CHAPTER 4   NEW LINKS WITH THE ETS CONCEPT

In this chapter two novel applications of the ets concept are considered. The first is a new method to use the ets values associated with food and energy expenditure to calculate both short-acting and long-acting insulin dosages for Type 1 diabetics. The second application is a discovery that was made after the ets concept could be implemented for glycaemic response prediction in the simulation model. It entails a new quantification method for describing the effects of stress and illness in terms of ets.

4.1 Introduction

In the previous chapter two links with the ets concept were derived. These links are firstly, the relationship between insulin secretion and consumed ets and secondly, the relationship that energy expenditure of the human energy system has with ingested ets. During both the processes of establishing the links, the ets concept and its applicability were verified. Comparison of results given by the ets concept with those given by current methods as predictors revealed that ets does indeed provide good correlations with both links.

Now that the concept has been verified the logical next step is to employ the concept for new applications in other areas of the human energy system. In this chapter two new applications are discussed. These are:

- Implementing the ets concept to help Type 1 diabetics with calculations of insulin requirement and dosages. It is shown that ets, as a predictor, can be used for calculating both short-acting and long-acting insulin dose requirements.

- Using ets as a quantity for describing the impact of stress and illness on the human energy system. Currently there are no measurable units for evaluating the effect of stress and illness, but with the aid of simulation modelling (described later in this study), it was possible to apply ets with reasonable success to provide a solution to this problem.

In the following sections these two new applications of the ets concept are derived as well as evaluated in comparison to current suggestions in the literature.

4.2 Diabetic insulin requirement

Type 1 diabetes mellitus is a condition in which the patient's pancreas does not produce any (or adequate amounts) of insulin for glycaemic control [1]. The insulin therefore has to be injected manually on a regular basis. As mentioned in Section 1.2.2, Type 1 diabetics usually find it relatively difficult to control their blood sugar levels due to the uncertainties associated with insulin requirement.

In most control efforts two types on insulins are injected. These are long-acting and short-acting insulin [2]. The long-acting insulin is also sometimes referred to as basal and storage injections. The reason for this is the following:

The purpose of the long-acting insulin is to mimic the basal insulin level a healthy person normally has in his / her blood. The insulin is usually injected once (or twice) daily and the effective release of insulin from the injection into the bloodstream occurs continuously throughout the day. Because a constant release of insulin is essential to mimic a healthy person's basal level, the best type in insulin for long-acting effect is obviously one with a constant release profile [2],[3]. Today only one type of insulin sufficiently adheres to this specification, namely "Lantus" manufactured by Aventis [4].

Short-acting insulin on the other hand is required to lower intermittent and irregular elevations in blood glucose concentration. These elevations may occur due to a number of disturbances of which carbohydrate (CHO) ingestion is the most common. The short-acting insulin activates the storage cells in the human energy system to absorb the extra available blood sugar and hence regulates the glycaemic response. This is the reason why it is called storage insulin, and also why it is usually injected in conjunction with meals [2].

Walsh et al as well as a number of other researchers suggest that the dosages of long-acting and short-acting insulin should be equal throughout the day [2]. In other words, the sum of all short-acting insulin dosages injected to regulate ("store") each meal should be equal to the sum of the long-acting insulin dosages for each day.

However, a common mistake made by diabetics (and their medical advisors) is to inject too little long-acting insulin. The result is blood sugar levels that gradually keep rising throughout the day. The patient then has to inject more short-acting insulin to lower the high concentrations of blood glucose. However, because the effect of the short-acting insulin is exhausted relatively quickly, the blood sugar levels again start to rise and another injection is required. The result is an undesirable see-saw glycaemic response.

In this section a new approach is therefore presented to calculate both long-acting and short-acting insulin dosages according to daily energy requirement and with the aid of the ets concept.

