A novel quantification of the relationship between blood sugar and stress

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ABSTRACT

Title: A novel quantification of the relationship between blood sugar and stress

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Key terms: Acute stress; blood glucose; cardiovascular disease; chronic stress; cortisol; diabetes; energy expenditure; epinephrine; equivalent teaspoon sugar; hypothalamo-pituitary-adrenocortical; insulin; psychological stress; relative risk factor; sympathetic nervous system

The rapid growth of biotechnology has promoted industries to harness the market in the field of human energy systems. A growing literature of research has linked human energy systems to weight loss, major diseases or illnesses.

In our modern society, the general public is exposed to everyday stress, which often results in the development of chronic stress. Therefore, stress becomes an important area of medicine. It has been postulated that suppressing these physiological responses may help in disease prevention. Consequently, there is an urge for defining a model integrating stress with the human energy model.

Over the past decades, a large amount of research has been put forward in defining the physiological responses or changes when an individual experiences psychological or environmental changes such as interpersonal dysfunction, traumatic experiences and diseases. Interestingly, it reveals that blood glucose fluctuation tends to be the end product of most psychological or physiological stressors.

The blood glucose system is one of the major subsystems of the complete metabolic fuel system in humans. In this study, an empirical model and procedure for the derivation of the model due to various psychological influences on the human energy system are presented.
This study can be divided into two main sections. An overview of a previously developed unit (ets: equivalent teaspoon sugar) for blood glucose quantification is given in the first section. Stress quantification methods are derived in the second section and a link between these methods and ets is drawn. A verification study of the derived model is also presented in the second section.

Stress can be divided into physiological stress and psychological stress. Between the two types of stress, a generalised model based on studies of physiological stress has been drawn and accepted by the public. However, the generalised model does not account for psychological stress.

Evidence shows that depending on the specific nature of a stressful circumstance, it can cause different activations of central circuits leading to the release of different neurotransmitters. However, these neurotransmitters have a common effect of increasing blood glucose concentrations.

A substantial amount of literature shows that, when stress involves mental effort, epinephrine (EPI) is the main endocrine response. However, stress that does not require mental effort mainly induces cortisol release.

The response models for different types of stress were derived using these relations. Furthermore, it is known that prolonged stress may lead to the development of disease. Several studies have used this observation and associated chronic stress with the relative risk factor of cardiovascular disease (CVD). Previously, different quartiles of risk factors for CVD have been related to blood glucose energy and ets expenditure. This link was further utilised to quantify chronic stress in this study.

Increases in either of the two endocrine concentrations have been shown to raise the blood glucose level. In order to demonstrate the benefits of applying the ets concept, the cortisol and epinephrine responses were further quantified using the new glucose quantification method, the equivalent teaspoon sugar (ets) concept.

The models derived in this study were verified against measured data. The models reveal a strong agreement with the measured data and therefore support the feasibility of these quantification methods.
In conclusion, a link does exist between blood glucose energy and stress, and the highly accurate models derived for this association may serve as an adjunct tool for glycaemic control and stress management.
OPSOMMING

Titel: ‘n Nuwe kwantifisering van die verhouding tussen bloedsuiker en stres

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Departement: Elektroniese Ingenieurswese

Fakulteit: Ingenieurswese

Graad: Philosophiae Doctor

Sleutel terme: Akute stres; bloedglukose; kardiovaskulêre siekte; kroniese stres; kortisol; diabetes; energiegebruik; adrenalien; ekwivalente teelepels suiker; hypothalamo-pituitêre-adrenokortikaal; insulien; psigologiese stres; relatiewe risiko faktor; simpatiese senuweestelsel

Die vinnige groei in biotegnologie het die industrie se belangstelling in menslike energiestelsels baie bevorder. ‘n Groeiende navorsingsveld koppel menslike energiesisteme met gewigsverlies en sekere ernstige siektes en toestande.

In ons moderne samelewing word die algemene publiek elke dag blootgestel aan stres, wat dikwels die ontwikkeling van kroniese stres veroorsaak. Stres is dus ‘n belangrike mediese navorsingsveld. Dit word gepostuleer dat die fisiologiese response van stres onderdruk kan word om sekere siektes te voorkom. Daaruit volg dit dat daar ’n behoefte is om ‘n model te definieer wat stres met die menslike energiemodel kan integreer.

Oor die laaste paar dekades is ‘n groot hoeveelheid navorsing gedoen om die fisiologiese response of veranderinge wat in die menslike liggaam plaasvind te definieer wanneer individue blootgestel word aan psigologiese of omgewingsveranderinge soos interpersoonlike probleme, traumatiëse ondervindings, en siektes. Daar is ontdek dat bloedglukose wisseling die eindresultaat van psigologiese en fisiologiese stres is.

Die bloedglukosesisteem is een van die hoofsubstelsels van die volledige metaboliese brandstof sisteem in mense. In hierdie studie word ‘n empiriese model wat die invloed van verskillende psigologiese veranderinge op die menslike energiestelsel het (en ‘n procedere om dit af te lei), voorgestel.
Die studie kan hoofsaaklik in twee dele ingedeel word. 'n Oorsig van 'n voorheen ontwikkelde eenheid nl. ets (ekwivalente teelepels suiker) vir bloedglukose kwantifisering word in die eerste deel bespreek. Stres kwantifiseringsmetodes word afgelei in die tweede deel en 'n skakel tussen die metodes en ets word bepaal. 'n Verifikasiestudie van die afgeleide model word ook in die tweede deel bespreek.

Stres kan onderverdeel word in psigologiese stres en fisiologiese stres. 'n Algemene model is tussen die twee tipes stres opgestel deur gebruik te maak van studies van psigologiese stres; maar daar is nog steeds 'n tekort aan 'n generiese model vir psigologiese stres.

Bewyse toon dat die spesifieke aard van 'n stresvolle gebeurtenis die spesifieke sentrale senuwee stroombaan wat geactiveer word, bepaal, wat weer lei tot verskillende neurosenders wat vrygestel word. Hierdie verskillende neurosenders het almal 'n gemeenskaplike effek, naamlik die verhoging van bloedglukose konsentrasies.

Baie literatuur dui daarop dat wanneer stres verstandelike inspanning behels, ephinephrine (EPI) die hoof endokriniese respons is. Stres wat nie deur verstandelike inspanning vergesel word nie, indueser hoofsaaklik kortisolvrystelling.

Hierdie verhoudings is gebruik om die responsmodelle van verskillende tipes stres af te lei. Verder is dit bekend dat kroniese stres mag lei tot die ontwikkeling van 'n siektetoestand. Talle studies het hierdie observasie en die geassosieerde kroniese stres aan die relatiewe risikofaktor van kardiovaskulêre siekte (KVS) gekoppel. Die verwantskap tussen verskillende kwadrante van die risikofaktore van KVS en bloedglukose (ets gebruik) is gevind. Hierdie koppeling is verder gebruik om kroniese stres te kwantifiseer.

Daar word gewys dat die verhoging van enige van die twee endokriene konsentrasies die bloedglukose vlak verhoog. Om die voordele van die toepassing van die ets-konsep te illustreer, is die kortisol en epinephrine response verder gekwantifiseer deur gebruik te maak van die nuwe glukose kwantifiseringsmetode, die ets-konsep.

Die modelle wat afgelei is uit die studie, is teen gemete data geverifieer. Daar is bevind dat die modelle goed ooreenstem met die gemete data. Dit versterk die uitvoerbaarheid van hierdie kwantifiseringsmetodes.

Die gevolgtrekking is dat daar 'n skakel bestaan tussen die bloedglukose vlak en stres, en dat die hoog akkurate modelle wat van die assosiasie afgelei is, mag dien as gereedskap vir glisemiese en stresbeheer.
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<th>Description</th>
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<tr>
<td>ABG</td>
<td>average blood glucose</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BS</td>
<td>blood sugar</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck depression inventory</td>
</tr>
<tr>
<td>BEE</td>
<td>basal energy expenditure</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CBG</td>
<td>corticosteroid-binding globulin</td>
</tr>
<tr>
<td>CFS</td>
<td>chronic fatigue syndrome</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CHO</td>
<td>carbohydrate</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotrophin releasing hormone</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>A</td>
<td>delta (change)</td>
</tr>
<tr>
<td>DHEA</td>
<td>dehydroepiandrosterone</td>
</tr>
<tr>
<td>dl</td>
<td>decilitre</td>
</tr>
<tr>
<td>EE</td>
<td>energy expenditure</td>
</tr>
<tr>
<td>EPI</td>
<td>epinephrine</td>
</tr>
<tr>
<td>ets</td>
<td>equivalent teaspoons sugar</td>
</tr>
<tr>
<td>FFA</td>
<td>free fatty acid</td>
</tr>
<tr>
<td>GH</td>
<td>growth hormone</td>
</tr>
<tr>
<td>GI</td>
<td>glycaemic index</td>
</tr>
<tr>
<td>GL</td>
<td>glycaemic load</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HbA1c</td>
<td>glycated haemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoproteins</td>
</tr>
<tr>
<td>HDLC</td>
<td>high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamo-pituitary-adrenocortical</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IDDM</td>
<td>insulin-dependent diabetes mellitus</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like Growth Factor-1</td>
</tr>
<tr>
<td>KBW</td>
<td>knowledge-based work</td>
</tr>
<tr>
<td>kCal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>MMPI</td>
<td>Minnesota multiphasic personality inventory</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NK</td>
<td>natural killer</td>
</tr>
<tr>
<td>nmol</td>
<td>nanomole</td>
</tr>
<tr>
<td>PTSD</td>
<td>posttraumatic stress disorder</td>
</tr>
<tr>
<td>RDA</td>
<td>recommended daily allowance</td>
</tr>
<tr>
<td>REE</td>
<td>resting energy expenditure</td>
</tr>
<tr>
<td>REM</td>
<td>rapid eye movement</td>
</tr>
<tr>
<td>RQ</td>
<td>respiratory quotient</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SI</td>
<td>standard international</td>
</tr>
<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SAM</td>
<td>sympathetic-adrenomedullary</td>
</tr>
<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
</tr>
<tr>
<td>SPS</td>
<td>severe personal stressor</td>
</tr>
<tr>
<td>TEE</td>
<td>total energy expenditure</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>TSST</td>
<td>trier social stress test</td>
</tr>
<tr>
<td>umol</td>
<td>micromole</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>W</td>
<td>watt</td>
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### SYMBOLS

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{BS}$</td>
<td>area under the curve of blood glucose response</td>
</tr>
<tr>
<td>$BS(t)$</td>
<td>blood glucose response</td>
</tr>
<tr>
<td>$BS_{CHO}(t)$</td>
<td>blood glucose response induced by CHO ingestion</td>
</tr>
<tr>
<td>$BS_{stress}(t)$</td>
<td>blood glucose response caused by stress exposure</td>
</tr>
<tr>
<td>$BH_{stress}(t)$</td>
<td>stress hormone response caused by stress exposure</td>
</tr>
<tr>
<td>$\Delta BS$</td>
<td>total change of blood glucose response</td>
</tr>
<tr>
<td>$\Delta CORT$</td>
<td>total change of cortisol response</td>
</tr>
<tr>
<td>$\Delta EPI$</td>
<td>total change of epinephrine response</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>time elapsed between consumption and restoration of basal level</td>
</tr>
<tr>
<td>$E_{CHO}$</td>
<td>converted carbohydrate energy potential</td>
</tr>
<tr>
<td>$E_{ets}$</td>
<td>total amount of blood glucose energy available from ingested ets</td>
</tr>
<tr>
<td>$E_{Liver}$</td>
<td>energy extracted from the liver store</td>
</tr>
<tr>
<td>$EE_{Expended}$</td>
<td>total amount of energy expended by the body</td>
</tr>
<tr>
<td>$EE_{CHO}$</td>
<td>total amount of blood glucose energy expended by the body</td>
</tr>
<tr>
<td>$EE_{CHO, mental stress}$</td>
<td>glucose energy required during mental stress</td>
</tr>
<tr>
<td>$ets$</td>
<td>equivalent teaspoons sugar</td>
</tr>
<tr>
<td>$ets_{Stress}$</td>
<td>amount of ets secreted due to stress or illness</td>
</tr>
<tr>
<td>$f_{CHO}$</td>
<td>efficiency factor for converting ingested carbohydrates into blood sugar energy</td>
</tr>
<tr>
<td>$f_1$</td>
<td>insulin response / ets relationship efficiency factor</td>
</tr>
<tr>
<td>$G_{blood}$</td>
<td>blood glucose concentration</td>
</tr>
<tr>
<td>$GI_{CHO}$</td>
<td>conversion potential of energy from ingested food (approximated with GI)</td>
</tr>
<tr>
<td>$GI_{sugar}$</td>
<td>conversion potential of energy from sugar</td>
</tr>
<tr>
<td>$K$</td>
<td>blood sugar / ets conversion factor</td>
</tr>
<tr>
<td>$k_{CHO}$</td>
<td>maximum amount of energy available from carbohydrates</td>
</tr>
<tr>
<td>$m_{CHO}$</td>
<td>mass of carbohydrates contained in the food</td>
</tr>
<tr>
<td>$m_{teaspoon sugar}$</td>
<td>mass of carbohydrates contained in a teaspoon of sugar</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$%E_{\text{blood glucose}}$</td>
<td>percentage of energy derived from blood glucose</td>
</tr>
<tr>
<td>$t$</td>
<td>time</td>
</tr>
<tr>
<td>$V_{\text{Blood}}$</td>
<td>volume of blood</td>
</tr>
<tr>
<td>$VO_2$</td>
<td>amount of oxygen consumed by the body</td>
</tr>
<tr>
<td>$VO_{2,\text{max}}$</td>
<td>maximum amount of oxygen the body can consume</td>
</tr>
</tbody>
</table>
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1.1 Introduction

In the past couple of decades, the study of stress and physiology of the stress response has gained a prominent place in human health research. Between 75 and 90 percent of all disease prevalent in Western society is related to the activation of the stress mechanism [1].

