Table 9.2: Depression as a risk factor for cardiac disease.

Table 9.2 shows that depression more than doubles the risk of CHD and other cardiac diseases. In some cases severe depression more than triples the risk of CHD and cardiac death.

9.2. The correlation between stress and ets

Stress triggers the counter regulation system to secrete hormones that both raise the blood glucose concentration as well as impairing insulin action [58]. Depression is a form of stress and thus also increases blood glucose levels. The higher blood glucose levels also have a negative effect on general well-being and health, as discussed in previous sections [59].

With empirical measurements and simulations it was found that the effect stress has on blood sugar levels can be approximated with a similar effect as that of ingested carbohydrates. In other words, if a person experiences stress, the blood glucose energy will increase as if the person has ingested *ets*. This is the reason why *ets*-stressed can be viewed as additional *ets* intake.

Table 9.3 shows the equivalent amount of *ets-stressed* by a woman of average size (± 60 kg) as a result of low, moderate, high and severe stress levels.

Variables	**Quintile 2 basis**	**Low Stress**	**Moderate Stress**	**High Stress**	**Severe Stress**
Ets secreted per hour	0	0	0.4	0.6	1.5
Ets secreted per day	0	0	9.6	14	36

Table 9.3: Increase risk of CVD associated with increase in blood glucose due to stress.

The higher the stress level the more blood glucose energy will be available in the blood. As discussed, this increase in blood glucose energy can be represented by an equivalent amount of *ets*.

9.3. Ets-stressed and CVD

Simin Liu *et al* illustrated the effect of increased *ets* intake on the risk of CHD. If *ets-stressed* is viewed as additional *ets* intake, *ets-stressed* can increase the risk of CHD.

In order to calculate the relative risk of CHD caused by *ets*-stressed the following steps were followed. Using measured data obtained from Simin Liu *et al* [15] the average amount of *ets* intake of 75,521 women was calculated. This amounted to a value of 35 *ets*. In section 9.2 the values for *ets-stressed* are given.

The sum of *ets-stressed* and the average *ets* intake was calculated. This increase in blood glucose energy (*ets*) caused by stress is compared to the relative risk factors obtained by Simin Liu *et al* associated with increased *ets* intake. This made it possible to calculate the risk factors associated with *ets-stressed*. The relative risk factors associated with *ets-stressed* is given in table 9.4.

Variables	Quintile 2 basis	Low Stress	Moderate Stress	High Stress
Ets-stressed per day.	0	Not measured	9.6	14
Sum of average *ets* intake and *ets-stressed.*	35	Not measured	44.6	49
Relative risk associated with sum of *ets-stressed* and average *ets* intake.	1.23	Not measured	1.93	2.25
Relative risk of CHD associated with *ets-stressed.*	1	Not measured	1.57	1.84

Table 9.4: Increase in risk of CHD caused by *ets-stressed.*

Table 9.4 shows that the increase in blood glucose energy caused by stress will result in an increased risk of CHD. Low stress situations will have little effect on the risk of CHD while high stress situations typically caused by high job stress situations can almost double the risk of CHD.

The table only indicates an increase in the risk of CHD associated with moderate and high stress situations. There is no risk factor associated with *ets-stressed* in severe stress situations. The reason is that the risk factors obtained from Simin Liu *et al* [15] did not measure the effect of such a high *ets* intake on the risk of CHD. There is no measured data available to link such a high amount of additional blood glucose energy caused by stress, with CHD risk factors.

However, the risk of CHD shows a linear regression with increased *ets* intake. It is possible to estimate the risk associated with the increase in blood glucose energy caused by severe stress. If an amount of 36 *ets* is stressed, the relative risk factor associated with this increase in blood glucose will be of the order

of 3.6. This is only an estimation and is not obtained from measured results.

The results obtained are associated with a woman of average size since the risk factors obtained from Simin Liu *et al* represents the effect of blood glucose energy on women.

9.4. The comparison between risk factors obtained from ets-stressed and risk factors obtained from prospective studies

Research shows that prospective studies found similar risk factors of CVD and CHD. The reason is that CHD is the number one cause of death for cardiovascular disease. In this section the relative risk factors of CHD associated with *ets-stressed* is compared to risk factors for cardiovascular diseases associated with stress and depression.