4.2.1 Short-acting insulin requirement

In Section 3.2 the insulin response of a healthy person to ingested CHO was discussed. It was shown that there is a direct relationship between the integral insulin response (AUC_I) and the

amount of ets consumed. The relationship was described by Equation (3.9) and for the sake of clarity is repeated here.

$$AUC_I = f_{AUCI}ets$$

(3.9)

If AUC_I is divided by the total time of the response curve (total time it takes from time of ingestion to the time basal level is reached), the quotient represents the total amount of insulin secrete for storage of the extra blood sugar. It can therefore be deduced that there is a direct linear relationship between the integral insulin response (AUC_I) and the total amount of insulin secreted. This relationship is shown in Equation (4.1)

$$AUC_I \propto I_{Secreted}$$

(4.1)

A new variable can be defined to equate the linear relationship in Equation (4.1). The variable, f_I, is then a constant multiplied with f_{AUCI} found in Equation (3.9). If f_I and Equation (4.1) is substituted into Equation (3.9), Equation (4.2a) is the result.

$$I_{Secreted} = f_I ets$$

(4.2a)

This implies that there is a direct linear correlation between the amount of insulin a healthy person secretes and the amount of ets the person ingests. However, the magnitude of f_I, which describes this relationship, is still unknown. If Equation (4.2a) is rewritten to make f_I the object of the equation (Equation (4.2b)), it can be seen that f_I describes a value that is equivalent to insulin sensitivity.

$$f_I = \frac{I_{Secreted}}{ets}$$

(4.2b)

It is very difficult to measure the exact amount of insulin a healthy person secretes ($I_{Secreted}$). But, as already mentioned, the aim of the insulin injections of the Type 1 diabetics is to mimic the insulin response of healthy people [2],[3]. It can therefore be assumed that a diabetic person has to inject the same amount of insulin that a healthy person secretes. This solves the problem of not being able to measure the insulin secretion. The insulin injected by a Type 1 diabetic can be measured very accurately.

However, it is still unknown exactly how much insulin should be injected to regulate a certain amount of ingested ets. If this amount had been known, the values for $I_{Secreted}$ and *ets* could simply have been substituted into Equation (4.2b) to determine the insulin sensitivity (f_I). Since this is not the case, the following procedure for determining f_I is proposed:

For blood sugar control diabetics try to mimic healthy people's insulin secretion [2],[3]. The assumption is therefore made that correct blood sugar control for a diabetic would result if the diabetic injected the same amount of insulin ($I_{Injected}$) that a healthy person with an equal f_I and an equal ets consumption secreted ($I_{Secreted}$). Then $I_{Secreted}$ is equal to $I_{Injected}$ if the blood sugar levels before the meal and after the meal are equal.

Now ΔBS_{Rise} can be defined as the absolute rise in blood sugar concentration due to a meal (from time of ingestion to maximum concentration). Also, ΔBS_{Fall} can be defined as the total reduction in blood sugar concentration due to the injected insulin (from maximum blood sugar level to stabilised level after the insulin is fully absorbed). The insulin injection should be taken only after the blood sugar concentration has stabilised at its maximum level. These two definitions are shown schematically in Figure 4.1.
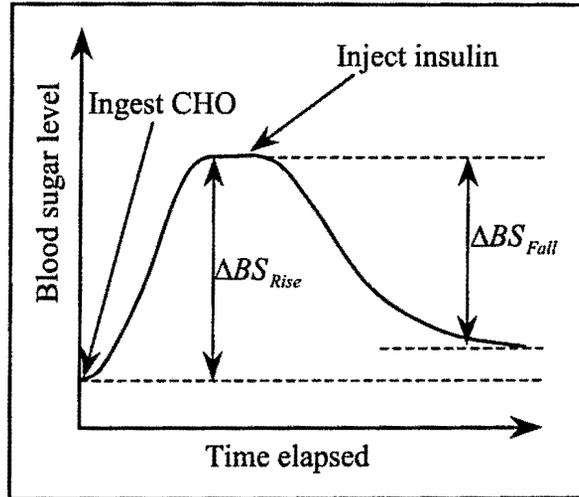
Figure 4.1 – Schematic representation of the definitions of ΔBS_{Rise} and ΔBS_{Fall}.