Approximately 22% of the adult United States (US) population in any given year is affected by diagnosable mental disorders. Stress is considered both a causal factor and an outcome of disordered thought and disrupted interpersonal relationships [2].

Considerable efforts have been spent on investigating stress. It has led to a common belief that any situations that may lead to disturbances of metabolic homeostasis should be avoided. Occurrences of diabetes onset after extreme stressful situations are commonly observed in humans [3].

Evidence suggests that psychological stress may play a significant role in the development of diabetes. However, sophisticated psychological and physiological mechanisms are typically involved in organisms when dealing with stress. There is a lack of accepted animal or human models.

Clinically or in the general public, stress is only being taken seriously when it results in some significant biological changes. There are still many controversies and difficulties in evaluating everyday stress. The link between psychological stress and physiological aspects remains unclear. One major reason for this controversy is the subjective experience of stress and the extremely heterogeneous personal reaction to stress [3].

To provide a better evaluation of the relation between psychological stress and glucose metabolism, this study examined the possibility of linking physiological responses of psychological stress via different endocrines.

Physiological mediators (endocrines or hormones) of stress are associated with both adaptation and pathophysiology. These mediators participate in pathological changes over time. Measuring changes of the endocrine concentrations in the blood during the course of both acute stress and chronic challenge indicates a link between stress and resilience or stress and the risk for disease [2].
The stress systems are important protectors of the body during acute challenges. However, a long period of activation of the stress systems may cause damage and accelerate disease [4].

There is growing evidence of influences of stress on disease progression [5][6]. The effects of stress on the physiological responses causing changes in plasma concentrations of endocrines are well supported. Several studies showed that chronic or repeated exposure to stress could cause plasma concentrations of the endocrines to remain elevated [6]. Consequently, it has been generally hypothesised as a possible mechanism linking stress to adverse health outcomes.

Furthermore, severe stress and chronic stress may cause immune function suppression accompanied by long-term immune dysregulation. Research has shown that stressful life events may also contribute to the incidence and progression of cancer. Studies suggested this adverse outcome might be associated with stress-induced changes in immune function [7].

It has also been shown that lack of energy expenditures can cause inefficient glucose utilisation and lead to chronic elevations of the two primary stress hormones, cortisol and epinephrine (EPI). Such elevations of the neuroendocrine concentrations will impede the action of insulin to promote glucose uptake and cause an increase in insulin levels. This adverse interaction between insulin and stress hormones will promote the deposition of body fat and can have dangerous effects on the body [8].

In extreme circumstances (such as major depression), elevations of endocrine concentrations may result in atrophy of pyramidal neurons in the hippocampus and shutdown of on-going neurogenesis in the denate gyrus [2].

Despite the general trend of stress on the health condition, an individual’s cognition of stress perceived can increase or decrease further risk of harm or diseases. Each individual interprets stressful situations differently [9]. Over-perceiving stressful situations can lead to high cost in physiological over-reactions and wasted behaviours.

Furthermore, the physiological conditions of an individual can also lead to different stress responses. People who are in good physical condition can have a rapid effect to increased glucose utilisation. On the other hand, individuals who experience metabolic imbalances (such as obesity and diabetes) can experience increased vulnerability to stress [2]. The vast variability of these effects and the difficulties in isolating different personal cognitive or emotional factors contribute to the main reason that hamper researchers’ efforts to quantify stress.
Over the past decades, most of the investigations have relied on endocrines or autonomic nervous system responses to stress for the evaluation of stress. However, clear definitions and a defined aetiology of stress remain to be justified.

The term stress has been applied to a vast array of adverse situations. There are difficulties in monitoring physiological responses and interpersonal variability. Distinguishing different psychological factors is an ambiguous problem and modelling these unjustified variables with endocrines or catecholamines is inevitably daunting.

Nevertheless, the impact of stress on health cannot be neglected. The ultimate goal of this thesis is to address the challenge in differentiating stress and to develop a biological model of stress responses in terms of the blood glucose subsystem of the human energy system that can be better understood by the non-specialised public.

Stress can be defined as any situation provoked by a psychological, environmental, or physiological stressor that threatens to disrupt the metabolic homeostasis \[10][11\]. It is generally divided into two categories viz. physiological stress and psychological stress. Physiological stress is mainly caused by exercise, illness and injury. Factors contributing to psychological stress include emotions and personal traits in reacting to specific psychosocial or environmental situations.

It must be emphasised that factors that result in physical and psychological stress are different for different people. That is, a stressor that may be stressful for one person at a particular time may or may not act as a stressor at a later point.

Daily life experiences may contribute to adverse health outcomes and be quantified as stress. However, measuring the physiological effect of stress is daunting, unless health conditions become pathophysiological or result in a disease \[6\]. Furthermore, states of stress overlap considerately, and for the evolutionary reason that stress does not have distinct boundaries \[12\]. Attempts to define stress have a long and unsatisfying history.

When an organism is confronted with any form of challenge (physically or psychologically), it causes a shift in the homeostasis of the organism. This may occur either in the short term or in the long term. Long-term homeostatic changes will normally lead to an alteration of any of the constituent parts within the organism.

Despite the possibility of interactions between different metabolic pathways, it has been shown that the demands for energy sources are increased when humans are exposed to stress \[13\]. The
scenario is generally problematic for individuals who experience hypoglycaemia or have poor glucose tolerance. Taken together, the findings suggest the importance of developing a sound model for quantifying stress.

1.2 Background for the development of stress models

In this section a short introduction concerning the development of stress models is given.

In the early 1900’s Walter B. Cannon demonstrated that when an organism confronts a situation, whether physical, mental, or emotional, which poses as a threat or a danger, it has a “fight or flight” response. This response involves the activation of the sympathetic portion of the autonomic nervous system and the activation of the adrenal medullary axis [4].

Cannon’s work was followed by Hans Selye. He approached the field of integrative physiology from a psychosomatic point of view. Selye focused much of his attention on stress-related disorders and the resulting disease states [4].

The early work of Selye suggested that both mental and emotional mechanisms appear to play a role in the regulation of the pituitary-adrenal cortical axis. Selye further stated that, despite the fact that an individual may experience different distress or emotions in a stressful situation, the physiological responses are uniform and non-specific. However, in contrast to Selye’s dogma, continuing scientific investigations dealing with the stress response and stress reactivity showed that the endocrine regulation is very likely to be much broader based [4].

The outcome of various investigations suggest that it is necessary to view integrative physiology from a broader perspective. The stress response is associated with physiological changes that occur in the physical body caused by physical, mental, or emotional influences. It must be incorporated while studying the interrelationships of the physiological regulatory mechanisms that occur within an organism [14].

1.3 Background: Psychological stress

In the presence of stressors, the hypothalamo-pituitary-adrenocortical (HPA) axis and sympathetic nervous system (SNS) play an important role in maintaining homeostatic stability. However, the HPA axis has been recognised as the major mediator that determines most of the acute and prolonged effects of stressors [15]. Upon the activation of the HPA axis, cortisol is secreted to redirect energy resources [16]. The end response to a stressor is a coordinated
biological response and behavioural depression. A strong relation between the HPA axis response and glucose metabolism has been recognised.

When facing a classical “fight-or-flight” situation, the sympathetic nervous system is consistently activated. An increase in sympathetic activity would generally cause increases in the heart rate and force of contraction; stimulated breathing; constriction of the blood vessels of the internal organs and dilation of skeletal muscles [17].

The role of the HPA axis during stress can also be fitted into the same paradigm. In a stressful condition, the HPA axis is activated. It subsequently stimulates the release of glucocorticoid. The major effects of cortisol are related to organic metabolism and glucose handling. When cortisol reaches the target cells, it simulates the liberation of amino acids. Many of these amino acids are converted by the liver into glucose and released into the blood stream. Secondly, glucocorticoid blocks the entry of blood glucose into various tissues when a stressful situation is experienced. Both of the effects cause the blood glucose concentration to rise [18].

In stressful situations, glucocorticoid is released to permit small blood vessels to remain partially constricted for long periods. Stress induces a tendency for small blood vessels to dilate. Nonetheless, this dilation is generally opposed by the increased activity of sympathetic nerves. It can only be prevented when the glucocorticoid concentration is high. If it should happen, the blood pressure would fall due to the lack of blood in the large arteries. Eventually, not enough blood could flow to the brain and heart muscle [18].

The major glucocorticoid in humans is cortisol. It has been found that about 90% of circulating serum cortisol is bound to corticosteroid-binding globulins (CBG) and albumin. Only about 5-10% of total serum cortisol is free. Studies showed that only the serum free cortisol is responsible for the physiological function of hormones [19].

It has been suggested that free cortisol index (calculated as the ratio between the serum total cortisol concentration and the serum corticosteroids-binding globulin concentration) is a better marker for defining glucocorticoid secretion [20].

Exposure to stress will cause the detachment of serum cortisol from CBGs and hence alters the percentage of free cortisol levels [20]. Unfortunately, many studies were conducted solely investigating serum total cortisol levels. Using unjustified serum total cortisol concentrations, a degree of uncertainty in quantifying the relationship between stress and physiologic hormones persists.
Chapter 1

Introduction

However, one study found that saliva cortisol is a better representation of free cortisol. It was further found that salivary cortisol is closely related to serum cortisol and suggested that they could be used interchangeably [21].

Besides cortisol and epinephrine, scientists have also observed changes in secretion rates of other hormones (such as glucagon, growth hormone and prolactin) during stress. However, there remains a difficulty in explaining the adaptive significance of these changes in terms of preparation for survival. Responses of glucagons, growth hormone (GH) or prolactin to stressful stimuli are controlled by other types of inputs and would not provide a good indication of stress. Changes in the activity of the SNS and the HPA pathways have conclusively been accepted as being virtually synonymous with stress [22].

Stress has various dimensions viz. duration, quantity, quality [23], and previous stress experiences [24]. Each individual copes differently with stress and the coping capacity often, but not always, depends on the two psychological variables viz. emotional ego involvement and suspenseful anticipation of noxious events [25]. Whenever physiological or psychological stress is experienced, the body metabolism is altered in a number of significant ways [26]. The ability to respond to the stressors with the necessary defence mechanism is crucial for survival in a potentially harmful environment [27]. However, the capacity for stress adaptation declines with age [28].

It has been shown that endocrine response is related to stressful situations [29]. Depending on the nature of the stimulus, the magnitudes of responses of hormones and time courses may vary considerably [22]. The release of endocrine hormones directly reflects on plasma glucose levels [23]. Unfortunately, research on the relationship between stress intensity and endocrine response in humans is inconsistent and scarce [29].

In many studies, endocrinological response to stress is tested with experimental simulated stress conditions or infusion of stress hormones. Only a few studies have been done on real-life situations and it is unclear whether the experimental stress response can be generalised for application to a real-life situation. Furthermore, in most protocols hormonal responses are investigated in subjects exposed solely to typified stressors.

As mentioned, studies on hormones in response to psychological stress in humans have been inconsistently observed. The dependency of specific hormones on responses to specific stressor stimuli remains unclear. Psychological stress induced surges in a few hormonal plasma concentrations notwithstanding, the majority of them have not yet been included in the theory of
stress and their contribution to the stress response is unproven [30]. Nevertheless, cortisol has been shown to be associated with the psychological stress of threatening situations and is generally considered to be the hormone related to psychological stress that does not require mental effort [30]. Furthermore, only deteriorated affects or emotions can cause cortisol levels to increase [31].

Steptoe et al. [31] conducted research on the relationship between positive affect and cortisol concentrations. They showed that positive affect is inversely related to cortisol output over the day. There is an average difference in cortisol level of 32.1% between the lowest and highest happiness quintiles. It is thus suggested that reduced cortisol and maintaining a positive affect is potentially relevant to health.

Aerobic glucose degradation is almost the only energy supply for the brain. At rest, the brain accounts for approximately 20% of total energy consumption. Compared to this large energy requirement, the energy stores in the brain are extremely small. The brain, therefore, requires continuous glucose supply [32].