The increase in relative risk of CHD caused by *ets-stressed,* correlates remarkably well with the risk factor of CVD obtained by Mika Kivimaki *et al* [57] for different stress levels. The study by Mika Kivimaki *et al* [57] showed a risk factor of 1.5 for intermediate work stress and a risk factor of 2.2 for high work stress. The relative risk factor associated with *ets-stressed* caused by intermediate stress is 1.5 and that of high stress is 1.8. The comparison of the results is given in figure 9.1.

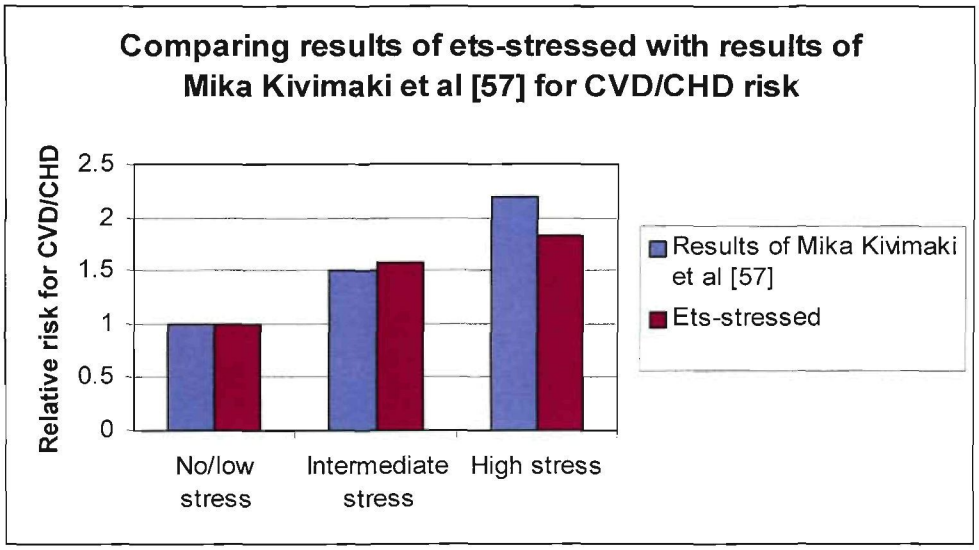

Figure 9.1 CHD risk caused by *ets*-stressed compared to CVD risk factors obtained by Mika Kivimaki *et al.*

The results also correlate remarkably well with the CVD risk factors associated with depression. Table 9.2 show that most of the risk factors associated with depression are between 1.5 and 3. This is in the same order as the results obtained from calculating the relative risk associated with an increase in blood glucose energy.

As explained in section 9.3, the effect of severe stress on CHD risk could not be calculated accurately because of the lack of measured data. However, it is estimated that the increase in blood glucose energy caused by severe stress could increase the risk of CHD to a risk factor of 3.6. If this is taken into account the increase in risk caused by *ets*-stressed correlates with risk factors obtained from different cohort studies. The prospective study conducted by Pennix *et al* calculated a risk factor of 3 associated with severe depression.

The close correlation between risk factors obtained from *ets-stressed* and prospective studies is a strong indication that additional blood glucose energy available in the bloodstream during stressful periods can indeed be one of the major causes of CVD.

9.5. Summary

Stress is known to increase the risk of CVD. In our modern, high paced world stress is known to be a killer and is especially associated with coronary heart disease.

Stress is known to increase the blood glucose level of the person. The risk factors found by associating stress with an increase in blood glucose energy were similar to those obtained from prospective studies which measured the effect of stress on the incidence of cardiac diseases.

This section shows that the effect that stress has on the blood glucose level can play a big part in the formation of CVD. This study verifies the fact that blood glucose does play an important part in the formation of CVD.

10. *ETS-EXPENDED* DURING EXERCISE AND CVD RISK

10.1. Introduction

Through research, measured data linking exercise with CVD risk was obtained. The data shows a correlation between calories expended in exercise and the reduction in risk of CVD. Research done by Human-Sim (Pty) Ltd shows that there is a link between *ets-expended* during exercise and KCal expended during exercise. Thus the link between *ets-expended* during exercise and the risk of CVD could be made.

10.2. Exercise and the risk of CHD

Physical inactivity doubles the risk of developing heart disease, Type 2 diabetes and obesity. Physical inactivity doubles the risk of dying from CVD and stroke [36] [53].

Physical activity helps control weight and reduces stress, anxiety and feeling of depression, risk factors of CVD, increases HDL cholesterol and lowers triglycerides. Moderate activity such as brisk walking for 30 to 60 minutes a day most days of the week, is associated with a significant reduction in the incidence of mortality in CVD [36] [53] [54].