ΔBS_{Rise} and ΔBS_{Fall} would be equal if it could be measured for a healthy person. Therefore, the quotient of the two variables would be unity. Also, $I_{Secreted}$ is equal to $I_{Injected}$, so this can be substituted into Equation (4.2b) as shown in Equation (4.3).

$$f_I = \frac{I_{Secreted}}{ets} \frac{\Delta BS_{Rise}}{\Delta BS_{Fall}} = \frac{I_{Injected}}{ets} \frac{\Delta BS_{Rise}}{\Delta BS_{Fall}}$$

(4.3)

However, if a Type 1 diabetic injects insulin manually, and the amount ($I_{Injected}$) is not the correct amount to ensure that final blood sugar level is equal to the starting level, then ΔBS_{Rise} and ΔBS_{Fall} will differ. This is not a problem, because due to the linearity of Equation (4.3), the $\Delta BS_{Rise} / \Delta BS_{Fall}$ quotient will scale the equation linearly and keep f_I constant.

Therefore, Equation (4.3) can be used as a method of calculating f_I for a Type 1 diabetic. The procedure is shown schematically in Figure 4.1. First the patient should have a relatively constant blood sugar level, typically after fasting for a few hours. Then a meal consisting of a certain number of ets should be ingested.

A number of consecutive blood sugar measurements should be taken during approximately the next hour to determine the total rise in blood sugar due to the ingested ets. The rise in blood sugar (ΔBS_{Rise}) is then the difference between the maximum measured level and the starting level.

After the blood sugar levels have stabilised, a certain amount of short-acting insulin should be injected. Over the next two to three hours the blood sugar should again be monitored until a constant level is reached. To determine ΔBS_{Fall}, the final stabilised blood sugar level has to be subtracted from the maximum level previously measured.

All these measurement can be substituted into Equation (4.3) and f_I can subsequently be measured. Lastly, the final value of f_I can be substituted into Equation (4.2a) (together with $I_{Secreted} = I_{Injected}$) to determine the required short-acting insulin injection for any meal containing a known number of ets. The final equation is shown in Equation (4.4).

$$I_{Injected} = f_I ets$$

$$(4.4)$$

4.2.2 Typical values of f_I

It could be insightful to consider a few examples for calculating typical values of f_I. Firstly, in Table 4.1 the calculation of f_I values for three Type 1 diabetic test subjects are shown. These test subjects formed part of the verification study discussed in Chapter 8.

	ets ingested (ets)	ΔBS_{Rise} (mmol/l)	$I_{Injected}$ (units)	ΔBS_{Fall} (mmol/l)	$f_I = \dfrac{I_{Injected}}{ets} \dfrac{\Delta BS_{Rise}}{\Delta BS_{Fall}}$ (units/ets)
Subject 1	4.3	5.0	8.0	12.5	0.74
Subject 2	7.0	4.6	6.0	6.5	0.61
Subject 3	7.7	3.6	8.0	4.3	0.81

Table 4.1 – Calculations of f_I for three Type 1 diabetic test subjects.

A second method for estimating the typical values for f_I is by considering insulin sensitivities as calculated by other literature sources. The 450 rule presented by Walsh et al can be used as an example [2]. They provide a table for estimating the amount of insulin that has to be injected to counter a certain amount of ingested CHO. If it is assumed that the average GI of the CHO is 55, the ets values for the ingested CHO can be calculated. These values, together with the subsequent calculations of f_I are shown in Table 4.2 [2].

Total daily insulin dose (units)	Amount of CHO to counter 1 unit of insulin (g/unit)	Amount of ets to counter 1 unit of insulin (ets/unit)	$f_I = \dfrac{I_{Injected}}{ets}$ (units/ets)
20	22	3.7	0.27
25	18	3.0	0.33
30	15	2.5	0.39
40	11	1.9	0.54
50	9	1.5	0.66
60	8	1.4	0.74
75	6	1.0	0.98
100	5	0.8	1.18

Table 4.2 – Calculations of f_I from the 450 rule by Walsh et al.