Studies showed that mental inactivity requires a lower rate of brain metabolism than when information is processed. When mental activity is increased, glucose in the blood enters the brain. It is then directed to the areas that are metabolically active. Glucose administration has been shown to increase memory, especially when glucose is administered directly into the brain [32].

A number of studies have been conducted to investigate the cortisol response due to the experimental manipulation of control. Peters et al. found that uncontrollable tasks led to a higher increase in cortisol levels [33].

Generally, when a stressor is repeatedly exerted there is an adaptation to the stress response [33], indicating an effect of increasing subjective perception of controllability. Interestingly, the biological habituation patterns are not associated with the subjective stress ratings for subjects exposed to the Trier Social Stress Test (TSST). The degree of habituation depends on the response to cortisol. The HPA high responders generally show a greater activation and slower habituation compared to the HPA low responders [33].

Data shows that cortisol has potent immunosuppressant effects [34]. It implies that HPA high responders to repeated stress may have a decreased responsive immune system and be more
vulnerable to various diseases. However, dissociation between subjective and biological indices of stressors has been observed with respect to habituation.

Despite the habitual response of human behaviours, habituation to some of the repeated stressors does not occur. The hippocampus is associated with the downward regulation of cortisol production by corticosteroid feedback. Repeated episodes of non-habituated acute stressors or chronic psychological stress may cause a sustained high level of cortisol and result in certain cardiovascular diseases (CVD) and hippocampal damage. The induced hippocampal damage is generally accompanied by diminished inhibition to HPA hyperactivity [35][36].

A short background concerning the types of psychological stress is given in the following subsections.

**Emotion**

Expressed emotions developed from primitive actions are necessary for the survival of individuals. In humans, the affects are evolved and developed highly varied patterns of emotional expression (such as anger, fear, anxiety, love and joy) [37].

Exposure to acute emotions often leads to a series of parallel physiologic responses. Recently, several studies claimed that specific physiologic responses are correlated with different emotional states.

Evidence showed that a higher increase in heart rate is associated with negative emotions compared to positive emotions [38]. Other studies demonstrated that peripheral vascular resistance decreased during fear. Heart rate and systolic and diastolic blood pressure also increased, however, to a lesser extent, during sadness [39]. Most researchers believe any kind of emotional arousal is associated with increased activities in certain regions of the brain [40].

Differences in emotions that are encountered notwithstanding, emotional arousal generally involves the activation of the HPA and SNS systems. As previously discussed, the activation of the HPA axis stimulates the cortisol release, and the activation of the SNS system causes the secretion of epinephrine. Both stress hormones increase blood glucose levels.

**Depression**

Stress has long been considered to play a role in illness development [32]. The effects of chronic stressors on physiological system have been related to several adverse health conditions [41]. A
traumatic event may result in the development of depression and post-traumatic stress disorder [32].

Studies have demonstrated that major and prolonged depression is accompanied by a decrease in the volume of the hippocampus. The atrophy has a tendency of increasing with long-term depression and persists for decades after the illness has been resolved [42].

These phenomena prompt investigation of the possible causes of the volume loss. The loss may precede major depression; emerge as a consequence of the affective disorder, or a number of cellular phenomena. After all, one may argue that such mechanisms occur as a result of sustained stress. It is known that about half the cases of major depression involve some variant of hypercortisolism. As a result, it was suggested that excess cortisol is the prime mediating agent that causes the hippocampal volume loss [42].

When a stressful event is perceived, levels of cortisol increase through secretion by the adrenal cortex to modulate the usage of various fuel sources [26]. Simultaneously, dehydroepiandrosterone (DHEA) decreases and leads to muscle loss and fat gain [26].

Cortisol has important enhancing effects on the cardio-vasculature due to their augmentation of neuronal excitability of norepinephrine (NE) [28]. It is well known that excess cortisol will result in a high frequency of behavioural disturbances [36] and contribute to the onset of depression [23]. Studies showed that patients with depressive symptoms are most likely to develop and increase the risk of type 2 diabetes than healthy individuals [35].

Hypercortisolism is well known to be associated with hyperglycaemia. Research suggests that an excess of glucose may suppress adrenal medullary activity. Cortisol excesses are typically associated with obesity; elevated cholesterol levels, blood pressure, insulin resistance and serum glucose levels, and suppression of immune-cell activity [26][43].

It has long been known that cortisol inhibits glucose transportation to various peripheral tissues. A similar inhibition has been reported in the hippocampus.

(Chronic) work/job stress

Over the past decades, considerable attention has been paid to the relation between stress and the HPA axis. Several sources have demonstrated elevated cortisol levels in response to laboratory stressors [44]. However, clear links between work stress and cortisol have not been established.
It is clear that job stress will lead to negative physical health outcomes and causes 50-80% of serious illness [45]. Some authors have indicated the interaction of demands and control in causing job strain. However, there is no consensus among researchers regarding the best method for quantifying the interaction between job demands and job decision latitude.

A number of research studies have linked job strain to hypertension and cardiovascular disease and identified it as a risk factor for CVD. Studies showed that negative mood states are associated with an increase in cortisol levels. It was shown that chronic high job strain was associated with larger increases in cortisol levels than low job strain [46].

The prolonged psychological stress then leads to chronic elevations in stress hormones and contributes to the development of hypertension and CVD. Interestingly, the neurohormonal patterns are not associated with neutral mood states and positive affect [47].

In contrast to the result demonstrated by Steptoe et al. [31], it was shown that intense bouts of an activated state of positive affect can result in triggering short-term rises in physiological arousal and associated effects on immune, cardiovascular, and pulmonary function. However, the trait of positive affect has always been associated with increased longevity [48].

It was speculated that the arousing effects of extreme positive affect are typically less intensive and often associated with health protective responses [49]. Furthermore, it may be considered as a potential buffer against the adverse effects associated with chronic psychological stress. Recent studies have linked various positive affects to a number of beneficiary health outcomes [48].

Fredricson et al. [50] demonstrated that positive emotions could shorten the recovery of physiological indices after exposing test subjects to induced negative emotions. Furthermore, positive emotions have also been linked to lower overall mortality rates [51][52][53] and reduced susceptibility to the common cold [54].

It was shown that individual factors play a role in work-related illness. 75% of job strain is caused by interpersonal conflict [45]. Providing social support in the work place can certainly alleviate a stressful event.

Evidence showed that when three or more life events were experienced there was a significantly greater mortality from all causes. Over the past few years, work stress has been correlated with physical and mental health. Chronic job stress has been found to be associated with an increased risk of cardiovascular disease [28]. Individual susceptibility to stressors is an important
determinant of risk for future cardiovascular disease [28]. In most studies, data showed that cortisol diurnal rhythm is disturbed with chronic stress [46].

**Posttraumatic stress disorder (PTSD)**

Being exposed to a life-threatening or extremely distressing situation inducing intense negative feelings may result in the development of posttraumatic stress disorder. It exhibits as a delayed response to a traumatic event. Some findings suggest that previous distressing experiences (such as child abuse) may lead to persistent biological changes and increasing individuals’ proneness for developing PTSD [55].

In PTSD patients, certain memories of traumatic events (flashbacks) persist in the absence of the original traumatic stimuli. Consequently, patients become chronically anxious, tense, easily aroused and frightened [56]. It was shown that there was no association between PTSD and grief [57].

Research shows that PTSD and depressive disorders are both the outcomes of traumatic events. However, it has been difficult to provide a definite conclusion on aspects of biological differences and similarities between the two disorders [58]. However, some studies have shown that PTSD is associated with a downward regulation of the HPA axis. PTSD patients typically exhibit low cortisol responses relative to the amount of stress [56][59].

**Chronic fatigue syndrome (CFS)**

Chronic fatigue syndrome is typically characterised by severe debilitating mental and physical fatigue. The syndrome most likely represents the extreme illness of fatigue. As a result, this illness is accompanied by a significant loss of physical and social function for a minimum of 6 months [60]. CFS generally exhibits symptoms such as sleep disturbances, impairment in concentration, exacerbation of fatigue, and low-grade fever [61].

Cleare cited that approximately 0.5-1.5% of the population develops CFS [60]. However, the aetiology of CFS is unclear. No diagnostic tests and no definitive treatment are available for this chronic illness [62].

It was observed that major depression and CFS share a high degree of co-morbidity. However, major depression is well known to be associated with hypercortisolism and CFS exhibits hypocortisolism. Dynamic challenges of the HPA axis have been widely investigated with the infusion of hormones. Several studies showed that CFS patients are associated with possible
HPA axis dysfunction exhibiting mild cortisol deficiencies and reduced adrenocortical activity [63].

**Hypertension**

Enhanced activation of the HPA axis and stress-reactivity of the HPA axis have been linked to an increased risk for hypertension. It was shown that persons with high circulating cortisol normally develop glucose intolerance, insulin resistance, cardiovascular disease and hypertension [64]. Evidence shows that hypertension also has a great impact on stroke and cardiovascular disease [65]. It has been recognised as the second most common cause of heart failure [66]. Nevertheless, serious consideration has not been given to hypertension and a large number of hypertensives remain undiagnosed [67].

Studies showed that hypertension is significantly associated with stress, obesity, and cholesterol levels [68][69]. Larger cortisol elevation was observed in hypertensives during mental stress [70]. Literature sources have suggested that hypertensives are linked to the dysfunction of the HPA axis activation and higher cortisol sensitivity [71]. However, the mechanisms leading to the alteration is unknown [64]. Cortisol responses to repeated stressors were shown to decrease at a slower rate than that observed in normotensives, suggesting lack of habituation. Consequently, it re-enforces the potential higher risk factors for cardiovascular disease [64].

The importance of social support in improving conditions related to chronic stress such as hypertension has been shown. Research showed that by improving quality of life physiological stress can be significantly reduced [72].

**Cardiovascular disease**

It has been widely hypothesised that chronic stress is associated with cardiovascular disease. Researchers have shown that individuals with high job strain and who often experience negative affects are associated with a higher risk of cardiovascular morbidity and mortality. Nevertheless, more chronic stressors may actually be the cause of adverse psychological conditions [73].

Research has shown that personal vulnerabilities are associated with great distress and poor health habits, which often lead to the exacerbation of pathophysiology and elevations of endocrines and metabolites. As a result, the vulnerability to CVD and coronary heart disease (CHD) is increased [74].
Insulin resistance in individuals is normally associated with lower high-density lipoprotein cholesterol (HDLC), elevated levels of blood pressure reactivity and elevated cortisol levels. This evidence supports the hypothesis that obesity, diabetes and hypertension are often linked to a higher risk of CHD [74].

Evidence shows that stress management and exercise training can significantly reduce emotional distress, and consequently improve markers of cardiovascular risk [75]. It suggests that behavioural interventions play an important role [76].

**Insomnia**

Sleep disorder is a result of maladaptive conditioning and 75% of insomnia patients are chronically ill [77]. The attempt to force sleep makes insomnia a stressor. Individuals with a higher degree of stress are generally associated with insomnia. It has been shown that sleep deprivation of up to 4 hours resulted in an enhanced evening cortisol secretion. Consequently, it may cause an adverse health outcome.

It is well known that the number of nighttime waking hours is positively associated with aging. Researchers have shown that waking hour increases and rapid eye movement (REM) decreases by approximately 30 and 10 minutes, respectively, per decade from middle age to aged life. REM sleep has been shown to be primarily associated with cortisol increases [78]. Alternatively, deep sleep has a suppressive effect on the stress system, particularly the HPA axis. The greatest elevation of cortisol and a strong correlation to sleep disturbance have been found in the first half of the night. This increased exposure to cortisol may result in a feed forward cascade contributing to the higher secretion of cortisol observed in insomniacs [77].

Problems related to sleeplessness generally lead to daytime sleepiness and fatigue. Similarities exist between the two symptoms. However, the latter has been shown to be linked to decreased performance but not the former. Vgontzas et al. have suggested that the two syndromes should not be viewed as interchangeable [78].

### 1.4 Background: Physiological stress

Studies showed that human bodies respond to psychological stress with the same hormonal cascade as that which takes place when physical stressors are experienced [26]. Aspects of physiological responses are addressed in this subsection.
Exercise

Physical activity has been considered as a metabolic stressor [79]. During exercise, the metabolic homeostasis is disturbed. A stimulus is secreted to release endogenous stores from the body providing substrate to fuel the metabolic reactions. The increased exercise intensity is reflected by the rate of substrate depletion.

The metabolic stress during physical activity is determined by the intensity and duration of the exercise, nutritional state and physical fitness. These factors influencing the stress can be controlled to some extent [79].

During physical activity, the major substrates used by muscle are fat and carbohydrate [79]. However, when both substrates are available carbohydrate is preferred. Generally skeletal muscle stores 1500-2500 kCal of glycogen. The hepatic glycogen stores serve primarily to maintain blood glucose concentration and amount to approximately 240 kCal. During prolonged exercise, blood glucose uptake can increase to about 1-2.5 g/min. Therefore, after 2-3 hours of exercise, glycogen depletion generally occurs and people typically experience hypoglycaemia [79].