Most metabolic studies found that exercise has a significant effect on glucose control and triglyceride levels. A meta-analysis of clinical trials on the effects of exercise on glucose control, found that interventions longer than eight weeks reduced the HbA_{1c} percentage from 8.31% to 7.65% in Type 2 diabetic patients. These findings are statistically significant with P-value of 0.001. By reducing the mean blood glucose level (HbA_{1c} percentage) the risk of CVD will also be reduced in diabetic patients [10] [55].

A person always expends some energy, even when asleep. A person of average size, weighing 70 kg, will expend 1,600 KCal if that person stays in bed for 24 hours. This is known as the basal metabolism [33] [51]. Energy expenditure can range from 1.2 KCal per minute during rest to 20 KCal during vigorous exercise. Physical activity has the greatest effect on energy expenditure.

In the fasted state, fat, including plasma-free fatty acids and muscle triglyceride, is the predominant source of energy during light and moderate levels of exercise intensity. At higher levels of intensity, carbohydrates in the form of muscle glycogen and blood glucose become the major fuel.

In a study conducted by Paffenbarger and associates [53] [56] the influence that activity, vigorous activity, and sports have on cardiovascular death was studied.

The study compares the relative risk ratios of people who were sedentary (less than 1,000 calories expended per week), those who were moderately active (1,000 – 2,500 calories per week) and those who were highly active (more than 2,500 calories per week). Table 10.1 gives the relative risk factors associated with the amount of calories used in exercise per week.

Amount of calories	Relative risk factor of CHD
Less than 1,000 calories per week	1
1,000 to 2,500 calories per week	0.71 (40%)
More than 2,500 calories per week	0.54 (85%)

Table 10.1: Relative risk factor associated with CVD compared to amount of calories exercised per week.

Thus, moderate activity yielded a 41% reduction in risk and high levels of activity yielded an 85% reduction as indicated in table 10.1. The study indicates that if activity continues on a continual basis, the relative risk for coronary heart disease will decrease.

Table 10.1 shows the correlation between CHD risk and KCal expended in exercise. In section 6.8 the link between KCal expended in exercise and *ets* is explained. Since KCal expended can be linked with reduction in the risk of CHD, *ets-expended* during exercise can be linked with a reduction in the risk of CHD. The link between *ets-exercised*, and the risk of CHD is given in table 10.2.

Ets	**Amount of calories**	**Risk of CHD**
Less than 16 *ets* per week	Less than 1,000 calories per week	1
16 to 42 *ets* per week	1,000 to 2,500 calories per week	0.79
More than 42 *ets* per week	More than 2,500 calories per week	0.54

Table 10.2: The link between *ets-expended* during exercise and risk of CHD.

The data in table 10.2 show that if the amount of *ets-expended* during exercise increases, the relative risk factor of CHD decreases.

10.3. Correlation between blood glucose energy expended and blood glucose energy intake.

In this section the effect of additional *ets* intake on the risk of CHD is compared to the effect *ets-expended* has on CHD risk in order to illustrate the improvement in cardiovascular health resulting from increased activity.

Data obtained from Simin Liu *et al* were used to calculate the relative risk of CHD associated with increased *ets* intake. The relative risk of CHD associated with the increase in additional *ets* intake is discussed in the previous chapter. The results are illustrated in figure 10.1. The figure shows an increase in the risk with an increase in *ets* (blood glucose energy). An additional *ets* intake of 14 *ets* is associated with an 85% increase in the risk of CHD.