The Walsh et al method is of course only relevant if the total insulin requirement for the day is already known [2]. According to their specifications, the method is only applicable if the blood sugar control is "relatively good".

The Walsh et al data (Table 4.2) shows a spread from 0.27 to 1.18 units/ets [2]. That implies that an error of up to 75% can be made if f_I is unknown. Furthermore, measured data from clinical trials performed by Aventis (with 2327 test subjects) showed that the average person injects 49 units of total insulin daily [4]. If this "average" person is considered in Table 4.2 a typical f_I can be assumed to be approximately 0.66 units/ets. As can be seen from Table 4.1, the typical average value for f_I measured for this study is 0.74 units/ets, which correlates well.

4.2.3 Long-acting insulin requirement

Now that the short-acting insulin dose to counter a specific ets in a meal can be calculated (Equation (4.4)) the next objective is to derive a procedure to determine the best long-acting insulin dose. In this section a new method, which is also an extension of the ets concept, is derived.

The derivation follows from the earlier argument that the long-acting dose should provide insulin for the body's cells throughout the day in order to be able to absorb energy [2],[3]. This implies that the long-acting insulin dose has to have some correlation with the total amount of energy the person expends during the day.

With Equation (3.20) in Section 3.3.2, the optimum amount of ets a person should ingest during an exercise can be calculated. Equation (3.20) is rewritten here as Equation (4.5) with the ets term as the subject of the equation.

$$ets = \frac{1}{f_{Expended}} E_{Expended}$$

$$(4.5)$$

If Equation (4.5) is substituted into Equation (4.4), the following relationship is found:

$$I_{Injected} = \frac{f_I}{f_{Expended}} E_{Expended} \cdot$$

$$(4.6)$$

From the definition of Equation (3.20) this equation is however only applicable for a single exercise for which the energy expended is represented with $E_{Expended}$. But, normal every-day living can also be viewed as a continuous exercise. Furthermore, the amount of energy expended during this continuous exercise can be assumed to be equal to the total amount of recommended energy throughout the day. This is called the recommended daily energy allowance ($E_{Expended(RDA)}$) and can be substituted for $E_{Expended}$ in Equation (4.6).

The value for $E_{Expended(RDA)}$ is of course dependant on the daily routine the specific person usually follows. Published energy tables for typical routines are widely available [5]. It should however be noted that $E_{Expended(RDA)}$ as it is used in Equation (4.6) is measured in kCal.

If $E_{Expended(RDA)}$ is used in Equation (4.6), the result of the equation is the amount of long-acting insulin that the person requires in order to provide enough insulin throughout the day ($I_{Injected(Long)}$) for the "exercise" performed throughout the day ($E_{Expended(RDA)}$). The value of f_I can be found with the procedure discussed in the previous section and $f_{Expended}$ can be calculated as explained in Section 3.3. The final equation for calculating long-acting insulin dose is therefore:

$$I_{Injected(Long)} = \frac{f_I}{f_{Expended}} E_{Expended(RDA)} \cdot$$

(4.7)

4.2.4 Validation of the method

In order to establish the accuracy of the method presented in Equation (4.7), the Aventis trails are used again [4]. Due to the fact that a large amount of test subjects (2327 people) were used for the trials average values for the properties of the test subjects can be assumed.

The first assumption that is made is that the average person in the trials weighted 65 kg. From published energy tables it can be calculated that a 65 kg person should consume approximately 2200 kCal of energy every day ($E_{Expended(RDA)}$ = 2200 kCal). This value is applicable if the person follows a normal daily routine [5].