Evidence shows that physical inactivity and inappropriate diet consumption are linked with most chronic diseases [80]. Clearly, physical activity can improve a person’s health by stimulating healthy adaptation in numerous tissues and organs [79]. It is well known that there is an increase in fat oxidation during endurance training. Coyle [79] cited that during low-intensity exercise, the rate of fat oxidation in endurance-trained persons is 32% higher than that of untrained persons.

Critical illness and injury

Critical illness is linked to major metabolic stress and often results in systemic inflammatory response syndrome (SIRS) [81]. Severe metabolic stress such as critical illness, trauma and surgery are generally associated with the activation of the HPA axis resulting in an increase of serum cortisol levels. The activation of the HPA axis is necessary for maintaining metabolic homeostasis. Alterations in glucose metabolism and adaptive responses such as elevations of cortisol levels often cause critically ill patients to become hyperglycaemic. Due to the variation in diagnosis criteria, a blood glucose concentration ranging from 6.7 to 11.2 mmol/l is often used to indicate a state of stress hyperglycaemia [82].
Patients with septic SIRS have increased metabolic stress and an overall increase in resting energy expenditure. As a result, patients suffering from septic SIRS generally exhibit a higher mortality and a longer intensive care unit (ICU) stay than those with non-septic SIRS [81]. It was shown that the respiratory quotient (RQ) is decreased in septic SIRS patients indicating a decrease in glucose utilisation and an increase in fat and protein oxidation during septic SIRS [81].

It has been shown that mortality of head injury patients and blood glucose reveals a positive linear relationship [83]. Hyperglycaemia is generally associated with head injury. However, the mechanism of the excess blood glucose is unclear. Some researches postulate that hyperglycaemia causes secondary damage after severe injury, while others believe that is merely a stress response to severe injury.

Major injury or major surgical procedures often result in severe immunosuppression. It consequently leads to delayed wound healing and infectious complications [84].

1.5 Mission statement and objectives

The mission statement of this thesis is to develop a model that dynamically integrates stress responses to the bodily blood sugar energy system.

The objectives were formulated as follows:

- Different categories of stress had to be quantified;
- A link between blood glucose and stress had to be established;
- A model representing the integrated system of stress and blood glucose had to be formulated;
- The accuracy of the model had to be evaluated and verified.

1.6 Contributions of the study

The main contribution of this research the following:

During periods of increased stress, there is often an increase in the incidence of chronic conditions, such as diabetes, cardiovascular disease, and cancer. The primary effects of stress in
raising one’s risks of diabetes are related to chronically elevated levels of blood glucose and insulin. Over time, the body becomes less sensitive to the effects of insulin and develops insulin resistance. To prevent developing diseases or complications, a model underlining the physiological response of stress is necessary. This research provides a quantification method to describe the effect of stress on the human body.

The quantified relationship between stress and blood glucose is not well known. In this study, a link between blood glucose and stress was derived. Due to the specificity of different types of stress, the two endocrine systems (the HPA axis and the SNS system) were investigated. The glycaemic response of stress that requires effort was derived indirectly via the EPI response stimulated by the SNS system. The cortisol response stimulated by the activation of the HPA axis was utilised to derive the glycaemic response of effortless stress.

The derived glycaemic response was then associated with the equivalent teaspoon sugar (ets) concept. The ets concept developed by Human-Sim (Pty) Ltd. is a novel unit for quantifying energy and energy flow in the human energy system.

It has been shown that there is a linear relationship between the insulin response and the amount of ets ingested. From the stress-ets link, the insulin requirements for type 1 diabetics can thus be calculated. With the link established, individuals (especially patients with diabetes or poor glucose tolerance) can incorporate the concept with stress management and use it to achieve better glycaemic control.

1.7 Outline of the study

The rest of the study is presented as follows:

- Chapter 2 discusses the background of human physiology linked to the blood energy system. It also provides a discussion on the psychobiology of stress.

- In Chapter 3, the ets concept is presented and is used extensively for quantification of the energy flow processes.

- The link between blood glucose and stress is formulated in the first part of Chapter 4. Stress quantification models are derived in the second part of the chapter.

- In Chapter 5, the verification of the quantification models is performed.
Chapter 6 concludes the study. Recommendations for future work are provided.

1.8 References


Chapter 1

Introduction


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CHAPTER 2
HUMAN ENERGY SYSTEM
AND STRESS PSYCHOBIOLOGY
Chapter 2  
Human Energy System and Stress Psychobiology

2.1 Introduction

The first part of this chapter provides insight into the acquisition, storage and utilisation of the fuel energy used by the human body. The control system involved with glycaemic response is also discussed. The second part of the section provides evidence that stress fits the energy model. Subsequently, the psychobiology of stress is discussed.

2.2 Fuel substrates

All nutritious food contributes energy substrates for the human body. Through digestion, all food ingested is broken down into absorbable components. They are either used as direct energy supply or transferred to storage for later use.

Fuel sources are needed by humans for energy for metabolism, movement and mental functions. Glucose, fructose, keto acids, fatty acids and ketones are the main fuel types that can be combusted directly into energy for the human body [1]. Each part of the human body requires different energy substrates. The brain and the central nervous system rely primary on blood glucose [2]. The limbs and heart muscle require ketones [1].

Carbohydrates are converted into glucose, fructose and galactose. Only glucose can be used directly as energy. Fructose and galactose have to be converted into glucose before utilisation. Excess glucose is converted into glycogen by insulin, and stored in the liver and muscle tissue. When energy is required, counter-regulation hormones (such as cortisol, epinephrine and glucagons and growth hormone) convert glycogen stored in the liver and muscle tissue back to glucose [3] and release it into the bloodstream.

Fat is a fuel substrate that has the most available energy per mass. Ingested fat is decomposed into triglycerides and stored in the liver and adipose tissue. When the glucose level is low, the triglycerides are converted into glycerol and fatty acids in the adipose tissue. The glycerol is then converted to glucose by the liver to replenish the shortage of blood glucose [3].

Protein is another fuel source, and is converted into amino acids when ingested. Amino acids are then broken down into keto acids and fatty acids in the liver. During protein metabolism, fatty acids are burned for energy and ketones are released as by-product. When there is a shortage of blood glucose, protein in the muscle tissue is broken down into amino acids. These amino acids are converted into keto acids and then into glucose by the liver [3].
2.3 Energy utilisation

The requirement for human energy and the utilisation of specific fuel sources rely on an individual's health status, the ability to satisfy the demands imposed by the environment, and other physical activities. In this subsection, factors related to the variations in energy utilisation are discussed.

**Basal metabolism**

The basal metabolism is the minimum energy required to maintain the functionality of the human body and to keep an individual alive [1]. The energy output rate measured under the basal metabolism reflects the energy the body requires to perform only its essential activities, such as breathing and maintaining resting levels of organ function.

Basal metabolism is the highest form of caloric expenditure. Carbohydrates, fats, and proteins are the primary substrates that supply the body with energy for basal metabolism. At rest (in a neutrally temperate environment), the energy requirement for the basal metabolism results in approximately 70% of the total energy expenditure. Physical activity, and thermogenesis or digestion of food results in about 20% and 10% of an individual’s total energy expenditure respectively [3].

Any distortions to the metabolic homeostasis will cause an increase or a decrease in the demand for energy and alters the metabolic rate. For example, increased cardiovascular exercise will increase oxygen uptake and increase substrate oxidation [4]. Furthermore, under a stressful condition or experiencing severe illness, several metabolic pathways that consume large amounts of energy are activated [5]. All of these mechanisms have an influence on the metabolic rate and thus promote hypermetabolism.

**Growth**

Growth occurs through the successive division of cells. The rate of growth is determined by several factors, one of them being the energy available to an individual. Under optimal circumstances, growth appears to take place on a weekly basis instead of a day-to-day basis. During growth, the requirement for protein increases as the demand for lean tissue synthesis increases [6].
There is a great degree of inter-variability in individual patterns of growth. However, stages of growth generally follow an S-shaped curve. It is slow at the beginning (at birth), and is followed by a period of rapid body development up to the time of puberty. It then slows down after reproduction maturation [6].

Growth hormone is the primary regulator secreted by the pituitary gland that controls general body growth and influences the metabolism. GH is secreted in bursts. The peaks are most closely associated with the sleep cycle. Besides its obvious function in facilitating body growth, growth hormone is also associated with tissue maintenance and repair. Some studies have found that during stress, besides cortisol and EPI, growth hormone was also secreted to facilitate the energy demands required for coping [6]. Other studies suggested that the disappearance of deep sleep as a person ages is associated with a reduction of GH release [7].

**Physical activity and exercise**

At rest and during low intensity activities, the aerobic system is the primary mechanism for energy conversion, and uses primarily carbohydrate and fats as substrates. At rest, about 70% of energy is derived from fats and 30% from carbohydrates. There is a shift in substrate utilisation as the intensity of physical activity increases (as shown in Figure 2.1) [8]. Significant metabolism of protein only occurs during long-term starvation and long bouts of physical activity.

![Substrate utilisation during exercise](image)

**Figure 2.1: Substrate utilisation during exercise (VO$_{2\text{max}}$ is the maximal oxygen uptake)** [8].

During aerobic work, 50 to 60% of the energy comes from fats. Carbohydrates are used during the first several minutes of exercise. For a person of average fitness, it takes 20 to 30 minutes of continuous aerobic activity to burn 50% fat and 50% carbohydrate [8].
Proteins contribute less than 2% of the substrates used during exercise of less than 1 hour. It may reach 5 to 15% of the fuel supply during the final moments of exercise lasting 3 to 5 hours. If glycogen storage and energy intake are inadequate, protein can supply up to 10% of the total energy expenditure during prolonged intense exercise [8].

During high intensity or low duration aerobics, there is an increased blood level of epinephrine. High levels of epinephrine increase muscle glycogen breakdown, glycolysis and lactate production. Low intensity exercise (oxygen uptake < 30% VO$_2$$_{max}$) relies primarily on fat; whereas during high intensity exercise (oxygen uptake > 70% VO$_2$$_{max}$) the body primarily utilises carbohydrate [8].

**Stress**

It is commonly accepted that stress is a condition or feeling experienced (i.e. psychological, illness or injury) when a person perceives that ‘demands’ exceed the personal and social resources the individual is able to mobilise. Stress behaviour and emotions are sometimes regarded as problematic inappropriate responses to threatening situations in modern civilised society.

Stress is initially evoked by an external or internal stimulus that is perceived as a threat. If a stimulus is exerted externally, it is received by sensory receptors of the peripheral nervous system. The information is sent via sensory neural pathways to the brain. These signals are relayed on to the limbic system and may be integrated with emotional states [9].

The information is sent to the cortical levels of the brain where an analytical interpretation of the stimulus occurs. The interpreted signals are sent back to the limbic system where an emotional arousal will probably occur. If the stimulus is exerted internally, the sensory receptor activation is bypassed [9].

Once the stressful stimulus is interpreted, the body enters the final phase of the stress response, which is a result of activation of the endocrine axis. During stressful events, stress hormones such as cortisol and catecholamines are released. They trigger a series of responses that give the body additional energy. The blood glucose level is raised, heartbeat speeds up and blood pressure increases. These hormones focus our attention on the threat, to the exclusion of everything else. All of this significantly improves our ability to survive life-threatening events [9].
Unfortunately, the mobilisation of the body for survival also has negative consequences. Too much stress can cause physical illness, such as high blood pressure, ulcers or even heart disease. Stress also increases the frequency and severity of migraine headaches, episodes of asthma, and fluctuations of blood sugar in diabetics. However, physical stress from work or exercise is not likely to cause such ailments [9].

It is stated that the stress response is evoked as a direct result of the cognitive interpretation and emotional arousal of the organism. The stress response that occurs within the body is comprised of over 1,400 physiochemical changes. The changes can be activated to various degrees and at various periods. These reactions are ultimately mediated by neuroendocrine mechanisms [9].

**Illness**

Hyperglycaemia is common during critical illness. It is necessary to ensure an adequate supply of enhanced glucose uptake in the brain and at phagocytic cells. During critical illness, hyperglycaemia is promoted through an activation of the hypothalamic-pituitary-adrenal axis. Hyperglycaemia has been noted in approximately 50% of non-diabetic patients in the intensive care unit. It may be a presenting manifestation of occult diabetes mellitus [10].

Initially, glycogen is used as the fuel source in a critically ill person. However, the glycogen store is limited in the human body. The glucose supply derived from glycogen is rapidly depleted and protein hypercatabolism becomes functionally important [11]. Glucose is derived from amino acids by gluconeogenesis via the metabolism of protein. Simultaneously, the body also mobilises and oxidises fat stores.

Depending on the length of exposure to critical illness, the neuroendocrine responses can be quite different. It was observed that in an acute phase, the endocrine changes observed in critical illness is mainly characterised by an actively secreting anterior pituitary gland and a peripheral inactivation or inactivity of anabolic hormones. Prolonged critical illness is characterised by reduced neuroendocrine stimulation [11].