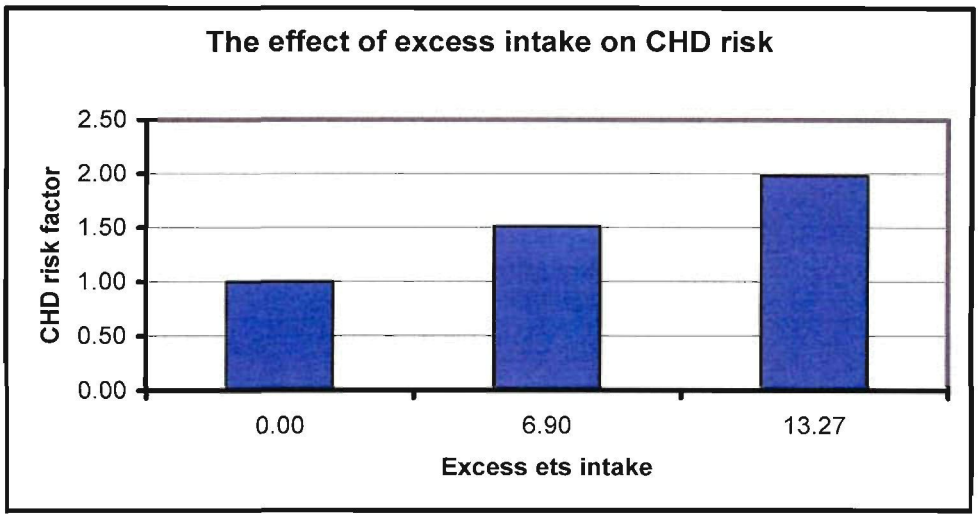

Figure 10.1: Increase in CHD risk caused by an increase in (excess) *ets* intake

During exercise blood glucose energy is used. This decrease in blood glucose energy is quantified by *ets*. The *ets-expended* during exercise is linked with a decrease in CHD risk as shown in figure 10.2.

If a person expends of the order of 6 *ets* per day with exercise that person will reduce his risk of CHD by 85%.

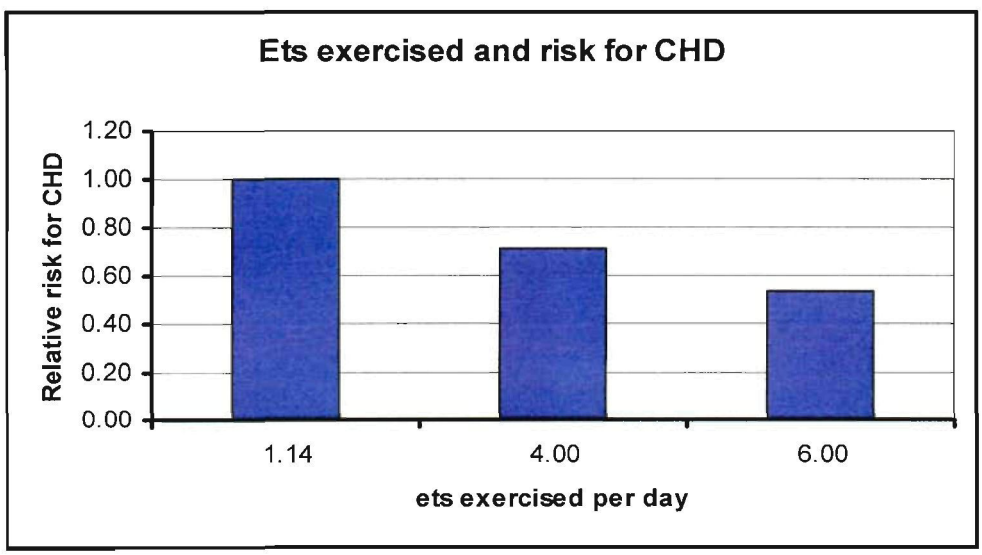

Figure 10.2: CHD risk factor associated with *ets* expended in exercise.

Figure 10.1 and 10.2 show that *ets* expended during exercise has more than double the effect in reducing the risk of CHD than that which increased *ets* intake has on increasing the risk of CVD. If viewed from an energy-balanced point of view, one will think that energy expended must equal energy intake, in order to obtain the same magnitude of CHD risk factors. However, the results show that *ets-expended* during exercise **decreases** the risk factor by a factor of two compared to the effect that *ets* intake has on **increasing** the risk factor.

The reason why *ets-expended* is more effective in reducing the risk of CHD is that physical activities change physiological aspects of the human body. One of the effects of exercise is the increase in insulin sensitivity. This enables the body to remove glucose more effectively from the blood, decreasing the blood glucose energy. Physical activity can increase the insulin sensitivity of a normal person 2 to 3 times. If the increase in insulin sensitivity is taken into account, figure 10.1 does represent an accurate reduction in the risk of CHD [63].

10.4. Summary

It is a well-known fact that exercise improves cardiovascular health. Numerous studies indicate the improvement that exercise has on the risk factors of CVD. Exercise is known to reduce the HbA_{1c} levels of diabetics, thus improving their blood glucose control. Improved blood lipids, blood viscosity and insulin sensitivity brings a further reduction in CVD risk for diabetics and non-diabetics alike.

Energy expended in exercise can be quantified by *ets*. For example, jogging for 30 min at 11 km/h for a person of average size, equals eight *ets-expended*.