In Section 4.2.2 it was shown that a typical average value for f_I is 0.6 units/ets. Also in Section 3.3.2 it was mentioned that a good assumption for the value of $f_{Expended}$ is 55. Therefore, if these values are substituted into Equation (4.7), a value of 24 units of long acting insulin is the result. This calculation is shown in Equation (4.8).

$$I_{Injected} = \frac{f_I}{f_{Expended}} E_{Expended} = \frac{0.6}{55} 2200 = 24 \text{ units}$$

(4.8)

However, the Lantus trials revealed that on average the people in the trials injected 23 units of long-acting insulin and 26 units of short-acting insulin [4]. The value of 24 units calculated with Equation (4.7) is therefore very close to the actual amount of insulin injected.

The value could be even closer to the optimum if the suggestion by Walsh et al is followed [2]. They insist that the total long-acting and short-acting insulin doses should be equal throughout the day and not 23 units and 26 units respectively. If more long-acting and less short-acting insulin were used, the suggested value of 24 units (Equation (4.8)) would be spot on. Therefore, the method seems to provide reasonable answers. With some more clinical trials Equation (4.7) can be verified even further.

4.3 Quantification of stress and illness

In this section another new application of the ets concept is discussed. This is the issue of quantifying stress and illness.

Stress is a term that has become synonymous with modern life. To date many studies have successfully been performed to establish a definite link between stress, and a host of illnesses [6],[7]. Maddock and Pariante for instance proved the existence of an increased risk factor for cardiovascular disease, cancer and depression due to changes in the immune system brought about by chronic stress [8]. Other studies have shown links with insomnia, infertility, Type 2 diabetes, and even mortality [9],[10],[11],[12],[13].

This link can however also be viewed from a different perspective. Instead of simply accepting an overdose of stress as one of the major causes of illness, stress can also be compared (and related) to illness in the sense that similar physiological symptoms are experienced during the occurrence of both. In both cases blood sugar concentrations are raised above normal [14],[15],[16]. These higher than normal blood sugar levels (hyperglycaemia) often cause complications for people [1],[17]. It is especially problematic for Type 1 diabetics who have the burden of self-administered blood sugar control [1],[2],[3]. However, despite numerous studies a method for quantifying stress and illness levels has not been found yet.

In this section an application of the ets concept derived in Section 2.4 is discussed. The ets concept led to the discovery of a new method of quantifying the effect of stress and illness. Making the discovery involved successful simulation modelling of blood sugar level response in the human energy system as will be discussed in Chapter 7. In this section a comparison is provided between suggestions by the ets concept and some empirical literature currently available. An easy-to-use equation for estimating the required long-acting insulin dose for Type 1 diabetics experiencing stress or illness is also derived.

4.3.1 Background

The first step is to perform a brief investigation into the reason why blood sugar levels are elevated when a person experiences stress. The cause predates to early times when humans had to be alert and ready for action during times of physical danger. When under stress, the counter regulation control system of the body releases hormones like cortisol and adrenaline [18]. (More detail is given

in Chapter 6.) These hormones trigger the release of energy in the form of glucose into the bloodstream to ensure that the person can flee or fight for survival if necessary [15]. (Short-term stress is therefore appropriately called "fight or flight" stress.)

When blood glucose concentrations rise in a healthy individual (non-diabetic), insulin is secreted into the bloodstream by the pancreas. Insulin is the only hormone that can lower blood glucose levels [19]. As mentioned earlier, Type 1 diabetics do not have insulin available in their bodies, so they have to inject it manually [1],[2],[3]. The insulin then activates the liver, muscle and fat cells to absorb the glucose from the bloodstream and consequently restore the normal glucose level. (These processes are also described in Chapter 6.) However, if blood sugar levels stay high because of stress or illness, insulin is continually secreted in vain.

The high blood sugar and hence high insulin levels unfortunately cause some complications for humans [20]. Many studies have emphasised the negative health implications associated with insulin. The two consequences that are probably most relevant to this study are the increased strain on the pancreas and the risk of induced insulin resistance (and ultimately diabetes) [17].