**2.4 Energy storage**

A certain amount of energy is necessary to sustain and regulate our body function. When extra calories are ingested the majority of the energy reserve is in the form of fat stored as triglycerides in adipose tissue. The major sites for energy storage in the human body are the liver, muscle, and adipose tissue [12].
The liver

The liver is one of the most complex organs in the body. It carries out more than 500 metabolic functions. Its role as energy storage for fuel substrates in the three major metabolic functions are given below [13]:

- Carbohydrate metabolism
  - Converts galactose and fructose to glucose;
  - Stores glucose as glycogen (with the maximum amount of glycogen amounting to about 100g in an average sized person) when blood glucose concentrations are high;
  - Converts glucose to fats for storage.
- Fat metabolism
  - Stores triglycerides (fats).
- Protein metabolism
  - Stores amino acids.

Muscle tissue

In muscle tissue, glucose is also stored in the form of glycogen. However, muscle tissue does not have glucose-6-phosphatase; muscle glycogen can only be used by the muscle fibres and cannot be transported to other tissues [12].

All proteins in the body are function proteins. They are either part of tissue structures or part of the metabolic system. Muscle tissue consists of protein filaments. These filaments are responsible for movement. However, if energy is required, these muscle proteins are catabolised to free amino acids and release energy [12].

Muscle tissue is metabolically more active than adipose tissue. If the percentage of muscle mass in the body is increased, it will cause the metabolic rate to increase as well [12].

Adipose tissue

Fats are found in the body mainly as triglycerides, phospholipids and cholesterol. Triglycerides are mainly stored in adipose tissue. It provides a long-term reserve of metabolic fuel [3].
Fat makes a major contribution to the production of cellular energy. However, it can only be used in the form of fatty acids. These acids must first be released from stored fats. They must then be directed into metabolic pathways in the mitochondria of cells to generate usable chemical energy [3]. During exercise, free fatty acids (FFA) mobilised from adipose tissue provide one of the major fuel forms of fat available to the muscle [14].

2.5 Control hormones

In the human energy system, there are two types of hormones controlling the internal homeostasis, viz. the regulatory hormone (insulin) and the counter-regulatory hormones (cortisol, glucagons, epinephrine and growth hormone).

Insulin

The pancreas secretes approximately 40 to 50 units (U) of insulin per day in normal adults. The basal blood concentration of insulin is 10 μU/ml.

Glucose is the most potent stimulant of insulin release. When glucose concentrations are increased above a critical level of about 80 to 100 mg per 100 ml, a rapid secretion of insulin is stimulated. This will cause glucose uptake in tissue cells. The subsequent decrease in blood glucose levels inhibits the further release of insulin [6].

The negative feedback relationship between blood glucose levels and insulin is modulated by several other hormones and metabolites. During stress, insulin secretion is influenced by factors that are related to blood glucose levels and the levels of other stress hormones [9].

The main function of insulin is to promote uptake and storage of ingested nutrients. The major effects of insulin on the liver, muscle and adipose tissue with regard to energy storage are given below [6] [13].

- Liver: Insulin promotes glycogen synthesis and inhibits gluconeogenesis through its effects on enzymes on the glycolytic pathway. The liver has a maximum storage capacity of approximately 100 g of glycogen.
- Muscle: Insulin promotes protein synthesis in muscle by increasing amino acid transport. By increasing glucose transport into the muscle cells, insulin promotes glycogen synthesis to replace glycogen stores expended by muscle activity. Approximately 400 g of glycogen is stored in the muscle tissue of an average sized man.
- Adipose tissue: The energy content of adipose tissue is approximately 100,000 kCal in a typical 70 kg man. Insulin promotes triglyceride storage by a number of mechanisms. It enhances hydrolysis of triglycerides from circulating lipoproteins by inducing the production of lipoprotein lipase. When the levels of glucose transported into fat cells are increased, insulin enhances the availability of a-glycerol phosphate. Insulin also inhibits intracellular lipolysis of stored triglyceride.

Cortisol

Cortisol is produced in the adrenal cortex under the control of the hypothalamic-pituitary-adrenal axis. It plays a key role at times of stress and exerts several physiological effects on the metabolism. Liver gluconeogenesis is the most prominent effect of cortisol [9].

Under the influence of cortisol, amino acids are transported out of extra-hepatic tissues (especially muscle tissues) into the liver. As a result of high levels of circulating cortisol, glucose uptake is decreased in some tissues [9].

High levels of cortisol cause a decrease in protein synthesis and an increase in protein breakdown in almost all cells of the body except the liver. Cortisol also increases cellular fatty acid oxidation. It stimulates lipolysis and promotes the lipolytic effect of epinephrine. As a result, the production of glycerol and lactate is increased, which in turn will enhance gluconeogenesis [9]. It has the physiological effect of increasing blood pressure, blood glucose concentrations and has an immunosuppressive action.

Cortisol obviously has profound effects on both glucose and protein metabolism. The enhanced preservations of metabolic substrates provide an excellent preparation for stressful situations. Liver glycogen serves as a readily available reserve of energy that can be used by glycogenolytic hormones in times of stress [9].

Blood cortisol levels exhibit diurnal variance, with the highest levels present in the early morning, and the lowest levels present around midnight, 3 to 5 hours after the onset of sleep. Psychological stress, clinical depression, fear, pain, illness, fever, trauma, and surgery have been shown in association with disturbed serum cortisol patterns.
Epinephrine

Epinephrine (also known as adrenalin) is also secreted in situations of stress. It acts as neurotransmitter in the central nervous system (CNS) and as a hormone in blood circulation. The hormone enhances the supply of oxygen and energy-giving glucose to the brain and muscles [9].

Epinephrine release plays a central role during short-term stress. When released into the bloodstream, epinephrine increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gut while dilating arterioles in skeletal muscles [9].

Increased epinephrine levels in the blood enhance catalysis of glycogen to glucose in the liver. It in turn elevates the blood glucose level. Abnormally high levels of epinephrine can occur in CNS trauma caused by stimulation and/or damage of nuclei in the brainstem [9].

Growth hormone

Growth hormone is a protein hormone. It is synthesised and secreted by somatotrophs in the anterior pituitary gland. The major function of the growth hormone is to stimulate growth and control metabolism. A majority of the growth promoting effects of growth hormone is due to insulin-like growth factor-I (IGF-I) acting on its target cells [15].

GH has important effects on protein, fat and carbohydrate metabolism. It is one of the major hormones that serve to maintain blood glucose levels. GH is often regarded as a counter-regulatory hormone that inhibits the ability of insulin to stimulate uptake of glucose in peripheral tissues and enhance glucose synthesis in the liver.

Production of growth hormone is modulated by factors such as stress, exercise, food intake and sleep. Basal concentrations of growth hormone in the bloodstream are often low. The most intense period of growth hormone release is shortly after the onset of sleep [16].

Glucagon

Glucagon is produced by the alpha cells in the islets of Langerhans within the pancreas, and is involved in carbohydrate metabolism. During hypoglycaemia, glucagon is released. The hormone causes the liver to convert the stored glycogen into glucose and release it into the bloodstream. It has a counter-regulatory effect of insulin.
Chapter 2

Human Energy System and Stress Psychobiology

The main effect of glucagon is to enhance the concentrations of blood glucose. When blood glucose levels fall below the normal range, glucagon is released and exerts control over the metabolic pathways within the liver [17]:

- Glucagon stimulates breakdown of glycogen stored in the liver;
- Glucagon activates hepatic gluconeogenesis;
- It also has a minor effect of enhancing lipolysis of triglyceride in adipose tissue and the formation of ketones and ketoacids.

Elevated blood levels of amino acids and exercise appear to trigger glucagon secretion.

2.6 The blood sugar control processes

The human energy system consists of three major pathways: the pathway for carbohydrate (glucose) metabolism, the pathway for fat metabolism and the pathway for protein metabolism. These systems are important for providing energy to different tissues in the body. They do not process exclusively. They are interlinked, with one pathway being more dominant than the other two processes depending on the internal and external stimuli [6].

Among the three pathways, perturbed blood glucose levels caused by a number of influencing factors are much more measurable when compared to the energy pathways for other fuel substrates. Furthermore, most of the clinical illness or diseases have been associated with blood glucose. For this reason, only the glucose (glycaemic) response is investigated in this study. Knowledge of the regulatory mechanism for the blood glucose control system is essential. A simplified control system of the human body is illustrated in Figure 2.2.

In the figure, changes in blood glucose concentrations and direction of energy flow are indicated by arrowed hairlines. Broken arrowed lines indicate control mechanisms and direction of targets. “Bs+” and “Bs−” indicate an increase or decrease in blood glucose levels [18].

Blood glucose is an important fuel substrate required by the human body in order to function properly. The maintenance of blood glucose at normal levels is controlled by an efficient regulatory mechanism.

As shown in Figure 2.2 when carbohydrate is ingested it causes an increase in the blood glucose level. The fluctuated glucose concentration stimulates the pancreas and causes it to release
insulin. The hormone then promotes glucose uptake by the target organs or tissues. A part of glucose is burnt to release energy while most of the portion of glucose is converted to glycogen and stored in the liver and muscle cells. A small amount of glucose is converted into triglycerides and stored as energy reserves.

In a situation when an external stimulus (such as stress or illness) is exerted, it requires the body to release energy to counteract the threatening environment. When a threatening stimulus is
sensed in the central nervous system, it causes the counter-regulatory hormones (i.e. glucagon, growth hormone, epinephrine and cortisol) to be secreted and released into the bloodstream. All of these hormones have the common goal of raising the blood glucose level by promoting glycogenolysis, gluconeogenesis, and lipolysis. However, depending on the type of stimulus exerted, one hormone may be more dominant than the other counter-regulatory hormones.

Normally, blood glucose concentrations remain at levels between 4 to 6 mmol/l throughout the day. However, the concentrations are higher after meals and usually lowest in the morning. If a person has diabetes or is ill, their blood glucose levels usually increase beyond this limit [19].

Physiological and clinical evidence indicates that blood glucose regulation is the result of both dissipation of insulin and activation of glucose counter-regulatory systems. Insulin was identified as a dominant hormonal regulator (a regulatory hormone) of both glucose appearance and disappearance in the circulation. In defence against decrements in plasma glucose, glucagon, epinephrine, growth hormone, and cortisol play counter-regulatory roles. They are characterised as stimuli of hepatic glucose production [19].

**Regulatory hormones**

A regulatory hormone is a hormone that stimulates the liver and muscle cells to facilitate storage of blood glucose in the form of glycogen. It also causes fat cells to take in blood lipids and decompose them into triglycerides. Insulin is the only regulatory hormone identified in the energy system.

Insulin is synthesised in the pancreas within the beta cells of the islets of Langerhans. The secretion of the hormone is mainly stimulated by high blood glucose concentrations. Some insulin synthesis and release generally takes place during food intake.

For short-term availability to the liver and in the muscle tissue, blood glucose is converted by insulin into glycogen. If the glycogen storage level reaches the liver’s storage capacity, excess blood glucose is converted into triglycerides for longer-term storage or other utilisation [19][20].

Substances such as amino acids and acetylcholine are also known to stimulate insulin release. However, their effect is considerably less when compared to that of glucose.
Counter-regulatory hormones

Counter-regulatory hormones are hormones that oppose the action of insulin. They have the effect of raising blood glucose levels by promoting glycogenolysis, gluconeogenesis, ketosis and other catabolic process. Concentrations of counter-regulatory hormones are expected to rise as glucose levels decrease. Persistent elevation of a counter-regulatory hormone can reduce a person’s sensitivity to insulin. These hormones include glucagon, epinephrine, cortisol and growth hormone.

The physiological roles of each counter-regulatory hormone are described as follows:

Glucagon plays a key role in glucose metabolism. It is released into the bloodstream when circulating glucose is low. The main physiological role of glucagon is to stimulate hepatic glucose output in response to insulin-induced hypoglycaemia. It has often been considered as the major counter-regulatory mechanism for insulin in maintaining glucose homeostasis [17].

During “fight or flight” responses, epinephrine is released from the adrenal glands. When secreted into the bloodstream, it causes hyperglycaemia in humans by both increasing glucose production and decreasing glucose clearance [21]. Epinephrine decreases glucose clearance by inhibiting insulin secretion [22].

Cortisol has the effect of stimulating several metabolic processes that collectively serve to increase blood glucose levels. These processes include stimulation of gluconeogenesis (conversion of amino acids into glucose), metabolism of amino acids from muscle tissues, inhibition of glucose uptake in muscle and adipose tissue, and stimulation of fat breakdown in adipose tissue [23].

Under conditions of stress, cortisol normally maintains blood pressure and limits excess inflammation. However, too much cortisol is often secreted and leads to the over-reactions of adrenal stress responses in an individual [23].