The results show that *ets-expended* in exercise has twice the effect on the relative risk factor as that of *ets* intake. This is mostly due to the improved insulin sensitivity.

11. CONCLUSION AND RECOMMENDATIONS

11.1. Summary and Conclusion

The objective of the study was to develop a link between blood glucose energy and the risk of CVD.

By gathering information through a literature search on the Internet, various risk factors associated with blood glucose energy were obtained. These risk factors were linked with the *ets* concept using different methods. This could be done because *ets* represents blood glucose energy.

The literature study shows that mean blood glucose and carbohydrate intake play an important indirect role in the formation of CVD. Risk factors associated with mean blood glucose levels represented by the HbA_{1c} percentage and risk factors associated with glycaemic load intake, were obtained through a literature search.

In the first study the Diabetic Toolbox was used to determine the effect of *ets* intake on the HbA_{1c} percentage (mean blood glucose level) of a typical Type 2 diabetic. The results did indicate an increased HbA_{1c} percentage. However, the effect of *ets* intake on the HbA_{1c} percentage was not significant enough to link the results obtained with a significant risk factor of CVD.

The poor results obtained from the Diabetic Toolbox linking the HbA_{1c} percentage with *ets* intake and thus linking *ets* intake with the risk of CVD, led to the development of study 2.

In study 2, measured data obtained from Simin Liu *et al* [15] linking glycaemic load intake with the risk of CHD, were analysed. The data provided were complete enough to determine the equivalent value of *ets* intake associated with CHD risk. The result clearly indicates that if a certain amount of daily *ets* intake is exceeded the risk of CHD increases. This amount of *ets* intake is of the order of

32 *ets* for a woman of average size.

Through using the *ets* concept, the percentage of energy intake from carbohydrates, compared to the total daily energy intake, was calculated. The results show that if the percentage of energy obtained from carbohydrates exceeds 23 percent of the total energy intake, the risk of CHD increases. People consuming of the order of 19 percent to 23 percent showed no increase of CHD risk.

The literature shows that the brain uses 20 percent of the body's total metabolism. The brain only uses blood glucose as an energy source. The results obtained from Simin Liu *et al* [15] correlates remarkably well with this fact as explained in the following paragraph.

Carbohydrate intake is largely responsible for blood glucose energy. If the carbohydrate intake is just enough to supply the brain with energy the risk factor of CHD is equal to 1 (no increased risk). If the energy obtained from carbohydrates exceeds the energy needed by the brain, the risk factor of CHD increases. In the study done by Simin Liu *et al,* the percentage of energy intake associated with CHD risk is of the order of 23 percent. This is a valuable correlation and can give new insight into the composition of a healthy diet.

Risk factors associated with stress and depression were obtained through a literature search. Stress increases the risk of CVD. Through empirical measurements and simulation it was found that the effect of stress on blood glucose levels could be compared with the effect of carbohydrate intake (*ets* intake).

Measured data from Simin Liu *et al* of the effect of additional *ets* intake on the risk factor of CHD were used to illustrate the effect of *ets-stressed* on CHD The results correlated remarkably well with the results obtained from Mika Kivimaki *et al* [57]. This verifies the concept that an increase in blood glucose levels caused by stress increases the risk of CVD.

Data obtained from this study were applied to verify effects of *ets-exercise* and *ets-stressed* on CVD risk factors.

The literature shows a link between KCal expended during exercise and CHD risk. It was found that energy expended in exercise decreased the risk of CHD. The energy expended in exercise can be linked with *ets*. This made it possible to link *ets-expended* during exercise with a decrease in the risk of CVD.

The results were compared to the results obtained from Simin Liu *et al*. The results show that *ets-expended* during exercise **decreases** the risk factor by a factor of two compared to the effect *ets* intake has on **increasing** the risk factor. The literature shows that insulin sensitivity can increase by a factor of two to three times of the normal insulin sensitivity. This enables the body to store blood glucose much more effectively. This effect seems to lessen the complications caused by blood glucose and decreases the risk of CHD.

The literature shows that blood glucose energy can be linked with the risk of CVD. It is established that the *ets* concept can be used to determine the risk of CVD. The data obtained from Simin Liu *et al* gave a valuable new insight into the effect high carbohydrate diets and blood glucose energy have on the cardiovascular health of people. It is clear that the risk factors of CHD increase if the amount of *ets* increases above a certain level. This level is 32 *ets* for healthy women of average size.