Nowadays people are exposed to longer periods of tension due to fast modern lifestyles and more frequent traumatic events [5]. Furthermore, illness also causes elevated blood glucose levels (hyperglycaemia) for longer periods than only fight or flight stress [21]. The problem is that the amount with which the blood sugar levels are elevated due to the stress (or illness) and the consequent insulin requirement is yet to be quantified.

In Section 2.4 the concept of equivalent teaspoons sugar (ets) was introduced. The concept was derived from first order energy principles so as to quantify the amount of blood sugar energy that is available to the human body from ingested food. It was shown that in many cases less than the assumed 4 kCal/g was available [22]. Furthermore, since it primarily describes energy, the ets concept was then successfully applied to quantify all the influences the human energy system experiences. These include exercise and insulin requirement (Sections 3.3 and 4.2 respectively).

In Chapter 7 a simulation model for simulating the human energy system and its response to certain external influences is described. (The details and verification of this model will be discussed in Chapter 8.) With the simulation model it is possible to simulate blood sugar response for any person due to any disturbance like food, exercise and even stress or illness.

4.3.2 A new quantification method

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 (CHO). Because (from Section 2.4) energy from ingested CHO can now be quantified in terms of ets, short-term stress can now be linked to an equivalent amount of ingested ets. In other words, it can be determined how much ets, if ingested in a meal, would produce a similar blood glucose response as a certain stressful situation would.

The same reasoning can also be applied to long-term stress or long-term illness. Only, instead of simulating a single meal containing a specific amount of ets, the ingestion can be simulated as a continuous or spread out meal throughout the entire day.

When this approach was applied to a few test subjects some interesting results were found. The method used was the following: First an individualised simulation model for each subject was constructed. Each of the models was verified according to measurements under various circumstances. Then it was attempted to mimic measured blood sugar levels for each subject while they experienced different stressful events.

One of the 75 kg subjects for instance had a fierce argument with another person, which induced a short-term stressful situation. The measurements showed glucose response that was very similar to that of a 7 ets meal taken at the start of the argument. By introducing the 7 ets meal to the simulation model, the simulated response matched the measured response very closely.

Another case was that of an 80 kg test subject who went through a very stressful ordeal concerning the possible loss of a child. The stress condition lasted for a few weeks and elevated blood glucose levels for the subject were measured throughout that time. The only adjustment to that person's simulation model that could reproduce the same prevalence of hyperglycaemia was a continuous ets ingestion of approximately 2 ets/hour.

All the results across the short- to long-term range of stressors for which simulations were performed were extrapolated and the estimated quantities for an average sized person are listed in Table 4.3.

Duration	Example	Amount of ets for similar response
Short-term Less than an hour	Fighting e.g. kickboxing	Up to 17 ets/hour
Medium-term More than an hour	Writing exam	Up to 8 ets/hour
Long-term More than a day	Great illness	Up to 1.7 ets/hour

Table 4.3 – Amount of virtual ets adjusted in the simulation model of a 65 kg person to mimic the maximum blood glucose response for stress.

As can be seen from the table the effect short-term stress has on the human energy system in the extreme can be similar to an ets consumption of up to 17 ets/hour. It is incidentally known that the liver of an average sized person can store approximately 30 ets of glucose energy. (The assumption is based on a conversion of the available liver glucose according to Noakes [23].) Therefore, while under extremely stressful conditions a person can usually continue a "fight" (like for instance kickboxing) for less than 2 hours. After that time the person will probably experience hypoglycaemia or "hit the wall".

Marshall and Agarwal published an article in which they investigated factors inducing immunological changes in children [13]. Their investigation found that examination stress on children was one of the major factors inducing hyperglycaemia. They could however not link a quantity to the "amount" of stress experienced. In Table 4.3 it is estimated that examination stress, which is a medium-term condition, may have the same effect on an average person (in the extreme) as ingesting up to 8 ets/hour.