The effect of anterior pituitary growth hormone on carbohydrate and lipid metabolism can be divided into acute insulin and chronic anti insulin-like activities. The acute insulin-like effects cause increases in glucose utilisation and decrease of blood glucose. The chronic anti insulin like effects result in inhibition of glucose utilisation and stimulation of lipolysis [24]. Inhibition of glucose utilisation is caused by reduced hepatic and peripheral insulin sensitivity [22]. It was considered that impairment of glucose uptake was a secondary effect of a growth hormone-
mediated increase in lipolysis, rather than a direct effect of glucose transport and metabolism [22].

Despite the glucose raising effect of each counter-regulatory hormone, Schwartz et al. showed that glycaemic thresholds for activation of glucose counter-regulatory systems are different [25]. The glycaemic thresholds for epinephrine, glucagon, cortisol and growth hormone under hyperinsulinemic clamp conditions are shown in Table 2.1.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Glycaemic threshold (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>3.83</td>
</tr>
<tr>
<td>Glucagon</td>
<td>3.77</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>3.66</td>
</tr>
<tr>
<td>Cortisol</td>
<td>3.22</td>
</tr>
</tbody>
</table>

Clearly, each counter-regulatory hormone is stimulated and released under different glycaemic conditions. It should be noted that the respective glycaemic thresholds shown in Table 2.1 should only be viewed as estimates of biologic thresholds and should not be used as estimates under other conditions [25].

Energy balance is regulated by the central nervous system. This regulation involves the monitoring of stored fuel (primarily glucose). This mechanism is critical. It must ensure that there are sufficient fuel stores and available fuel to meet immediate metabolic needs [26].

Glycogen forms an energy reserve that is readily available and can be rapidly mobilised to glucose. It is stored in the liver and skeletal muscles. However, muscle glycogen is not generally accessible to other organs [27].

When the blood glucose begins to fall below the threshold level, counter-regulatory hormones are secreted, stimulating liver glycogen breakdown into glucose. Muscle glycogen serves as immediate fuel energy of available glucose for muscle cells [27].

In skeletal muscle, pyruvate is reduced to lactate in the absence of oxygen. Lactate formed is then removed from muscle cells and is converted to glucose in the liver [27].

Glycerol, derived from hydrolysis of triacylglycerols, is also a significant input to glucose metabolism. It is found principally in adipose tissue. When the body uses stored fat as an energy source, glycerol is released and transported to the liver in the presence of counter-regulatory hormones. In the liver, it enters the gluconeogenesis pathway in order for the liver to produce glucose [27].
During the energy utilisation process, glucose is required by cells. Glucose transport and absorption occurs in the presence of insulin. When muscle fibres are stimulated by insulin, muscle cells become permeable to glucose. However, if insulin is absent, uptake of large amounts of glucose by muscle cells can only occur during moderate or active physical activities. This is essentially the problem for type 1 diabetic patients who normally experience poor glucose tolerance.

Fat oxidation is mostly dependent on the endocrine environment and blood glucose availability. When insulin and blood glucose concentrations decrease, the rate of lipolysis increases and more fatty acids are released from the adipose tissue and fats are used as an energy source [28].

2.7 Theoretical basis: stress and energy model

In the past decades, a number of research studies indicate that self-control relies on a limited energy source. Recently, Gailliot and Baumeister suggested that this energy source is blood glucose in particular. The authors suggested that acute self-control demands a large amount of blood glucose. If glucose concentrations are low or cannot be mobilised effectively, it usually causes self-control failures [29].

Self-control is the conscious form of self-regulation with effort. It includes controlling attention, regulating emotions, coping with stress, resisting impulses and aggressive behaviour [29]. Self-control is important for the optimal functioning of humans individually and collectively. It is helpful in facilitating interpersonal co-operation and group harmony.

For the past decades, many researchers believed that the human psyche involves some recognition of brain processes. Several studies indicate that self-control involves brain activity occurring mostly in the prefrontal cortex [30].

As is known, blood glucose is the main fuel substrate used by the brain. In its normal resting state, the brain accounts for over 55% of the body’s glucose consumption [31]. The brain has virtually no glucose reserves. Its metabolism and function are dependent on a continued supply of exogenous glucose in its circulation [31]. Actions that require intensive processing (i.e. self-control) require a relatively large amount of blood glucose. These can reduce blood glucose concentrations, and impair subsequent executive functioning [29].

It has been shown that performance at diverse mental tasks steadily declines. However, the performance is improved or restored, when participants are provided with glucose load. The
subject's blood glucose level at the time of tests was found to correlate with improved intellectual performance [32]. This finding suggests that during mental tasks glucose is consumed as an energy substrate. Glucose, thus, gained plausibility as one physiological substrate of self-control.

As mentioned, brain processes depend on energy consumption from blood glucose. However, the amount of glucose involved may be small or negligible. Self-control plays an important role in daily life and has a widespread influence on a broad range of behaviours. As a result, acts of self-control generally have large energy requirements. In contrast, most other psychological processes may be relatively low in energy requirements [29].

Research has shown that self-control depends on a limited energy source. Individuals are more prone to failures at subsequent self-control acts. It was indicated that this energy substrate appears to be the common source for many other forms of self-control, such as emotion regulation, attention control, impulse control, and performance optimisation.

Several laboratory studies reported that the consumption of breakfast is associated with improved mood shortly after the meal [33][34]. However, the consumption of a larger breakfast is associated with a poorer mood later in the morning. Nonetheless, this effect was reversed by eating a snack [35].

In another study, it was found that presenting oneself effectively to others tends to deplete the energy resource for subsequent self-control process. The resource depletion is worse when participants presented their most positive qualities to others. These findings suggest that the inner process (i.e. energy consumption or depletion) may serve individual or interpersonal functions [36].

Muraven and Baumeister suggested that coping with stress, regulating negative affect, and resisting temptations require self-control. The authors argued that coping with stress leads to a decreased ability to exert self-control. Evidences also confirm that exposure to stressful, uncontrollable situations tend to cause subsequent attempts at self-control to fail even after the stress has completely ended [37].

In principle, it was suggested that many different irrelevant behavioural operations (such as regulation of emotions and coping with stress) indeed rely on the same limited energy resource [36]. However, it has not yet been identified whether this energy resource is blood glucose or
other substrates such as fat or protein. Nonetheless, several studies suggested glucose as an important component of the energy source of behavioural operations [29].

As mentioned, the brain consumes blood glucose almost exclusively as an energy source. The brain generally consumes glucose at almost the same rate as it can be replenished. Thus, it is likely that under intensive cerebral activities this energy source could be depleted. Several studies indicate that subtle changes in glucose concentrations could lead to an alteration in thoughts and behaviours [38][39].

Indeed, cognitive functioning or coping with stress does not only depend on blood glucose concentrations. It also relies on the body's ability to use glucose effectively. Individuals with good glucose tolerance can store glucose and mobilise this energy source from its stores as required. It was found that individuals with good glucose tolerance tended to perform better than individuals with poor glucose tolerance [40].

In agreement to the relation between the degrees of success of subsequent self-control and the degree of effort for impression management, studies found that executive processes or processes that require effort deplete more glucose than simpler processes that require less effort [38][41]. Thus, it can be hypothesised that processes requiring effort are more likely to be impaired when the glucose concentration is low or when it cannot be mobilised effectively [29].

During a hyperglycaemic state, the blood-to-brain glucose transportation is restricted. Thus, blood glucose concentrations beyond the optimal level are not necessarily associated with increased levels of cerebral glucose [42]. Under normal conditions, if glucose concentrations fall within the optimum range the blood glucose partly underlies the energy source required during behavioural processes. However, if the glucose level is below the optimum range, the behavioural processes could be impaired. If the glucose level is above the optimum range, it is not necessarily beneficial to an individual for behavioural processing [29].

Patients with diabetes are associated with poor glucose tolerance and are less able to use glucose effectively than non-diabetic individuals. In several laboratory tests requiring cerebral processing, participants with diabetes often tend to perform worse that the non-diabetic participants. Poor glucose tolerance is thus suggestive of the consequences of poor glucose utilisation [29].

Emotions can generally be averse or disruptive. Either suppressing or amplifying emotions could lead to energy source depletion. During aversive emotional states, a large amount of glucose is
required to cope with these emotions. From this perspective, it can be speculated that people with poor glucose tolerance may be vulnerable to aversive emotions.

For instance, diabetics generally experience moderate to severe depressive symptoms. Furthermore, people with diabetes appear to have about twice the chance of being depressed as people without diabetes. Once the diabetic patients experience depression, the depressive symptoms tend to last longer and recur more frequently than depression experienced by people without diabetes [43].

Additional evidence also reveals that glucose administration can improve negative mood. Several studies showed that after a glucose drink, participants tend to suppress negative emotions and feel emotionally more positive.

In addition to emotional and self-control processing, coping with stress also requires glucose as part of its fuel [44]. One study showed when the glucose drink was given to both stressed and non-stressed participants, the stressed group used up more glucose compared to the non-stressed group [45].

Under stressful conditions, the cognitive function is generally increased. With the increase in cognitive processing, the body converts stored glycogen into glucose and releases it into the bloodstream. Therefore, it increases the glucose influx to the brain, and mobilizes to provide the brain with sufficient energy to cope with stress.

Mental stress describes situations where energy is mobilized to meet cognitive goals. If glucose is necessary for coping with stress, it is argued that increasing glucose should be advantageous under stressful conditions [29]. Many researchers reported that when computational demands of a task are high or during high processing loads, blood glucose concentrations are generally reduced [39][41]. However, individual performance is enhanced after glucose administration [32]. Glucose administration was also shown to be effective only when available fuel has been depleted. It was also reported that the increased level of glucose demands is indicative of greater efforts toward coping [46].

As mentioned above, increased cognitive demand is associated with an increased use of glucose by the brain. The success of an individual in overcoming such demands depends on the individual's ability to supply sufficient glucose to very active areas of the brain. A study performed by Donohoe and Benton showed that participants with hyperglycaemia (baseline glucose concentration > 5.2 mmol/L) were associated with poorer performance compared to
participants with normoglycaemia [47]. Healthy adults may improve their glucose tolerance by several existing methods. It is possible that enhancing the glucose tolerance could reverse the undermining effect for stress coping.

Studies also found that stressful conditions tend to impair glucose tolerance. Evidence showed that lifestyle factors have a significant bearing on many body functions, and on their disorders. Individuals under chronic stress were found to have a strong tendency to develop diabetes and impaired glucose tolerance [48][49].

In summary, evidence demonstrates that glucose provides energy for nearly all activities that require cerebral processing relating to behavioural or psychological stress. Evidence indicates that the brain is relatively susceptible to fluctuations in blood glucose levels that are within the normal range. Success and failure in overcoming the demands of cognitive processing is partly driven by the glucose availability and the efficiency of glucose utilisation. As a result, glucose appears to be one of the major resources that psychological stress depends on.

2.8 Psychobiology of stress

Physiological response of stress

Stress is an adaptive response that is not unique only to certain individuals. People often experience non-life threatening stress daily. Subjective emotion is often associated with such stressors. This emotion is frequently referred to as anxiety [50].
When stress is perceived, whether posed by events in the outside world or from within, the body provokes adaptive responses that serve to maintain the homeostasis of the internal environment and to assure the survival of the organism [50].

Despite the wide range of different stressors that one may encounter, the principal pathways underlying the stress response under these circumstances are similar. However, the operation of the physiological systems that promote adaptation and promote homeostasis through an individual’s ability to respond to challenges is not yet fully appreciated. Although the stress response is necessary for survival, frequent activations of physiological systems related to stress may increase the risk for future physical and mental health problems [50].

When coping with stress is required, physiological systems that are needed to deal with threats are mobilised whereas other physiological systems are suppressed. Therefore, during an acute stress response, certain tissues tend to reduce their consumption of energy while others receive sufficient energy for adequate functioning.

In stressful conditions, two distinct systems, viz. the sympathetic-adrenomedullary system (SAM) and the hypothalamic-pituitary-adrenal axis, are activated [51]. The stress physiological system is shown in Figure 2.3.

The SAM system is a subcomponent of the autonomic nervous system (ANS). It is activated in threatening situations and results in an increase in involuntary processes required to respond to physical threats. It was found that exposure to a variety of stressors can cause the activation of the SAM system resulting in an increased output of norepinephrine and epinephrine. Norepinephrine is released at various organ sites, including the adrenal medulla causing the release of epinephrine. The response of this system is rapid and can be activated within seconds [51].

When epinephrine and norepinephrine are released under stressful conditions, heart rate and cardiac output are increased. These physiological alterations cause vasodilatation in the skin and gut ensuring blood supply to the brain and muscles. These typical effects induced by EPI and NE are often described as “fight-or-flight” reactions [52].

The activation of the HPA system causes the release of cortisol. This neural pathway is linked to an integrated response in the hypothalamus, and the central nervous system is linked to the endocrine systems.
When the brain perceives stress, the corticotrophin-releasing hormone (CRH) is secreted from the hypothalamus. This hormone stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then travels through the bloodstream to the adrenal glands and causes the secretion of cortisol [51]. Studies showed that the brain is a major target for cortisol produced by the HPA axis [52].