11.2. Contributions to the field

This study not only shows that high carbohydrate intake is detrimental to a person's cardiovascular health, but also shows that the *ets* concept can be used as a predictive tool of CVD risk.

The *ets* concept can be used to improve cardiovascular health. *Ets* is a simple and easy to use concept which can be used to control blood glucose energy. This can have a tremendous impact on reducing the risk of CVD. Not only can the risk

of CVD be reduced but it is likely that the risk of other metabolic diseases (for example, cancer and diabetes) can be reduced as well.

11.3. Recommendations for further work

Metabolic diseases are complex and there are still a lot of unanswered questions. High blood glucose levels influence CVD risk factors. In this study, only the effect of carbohydrate intake, exercise, stress and blood glucose levels on CVD risk was investigated. However, more measured data is needed for accurate predictions of CVD. The following are recommendations for further work which could help improve predictions made of CVD risk.

1. More measured data of the effect of glycemic load intake on CVD risk is needed.

2. Integration of *ets* intake, *ets-stress*, and *ets-exercised* to determine a single risk factor of CVD.

3. Insulin levels have been identified as a risk factor of CVD. Since insulin is linked with carbohydrate intake and thus *ets* intake, the *ets* concept can be used to determine risk factors through insulin levels. This might prove to be more accurate way of determining CVD risk.

4. The link between *ets* and other metabolic diseases can be researched. It is possible that similar risk factors will be obtained for the various metabolic diseases such as cancer and stroke.

11.4. Closure

In conclusion, a correlation does exist between blood glucose energy and CVD. The *ets* concept quantifies blood glucose energy and therefore correlates significantly with CVD. The risk of CVD can be reduced if a person controls his

energy intake, manages his stress and exercises regularly. All of these above factors can be quantified with the *ets* concept, which is an easy to understand unit of blood glucose energy. The *ets* concept can thus be used as a tool to help a person keep his blood glucose energy levels at a healthy level considering carbohydrate intake, stress and exercise.

LITERATURE OVERVIEW

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Appendix A

Appendix A

Back ground on the simulation model.

DTB is the abbreviation for Diabetic Toolbox. DTB is a dynamic blood glucose simulation model incorporating the effects of the glycaemic index (GI) of carbohydrate food, energy utilisation and the principles of regulatory and counter regulatory mechanisms, for blood glucose level control.

DTB's output is a daily blood glucose simulation and its function is to advise the diabetic on an insulin dosage. An in-house developed food list is used to input the energy intake. Exercise and body type are both also entered as inputs. The previous insulin injection time and dose size are then also important inputs.

Characterization of simulation model

In order to characterize a patient certain physiological characteristics of a patients had to be put into the program. The program was adjusted to accurately simulate the blood glucose response of such a patients.