From the measurements and simulations on people in long-term stress situations it could be deduced that traumatic events or extreme illness, such as the loss of a loved one or bacterial infections, induces hyperglycaemia in an average sized person similar to a continuous ets consumption of up to 1.7 ets/hour.

4.3.3 Validation of the quantification method

The reliability of the new link can now be evaluated by qualitatively comparing it with other empirical suggestions. It is very difficult to measure the exact amount of virtual ets that the body secretes due to stress. A different approach therefore has to be found.

Studies have shown that there is a direct link between the amount of insulin that the body secretes and the amount of glucose in the bloodstream [24]. If insulin secretion can be linked with stress the problem would be solved. However, it is almost just as difficult to measure the amount of insulin a healthy person secretes. The only option is to investigate Type 1 diabetics, since they do not secrete insulin. They have to inject it manually, and the amount can accurately be measured [1],[2],[3].

In Section 4.2 the issue of insulin requirement for Type 1 diabetics due to ingested ets was addressed. An equation that linearly linked the required amount of insulin ($I_{Injected}$) with the amount of ets ingested in meal (ets) was derived (Equation (4.4)). The relationship was characterised with a personalised variable, f_I, that describes a person's insulin / ets ratio. The equation is only for one meal, but it can be extended for the entire day to describe the long-acting insulin requirement ($I_{Injected(Long)}$) according to the RDA of ets ingested throughout a day (ets_{RDA}).

$$I_{Injected(Long)} = f_I \, ets_{RDA}$$

$$(4.9)$$

Measured data from clinical trials performed by Aventis (with 2327 test subjects) showed that the average person injects 23 units of long-acting insulin and 26 units of short-acting insulin daily [4]. As already mentioned, the long-acting insulin is required for utilisation of previously stored energy. The short-acting insulin however is primarily responsible for storing available blood glucose in the storage cells and thereby lower blood glucose levels.

The values listed in Table 4.3 are for an average sized person weighing 65 kg. In Section 4.2.2 it was shown with some preliminary measurements that a typical average value for f_I can be assumed to be 0.6. Therefore, with Equation (4.9), it can be calculated that the ets_{RDA} for an average sized person is approximately 37 ets.

As shown in Table 4.3, when a person is under extremely high stress for long periods of time (long-term stress or illness) he / she could have an elevation effect of blood sugar levels of as high as 1.7 ets/hour. This amounts to an extra blood glucose load of up to 1.7 x 24 = 41 ets/day. Extra insulin has to be secreted from the pancreas (healthy person) or has to be injected (Type 1 diabetic person) to counter this additional elevation.

If the typical f_i of 0.6 is again used in Equation (4.9), the required insulin to counter the extra 41 ets when the person is under high long-term stress can be calculated. This comes to 0.6 x 41 = 25 extra units of insulin for the day. Because the stress is a long-term effect the extra 25 units of insulin should be taken as long-acting insulin.

It is important to note that the best long-acting insulin to use is one with a constant rate of uptake into the bloodstream [2]. This is essential because the blood sugar elevation due to long-term stress or illness is a continuous process that needs to be countered continuously. To date the only insulin that adheres to this requirement is the new insulin by Aventis, namely "Lantus" [4].

A few other suggestions should now be investigated in order to validate the above suggestion. Walsh et al suggested that diabetics could "easily" inject up to double the normal amount of storage insulin while they are very ill as compared to normal health situations [2]. They however do not specify exactly how much should be taken for which specific situation, but their suggestion is that at worst the "average" diabetic (used above) should inject more than 23 extra units of long-acting insulin per day. This correlates very well with the suggestion of 25 units made here.

Another suggestion is that of Beaser and Hill of the Joslin Diabetes Center [3]. They suggest that Type 1 diabetics should inject an additional 10% to 20% of the total insulin requirement for a day when they are ill or under high stress. This entails the following: The total insulin requirement for the average test subject who participated in the Aventis trials was 26 + 23 = 49 units in total [4]. The extra insulin required according to Beaser and Hill is therefore 20% x 49 = 10 extra units [3].