Unlike the rapid response of epinephrine, it takes approximately 20 to 40 minutes for cortisol to reach its peak levels. Recovery of cortisol response occurs approximately 40 to 60 minutes following the removal of a stressor [51]. Thus, the impact of cortisol on health develops over long periods.

Unlike the SAM system whose response can be fairly simply described by “fight-or-flight” responses, the HPA axis is a complex system. Over prolonged periods of activation, its response serves to suppress the “fight-or-flight” reaction. Chronic activation can result in the dysfunction of the HPA axis. The consequence of the dysfunction of the HPA axis is the hyperactivation or the hypoactivation of the system. Some states associated with the dysfunction of the HPA system are shown in Table 2.2.

Table 2.2: States associated with hyperactivation or hypoactivation of the HPA system [23][53].

<table>
<thead>
<tr>
<th>Hyperactive HPA axis</th>
<th>Hypoactive HPA axis</th>
<th>Disrupted HPA axis activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melancholic depression</td>
<td>Atypical depression</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Seasonal depression</td>
<td>Glucocorticoid deficiency</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Chronic fatigue syndrome</td>
<td>Glucocorticoid resistance</td>
</tr>
<tr>
<td>Memory concentration problems</td>
<td>Fibromyalgia</td>
<td></td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>Adrenal suppression</td>
<td></td>
</tr>
<tr>
<td>Panic disorder</td>
<td>Post glucocorticoid therapy</td>
<td></td>
</tr>
<tr>
<td>Chronic excessive exercise</td>
<td>Post stress</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Nicotine withdrawal</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Postpartum</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Menopause</td>
<td></td>
</tr>
<tr>
<td>Central obesity</td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Neural atrophy, death of nerve cells</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evidence showed that stress can regulate a wide variety of immune-cell functions. Stress hormones can modulate cytokine expression, chemo attractant expression, adhesion-molecule expression and immune-cell trafficking, proliferation, differentiation and effector function [54].
Exposure to acute stressors can enhance certain immune processes. However, during prolonged periods of stress, cortisol levels may remain elevated and hamper the immune-system integrity. Under this circumstance, the chronically stimulated immune-system cells start to break down and lose their ability to fight off invading pathogens. These immune-system cells can also start to unleash their destructive properties on the body's own tissues, and cause a variety of allergies and autoimmune diseases [23].

Researchers have found that chronic or repeated bouts of stress will lead to a shrinking of the thymus gland and to a general suppression of immune-system strength [23]. Furthermore, due to cortisol's anti-insulin effects, chronic stress can also worsen the symptoms of diabetes, and cause an increased rate of death of neurons.

Similarly, the prolonged or repeated activation of the sympathetic nervous system by chronic stress can cause an increase in blood lipid concentration. As a result, it may enhance the development of certain diseases, such as atherosclerosis and hypertension.

**Specificity in the physiological response to stressors**

As mentioned in Section 1.2, the famous notion of the “flight-or-flight” response was introduced by Cannon in the early 1900’s. Cannon introduced the term “homeostasis” to describe the coordinated physiological process that maintains the stability of the internal environment. He further identified the sympathetic system as the essential homeostatic system that responds to the disturbed homeostasis induced by stress. At the same time, Cannon also recognised the specificity of the stress response [55].

A few years later, the attention in the study of the stress response was shifted from the SNS system to the HPA system. This shift was the result of the introduction of Selye’s stress theory. Selye considered the HPA system as the main effector of the stress response, and proposed “general adaptation syndrome” as a general stress response [56].

The general adaptation syndrome consists of three stages, viz. the alarm, resistance, and exhaustion stages. In this theory, Selye stated that the intensity of the stress response might vary; however, the neural and endocrine patterns characterising the response stages would essentially be the same for different stressful conditions. The physiological response to stressors is non-specific [56].
In contrast to this generality model, many other researchers observed that responses to different stressors could cause the activity of the HPA axis to increase, decrease or remain unchanged. Increasing evidence shows that there is specificity in the relationship between stressors and physiology responses [56][57].

When stress is encountered, individuals cope by integrating behavioural and physiological responses that are appropriate to the task [51]. The model Figure 2.4 indicates that both behaviour and physiology form part of an integrated response to address a specific stressor. The specific combinations of psychological and behavioural responses depend in part on their respective potentials for effective coping in a given circumstance. However, an individual’s perception about a stressful circumstance may override the impact of the specific nature of the stressors [51].

Figure 2.4: The specificity model of stress [51].

Clearly, stress is compelling medically and socially. Many elements of stress responses have been shown to be protective. However, prolonged periods of exposure to stress can become pathological. The stress-specific pathways provide a step forward in the study of the prevention and the pathogenesis of stress-related disorders.

2.9 References


3.1 Introduction

In this chapter, the links between ets and cortisol and between ets and energy expenditure will be discussed. The relations will be used to quantify stress experienced by individuals in different situations.

Carbohydrate has been shown to be the second most widely consumed substance. The simplest form of carbohydrate, glucose, is the most essential fuel for the brain, red blood cells and muscles during intense exercise [1].

When carbohydrate is ingested, digestion starts and food is broken down into short chain molecules. The rate of digestion depends on food factors. If the mixture of food and enzyme is highly viscous, it requires a longer time for enzymes and starch to make contact.

The brain almost exclusively uses the fuel substrate, glucose for metabolism. Unlike other organs in the body, the brain does not store fuel energy. It relies essentially on small stores of carbohydrate in the liver. After hours of fasting or energy utilisation, the glucose stores may become depleted and cause hypoglycaemia. Lack in glucose availability may result in adverse consequences for brain function [2].

Hypoglycaemia is the term used to refer to conditions where glucose levels are below a threshold. The minimum threshold is generally defined as the level of blood glucose necessary to maintain the brain and central nervous system. Severe hypoglycaemia may cause trembling, dizziness, nausea and lack of energy. In extreme cases, death or coma may follow [2].

After food ingestion or upon exposure to a threatening environment, it is likely that external stimuli will elevate the blood glucose level. If the elevated glucose persists over a prolonged period, it will cause hyperglycaemia.

Hyperglycaemia happens when the body does not secrete sufficient insulin or the insulin sensitivity is low. In situations where insulin is insufficient or ineffective, blood glucose cannot be used or stored at the target cells. The consequence is excess glucose in the bloodstream. Prolonged hyperglycaemia often causes complications or death in many chronic diseases such as diabetes, patients with cardiovascular disease or patients with severe injury [3][4][5].

Thus, in order to prevent hypoglycaemia or hyperglycaemia, accurate predictions of blood glucose levels are important, especially for diabetics or patients with other chronic diseases.
Traditionally, the terms simple and complex have been used to describe the nature of carbohydrates. Simple or complex are used to describe types of carbohydrates according to their size. However, the concept of simple versus complex does not allow us to predict the effect of carbohydrates on blood glucose levels. The glycaemic index (GI) and glycaemic load (GL) were introduced to better describe the nature of carbohydrates.

However, GI does not take the amount of carbohydrate of foods into account. It cannot give a full measure of the glycaemic response to food ingested. To provide a better measure, the GL concept uses both the GI value and the amount of carbohydrate content in foods. However, it requires knowledge of the specific information of foods (the GI value and the amount of carbohydrate contents), which makes it difficult to use.

Recently, a new tool (the ets concept) for predicting the glycaemic response was introduced by Human-Sim (Pty) Ltd. [6]. The concept was derived from the GL contents of foods. It is a universally applicable unit. With this new unit, the glycaemic response due to the ingestion of a certain food can be compared to that of the generally known substance, sugar. The unit provides a better description for the carbohydrate content of foods. It can be easily understood by the general public.

In the following sections, a brief background on the development of the GI and GL concepts is discussed. Their associations to the development of the ets concept are given, followed by the GI and GL discussions.

3.2 Glycaemic Index and Glycaemic Load

In 1981, Professors David Jenkins and Tom Wolever introduced the term glycaemic index to compare the effects of different carbohydrates on blood glucose. It was first developed to help determine which foods were best for people with diabetes [7]. The GI concept is now being recommended for the avoidance and amelioration of numerous diseases in humans.

The glycaemic index of foods is a measure of the glycaemic response of a fixed amount of available carbohydrate from a test food compared to the response of the same amount of available carbohydrate from a reference food consumed by the same individual. Pure glucose or white bread in equivalent carbohydrate amounts have been used as reference for comparison [7].

The GI of food is characterised by giving an amount of food containing a standard amount of 25g or 50g of CHO to a person under test. Blood samples are drawn every 15 minutes during the
first hour and then every 30 minutes in the second hour. The incremental area under the curve (AUC) blood glucose response is then compared to that of the reference food, as shown in Figure 3.1. The incremental AUC is a measure of the change of blood glucose from the fasting concentration.

The glycaemic responses of different individuals may vary over a wide range. However, the variability between subjects is insignificant when the glycaemic response of a food is expressed relative to that of a reference food taken by the same subject [8].

The GI of the food is the average GI of 8-10 people. It is defined as the ratio of the glycaemic responses of the measured food and the reference food. The GI of the reference food is set at 100 and other food is ranked from 0 according to their effect on blood glucose [7]. The calculation for GI is given as:

\[
GI = \frac{AUC_{Food}}{AUC_{Reference}} \tag{3.1}
\]

where \(AUC_{Food}\) is the area under the glucose response curve of the test food and \(AUC_{Reference}\) is the area under the glucose response curve of the reference food.

In general, food with a high GI results in a higher peak. High GI foods can easily be digested and result in a fast and high blood glucose response. Conversely, glucose is released gradually into the bloodstream when low GI foods are ingested [7]. Thus, the blood glucose concentration is characterised by a slow response with a small peak after the ingestion of low GI foods.

Studies from Harvard University showed that individuals whose diet consisted mainly of refined, high GI food were two to three times more likely to develop chronic diseases such as type 2
diabetes and heart diseases. The risk becomes more dramatic for people who have been exposed to lifestyle changes over a shorter period of time [1]. This evidence showed the importance of effective blood glucose control.

Studies suggested that by incorporating the glycaemic index with daily activities, lower glucose levels could be maintained in people with diabetes or glucose intolerance. It may help to improve coronary conditions by reducing oxidative stress and thus prevent the tendency to form blood clots [1].

However, regardless of the implications of the GI concept for health management, the application was subject to criticism on several points.

Studies show that fructose produces a lower glycaemic response than most other carbohydrates. The consumption of low-GI foods is associated with prolonged suppression of plasma free fatty acids and reduced blood glucose. The effects are due to prolonged carbohydrate absorption and utilisation. In normal subjects, it has been shown that slowing carbohydrate absorption leads to blood cholesterol improvement [9].

The GI component of a food was found to be proportional to the amount of carbohydrate contained in food. Fat or protein had little effect on predicted glycaemic response [9]. However, the nature of the monosaccharide absorbed, the amount of carbohydrate absorbed and the rate of carbohydrate absorption can affect systemic metabolism [9].

GI alone cannot be used to represent the carbohydrate contents of foods quantitatively. The concept is difficult to apply in nutritional management. It does not take the amount of carbohydrate associated with foods into account.

In order to predict blood glucose responses to a meal, researchers at Harvard introduced the term “glycaemic load”. The glycaemic load depends on the amount of carbohydrate in the meal and the nature of the carbohydrate. The GL of a specific food portion is an expression of how much impact the food will have in affecting blood glucose levels. It can be calculated as

\[ GL = \frac{GI \times m_{CHO}}{100} \]  \hspace{1cm} (3.2)

where \( m_{CHO} \) is the amount of CHO consumed in g.
Evidence has associated high GL meals with an increased risk for heart disease and diabetes. It is advisable to restrict the GL of a typical meal to between 20 and 25. The GL of a typical snack should preferably be in a range from 10 to 15 [1].

### 3.3 Equivalent Teaspoon of Sugar (ets)

Since the invention of the GL concept, it has been used for health management. However, the wide variations of GI values and the amount of CHO contents of foods have made it difficult to use. In order to provide an easy-of-use unit describing the expected glycaemic response, the concept of equivalent teaspoons of sugar was established [6]. ets is a universally applicable unit that considers food portion size and reflects blood glucose response.

It was found that when CHO was oxidised in pure oxygen, it could release approximately 4 kCal/g of energy. Unfortunately, this optimum process is not obtained in the human energy system. To investigate the conversion efficiency, the blood glucose response curve was studied to investigate the amount of energy conversion in humans [6].

As known, when carbohydrate is ingested, it is converted to useful blood glucose energy. In healthy individuals, insulin is released even where there is a slight increase in blood glucose and causes the glucose to be removed from the bloodstream. This makes it difficult to measure the blood glucose response of CHO ingestion accurately.

However, in type 1 diabetes, the blood glucose energy released due to ingestion of carbohydrate food cannot be stored or utilised without insulin injections. The rise in blood glucose levels caused by ingested CHO in type 1 diabetics would give an indication of the approximate amount of glucose energy converted from the ingested CHO [6].

In the test, it was found that the blood glucose response to pure glucose is about four times more efficient than the response to fructose (as shown in Figure 3.2). This relation corresponds approximately to the glycaemic indexes of glucose (GI = 100) and fructose (GI = 23).