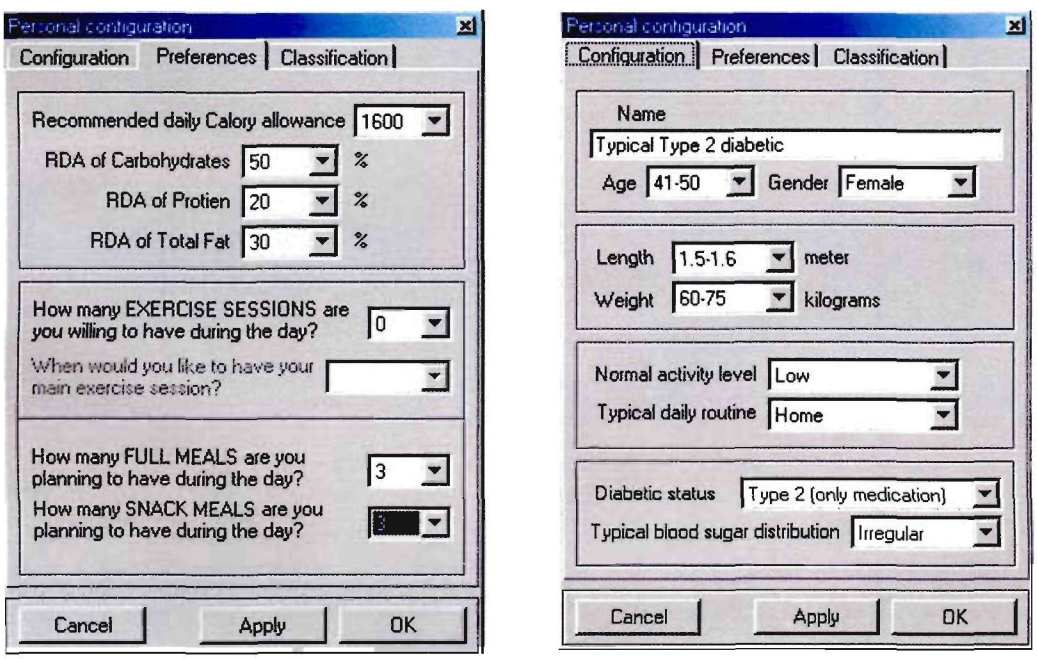

Figure 1: Characterization of a patient

Results obtained with ets intake

Simulations were run in order to calculate the mean blood glucose level of a patient. The effect of different amounts of ets intake was simulated. The following figures show the blood glucose response for a certain ets intake. The figures show the results of an increase in ets intake on the mean blood glucose levels and blood glucose response.

In the figures the red line indicates the blood glucose levels at a certain time interval. The y-axis shows the blood glucose level and the x-axis the time of day (0-24 hours).

Meals were ingested at 7:00, 10:00, 13:00, 16:00, 19:00, 22:00. The full meal were taken at 7:00, 13:00 and 19:00 and the "snacks" were taken at 10:00, 16:00 and 22:00. The blood glucose response due to ets intake is clearly visible in the figures.