This value is however believed to be a little bit conservative. Beaser and Hill make the common mistake of suggesting short-acting insulin for the extra injection instead of long-acting insulin [3]. This means that the diabetic will have sharp drops in blood glucose concentration and possibly experience temporary hypoglycaemia. That is possibly why their suggested dosages are too small. Furthermore, it should be remembered that the Joslin guide is written for self-treatment of diabetes and they would rather be safe than sorry [3].

4.3.4 Application of the discovery

The applicability of the findings can now be investigated. From a scientific perspective the optimum procedure for quantifying stress or illness is by using the simulation procedure described later in this study. This is however not a practically applicable method since the resources are not available

to construct a separate simulation model for every person in the world. Another, less accurate but more useful, method is therefore proposed.

The maximum amount of extra ets (ets_{Stress}) that an average sized person might secrete due to stress or illness is shown in Table 4.3. However, not all people are able to secrete that maximum amount because of physiological and psychological differences. This "ability" to secrete ets due to stress or illness can therefore be characterised with another personalised variable, namely f_{Stress}. The total amount of ets for which long-acting insulin has to be injected (ets_{Total}) can then be calculated with Equation (4.10).

$$ets_{Total} = ets_{RDA} + f_{Stress} ets_{Stress}$$

(4.10)

If ets_{RDA} found in Equation (4.9) is substituted with ets_{Total} from Equation (4.10) the total amount of long-acting insulin a Type 1 diabetic should inject is found. This is shown in Equation (4.11).

$$I_{Injected(Long)} = f_I \left(ets_{RDA} + f_{Stress} ets_{Stress} \right)$$

(4.11)

An estimate for ets_{Stress} (the maximum value) can be read from Table 4.3. The calculation of f_{Stress} however is a problem. It again involves tedious measurements similar to the ones performed on the test subjects.

A rule of thumb for an estimation of f_{Stress} is therefore established and presented here. The values in Table 4.3 are the maximum estimated values for an average sized person. If it is assumed that an average person weighs 65 kg the estimated values of f_{Stress} can then be scaled linearly according to the weight of the person.

Furthermore, f_{Stress} is dependant on an array of variables of which the capacity of the body's counter regulation control is one. Since it has been mentioned in the previous chapter that long-suffering Type 1 diabetics often have the counter regulation strength of only 25% of that of healthy people, it can be deduced that f_{Stress} for a long-suffering patient can be no more than 0.25.

The following example can be used: if the patient is a recently diagnosed Type 1 diabetic (and therefore has a healthy counter regulation strength) it can be assumed that his f_{Stress} is still close to unity. However, if the patient weighs 100 kg, f_{Stress} should be linearly scaled. Therefore the value of 1 x 100 / 65 = 1.5 should be used. This value can be substituted into Equation (4.11) and $I_{Injected(Long)}$ can be calculated accordingly.

With the aid of the simulation model a more accurate suggestion can be made for any person when more specific circumstances are known. An unpublished comparison between this suggestion and empirical literature however revealed that Equation (4.11) does hold some merit as a practical method.

4.4 Conclusion

The preliminary results of the two new applications of the ets concept yield promising prospects since many other applications and discoveries may yet be made. In the two discussions the initial validations do however indicate that the equations are useful, especially for Type 1 diabetics. Of course the two applications discussed in this chapter still require some verification. Because these validations were however not the main aim of this study it is recommended for future work.

Now that the ets concept has been established as a good property for quantifying energy in the human energy system the next step is to apply the concept for simulation purposes. In the next couple of chapters the implementation of the ets concept is discussed.

First, in Chapter 5, some background is provided on how the simulation procedure is executed. Chapter 6 then presents a detailed literature study to establish the energy pathways and controls in the body. The following two chapters thereafter finally discuss the simulation model design and verification.

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