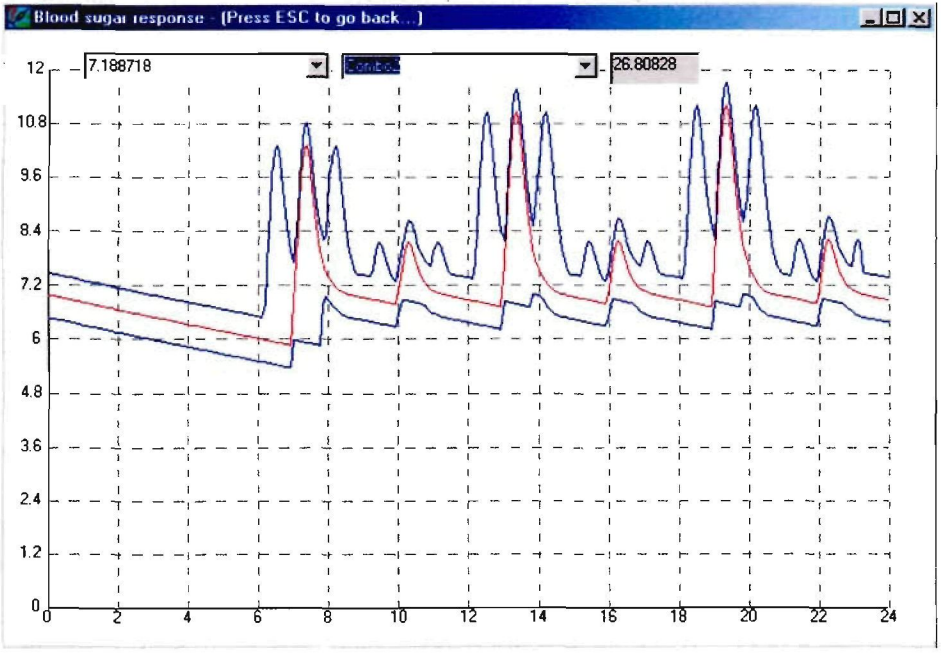

Figure 2: The blood glucose response caused by 24 ets consumed

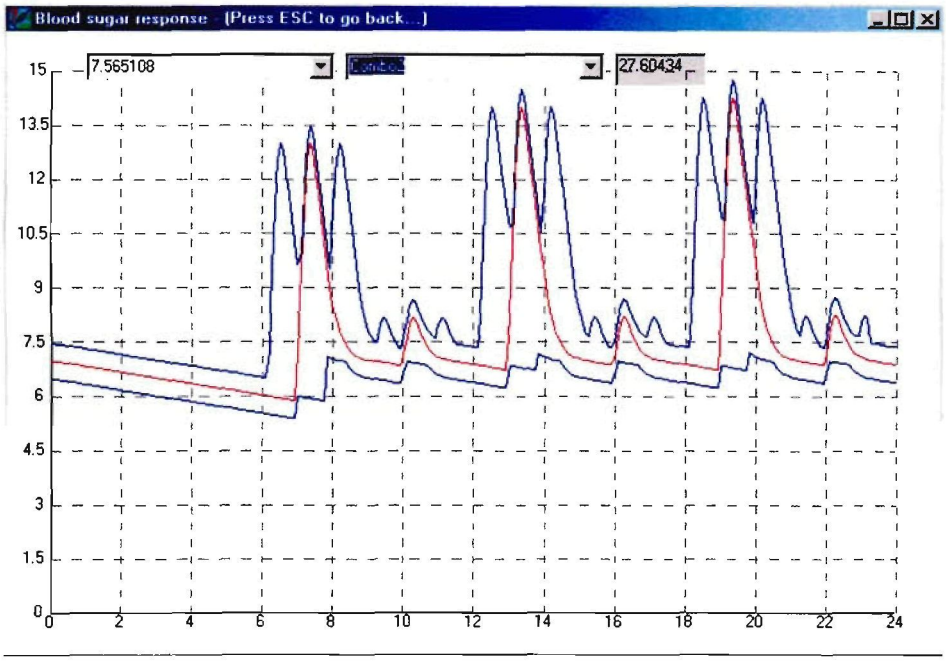

Figure 3: The blood glucose response caused by 33 ets consumed

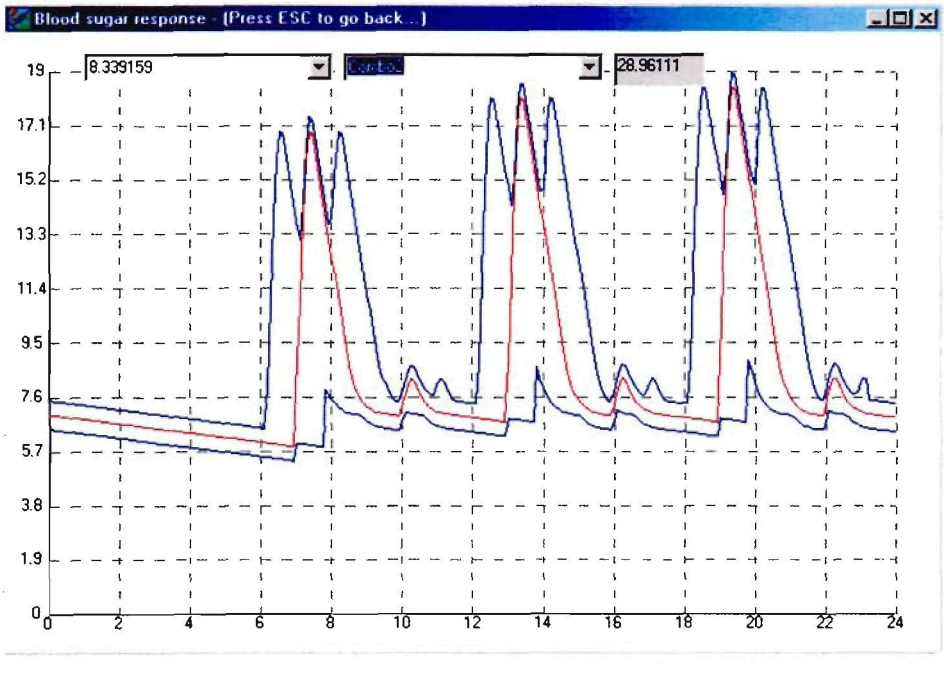

Figure 4: The blood glucose response caused by 45 ets consumed

The results of the simulations are given in table 1. The high lighted were obtained from the results shown in the figures above. The results show that an increase in ets intake increases the mean blood glucose level. The increase in mean blood

glucose results in an increase in HbA1c percentages and thus an increase in risk for CVD.

Ets intake	Mean blood glucose level	Ets intake	HbA1c percentage	Ets intake	Relative risk for CVD
24.00	6.74	24.00	5.57	24.00	1.23
27.00	6.84	27.00	5.62	27.00	1.25
30.00	6.97	30.00	5.69	30.00	1.27
33.00	7.12	33.00	5.76	33.00	1.31
36.00	7.30	36.00	5.85	36.00	1.34
39.00	7.48	39.00	5.94	39.00	1.38
42.00	7.70	42.00	6.06	42.00	1.42
45.00	7.90	45.00	6.16	45.00	1.46

Table 1: Results obtained from the simulations run

The same blood glucose response was obtained with ets-stressed. The reason is that ets stressed was simulated as additional ets intake. The more severe the stress situation, the higher the ets intake.

The effect of exercise on the mean blood glucose level was also simulated. However, there results did not show a significant decrease in mean blood glucose level