GI is defined as the index that indicates the energy conversion potential of carbohydrates. The amount of energy extracted from the ingested CHO can be approximated as [6],

\[
E_{CHO} = GI_{CHO} m_{CHO} k_{CHO} \quad [\text{kCal}] \quad (3.3)
\]
where $E_{CHO}$ is the amount of blood glucose energy available from any food of interest, and $k_{CHO} = 4 \text{kCal/g}$ is the energy conversion factor of carbohydrates. $GI_{CHO}$ is the GI value of CHO and is expressed as a percentage (%).

As discussed, GI provides an indication of the property of the food. It is not individual dependent. The amount of carbohydrates available in a meal is used to derive the ets concept. The digestion of fat and protein occurs significantly slower. Therefore, the blood glucose response caused by the intake of food is assumed to be mainly due to the energy conversion of carbohydrates.

With Equation (3.3) given, ets can now be derived.

As per definition, one teaspoonful of cane sugar contains approximately 5 g of carbohydrates ($m_{teaspoon.sugar} = 5 \text{g}$). Since the GI value of sugar equals 65, the energy extracted from one teaspoon of sugar ($E_{teaspoon.sugar}$) can be expressed as [6],

$$E_{teaspoon.sugar} = GI_{sugar}m_{teaspoon.sugar}k_{CHO} = (65)(5)k_{CHO} = 325k_{CHO}$$  \hspace{1cm} (3.4)

ets is defined as the ratio of blood sugar that can be extracted from any food to that of one teaspoonful of cane sugar. The relation can be expressed as,

$$ets = \frac{E_{CHO}}{E_{teaspoon.sugar}} = \frac{GI_{CHO}m_{CHO}k_{CHO}}{325k_{CHO}} = \frac{GI_{CHO}m_{CHO}}{325}$$  \hspace{1cm} (3.5)
The blood sugar response is calculated by integrating the blood sugar time-response curve from the time of response above the basal level to the time that the response curve returns to its basal value. The response curve is dependent on the individual’s glucose sensitivity and effectiveness.

### 3.4 Application for stress quantification

When food is ingested and absorbed by the body, the total glucose energy absorbed can be related to the total blood glucose response. If a person’s ability for converting the effective CHO from a meal into blood glucose is expressed by an efficiency factor $f_{CHO}$, the total blood glucose response due to food ingested ($\int_{t=\text{basal}}^{t=\text{response}} BG_{CHO}(t)dt$) can be expressed as,

$$\frac{\int_{t=\text{basal}}^{t=\text{response}} BG_{CHO}(t)dt}{\Delta t} = f_{CHO} \frac{325 \text{ ets}}{V_{\text{blood}}} \quad (3.6)$$

where $\Delta t$ is the time elapsed, and $V_{\text{blood}}$ is the blood volume of the individual under investigation. The personalised CHO efficiency factor $f_{CHO}$ is included in the equation, because the efficiency for converting the effective CHO from a meal into blood glucose differs from person to person. The values of $f_{CHO}$ are typically in the range between 0.8 and 0.9 [6].

Assume the hypothesis of glucose being the energy source required for stress coping. Thus, exposure to stress would generally cause a reduction in glucose stores in the body. If food is ingested to augment the glucose reduction during stress, the blood glucose response induced by stress ($\int_{t=\text{response}}^{t=\text{stress}} BG_{stress}(t)dt$) can then be expressed as,

$$\frac{\int_{t=\text{response}}^{t=\text{stress}} BG_{stress}(t)dt}{\Delta t} = f_{CHO} \frac{325 \text{ ets}}{V_{\text{blood}}} \quad (3.7)$$

If it is supposed that the blood glucose response induced by stress is mainly mediated by the stress hormone (cortisol or epinephrine) and a link can be established between the stress hormone response ($\int_{t=\text{response}}^{t=\text{stress}} BH_{stress}(t)dt$) and glucose response, a relation can be drawn:

$$\int_{t=\text{response}}^{t=\text{stress}} BH_{stress}(t)dt \propto \int_{t=\text{response}}^{t=\text{stress}} BG_{stress}(t)dt \propto ets_{stress} \quad (3.8)$$

The objective of this study is to establish a link between stress and glucose response. In [7], it was found that the amount of insulin secreted ($I_{secreted}$) is associated with ets ($I_{secreted} = f_I \cdot ets$
Chapter 3

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with $f_i$ being the insulin sensitivity. If the link described by Equation (3.8) can be established, the finding would provide a powerful tool for glycaemic control for diabetes.

3.5 Discussion

The aim of the formulation of ets is to provide a simple, easy-to-use measure of carbohydrate. With ets, the glycaemic response of food can be easily predicted. Depending on the glycaemic index and the quantity of food, the equivalent ets values of different foods provide an indication of equivalent blood glucose responses. The novel relation between the energy that can be extracted from food intake and that available from teaspoons of cane sugar offers an easier concept to grasp.

The ets values of different types of food are additive. The ets values of individual components in a mixed meal can be added. The summed result represent the total ets value of the meal. Based on this user-friendly method, the ets concept enables better management and control for individuals, especially patients with diabetes.

It should be noted that the ets concept was derived from the batch mean of the blood glucose response of individuals under investigation. The fluctuations in the glucose response among individuals were not accounted for.

3.6 Conclusion

It was shown that the GIs of food only reflect the rate of digestion of a specific food. It does not take into account the quantities of food ingested. Using GI alone will lead to mismanagement of blood glucose control.

As discussed, the ets concept was derived from the amount of energy that is available from carbohydrates ingested. Based on the concept that energy can neither be created nor destroyed, it can be reasoned that energy extracted is equivalent to energy utilised. The ets concept can therefore be extended to express energy utilisation in the human energy system.

3.7 References


CHAPTER 4

STRESS QUANTIFICATION
Chapter 4

4.1 Introduction

In the previous chapters, the pathways for the stress response were discussed. These pathways describe the mechanisms that increase an individual’s blood glucose during exposure to stress. In this chapter, the effect of acute and chronic stress will be addressed.

4.2 Specificity response of stress

The relationship between stress and somatic responses has been studied over the past decades. One theory was that individuals have a vulnerable body area that would break down under extreme stress. This theory formed the basis of response specificity and has been validated via several research studies [1].

It was suggested that, although each individual tends to respond differently to the same type of stress, one type of endocrine response usually predominates over all others under exposure to a certain type of stress [1].

It is believed that when a stressor demands some kind of mental effort or results in a high level of arousal; it will cause the stimulation of the sympathetic nervous system. If the stressor results in a low level of arousal, does not require mental effort or is chronic, it will evoke the activation of the HPA axis. One should note that, although either the SNS or the HPA axis is activated depending on the type of stressor experienced; different stressors of the same type can evoke different patterns of endocrine response [2]. For example, anger and tension are both high arousal stressors and both raise heart rate (one of the effects when the SNS system is activated). However, the total increase in heart rate is different in the two situations.

Due to response specificity as discussed above, different stress concepts are used for stress quantification. The links between different stressors and glycaemic responses are derived and presented in this chapter.

4.3 Acute stress and energy expenditure

In order to survive, all living organisms require a continuous energy supply to maintain basic metabolic requirements. Enough energy is required to support the bodily functions and various physical activities. The energy supply in the human body is mainly derived from anaerobic glycolysis and aerobic breakdown of glucose and free fatty acids (FFA) [3]. Amino acids from
hydrolysed body proteins play only a minor role in energy expenditure and can be considered insignificant compared to glucose and FFA.

Circulating metabolites are derived fuel substrates available in the bloodstream due to diet or from the stores of glycogen in the liver and muscles and from triglycerides in adipose tissue. Upon fuel ingestion, the digested substrates circulate in the blood and are utilised and oxidised by the required tissue cells to produce energy. Excessive energy substrates are converted to and stored as glycogen in muscles and the liver, and as triglycerides in adipose tissue.

During stress, blood glucose is monitored through the regulatory and counter-regulatory effects of hormones. Deviations in blood glucose may result in hypoglycaemia or hyperglycaemia and lead to pathological conditions. In hypoglycaemic conditions, glucose is insufficient. This causes improper functioning of nervous tissue. During hyperglycaemia, cell membrane proteins are glycosylated. This leads to dysfunction of several membrane processes [3].

Evidence showed that during exercise stress, the injected carbohydrate acts as a counterpart of blood glucose released by the liver. If the amount of carbohydrate ingested is equivalent to the amount of blood glucose required, the glucose produced by the liver will be approximately zero.

As discussed in Chapter 2, glucose energy appears to be the energy source required for coping with stress. If the glycogen store in the liver is depleted, when an individual is exposed to stressful conditions glucose intake has a positive effect on coping with stress. Glucose intake also appears to act as a counterpart of blood glucose released by the liver. Therefore, in accordance with the argument for the relation between exercise and ets, the amount of energy expended during stress can be related to the amount of ets required.

It has been shown that critically ill (highly stressed) patients often suffer from systemic inflammatory response syndrome (SIRS). As a result, patients with SIRS experience greater stresses and adverse physiological pharmacological factors. Their metabolic stresses and catabolic responses are significantly increased and result in an overall increase in resting energy expenditure (REE) [4]. Accompanying this increase in resting energy expenditure are elevated blood glucose concentrations. It is hypothesised that there is an association between the change in REE and the change in blood glucose concentration.

Several lines of evidence showed that REE corresponds to oxygen intake [5], and can be expressed as [4].
\[ \text{REE} = 1.44 \times (3.91 \, VO_2 + 1.10 \, VCO_2) - 3.34 \times (\text{urinary nitrogen excretion}) \]  
\[
\text{[kCal/day]}
\]

(4.1)

where \( VO_2 \) is the oxygen consumption (in \text{ml/min}), \( VCO_2 \) is the carbon dioxide production (in \text{ml/min}) and urinary nitrogen excretion is approximately 9.1 g/day. The ratio of \( VCO_2 \) and \( VO_2 \) is often referred to as respiratory quotient. Typically, respiratory quotient (\( RQ = \frac{VCO_2}{VO_2} \)) has a value of between 0.7 and 1.0 [3]. The variation is caused by the body state, such as increased heart rates or increased metabolism.

Exercise has been regarded as a physical stressor. Studies have shown that the reaction to exercise can be described as an activation of the sympathetic-adrenal system and the HPA axis increasing plasma hormonal concentrations. The degree of exercise-induced homeostatic disturbance depends on the type and duration of exercise.

Over the past decades, intensive research has been conducted to investigate the effects of exercise on energy expenditure. Studies showed that, during severely strenuous exercise, the maximum oxygen consumption and respiratory quotient of 1 will be reached. Figure 2.1 shows that at maximum oxygen consumption, almost all the energy expended is the result of carbohydrate metabolism. However, during severely strenuous exercise, transport of oxygen to active tissue becomes a limiting factor. In this situation, near-site carbohydrate utilisation becomes necessary, and muscle glycogen becomes the main substrate to cover energy expenditure during intense exercise [3]. As a result, the percentage of blood glucose utilisation decreases.

The relation between the aerobic power and the percentage of energy derived from blood glucose (%\( E_{\text{blood glucose}} \)) is given in

Table 4.1. As shown, the demands of blood glucose energy rely on bodily physiological responses. During exercise, as the oxygen consumption increases, the percentage of energy derived from serum glucose decreases accordingly.

<table>
<thead>
<tr>
<th>Aerobic power (%)</th>
<th>at rest</th>
<th>25</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>%( E_{\text{blood glucose}} ) (%)</td>
<td>40</td>
<td>4.167</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Table 4.1: Dependency of aerobic power and blood glucose utilisation during acute exercise [6].
From the discussion given above, it is clear that for glucose energy computation using energy expenditure requires the knowledge of $\%E_{\text{blood glucose}}$. If $\%E_{\text{blood glucose}}$ is defined or known, the energy expended as the result of blood glucose utilisation ($EE_{CHO}$) can be expressed as,

$$EE_{CHO} = \frac{1.44 \times (3.91 VO_2 + 1.10 VCO_2) - 3.34 \times \text{urinary nitrogen excretion}}{1440} \times \%E_{\text{blood glucose}}$$  \hfill (4.2)

[kCal/min]

In most situations, protein metabolism is negligible, and the urinary nitrogen excretion is approximately zero [4]. Thus, Equation (4.2) becomes:

$$EE_{CHO} \approx \frac{1.44 \times (3.91 VO_2 + 1.10 VCO_2)}{1440} \times \%E_{\text{blood glucose}} \times EE$$  \hfill (4.3)

where $EE$ is the total energy expenditure.

**Derivation of the link between acute stress and etps**

As discussed, many efforts have been made to identify the possible link between stress and the physiological response to stress. However, consensus has not yet been reached. Most of the studies have focused their research on cardiovascular responses or to hormonal responses.

Some researchers believe that if stress requires mental effort (such as information processing) or causes high arousal, it will cause the activation of the sympathetic nervous system. The activation of the SNS system causes several physiological responses. Some of these responses are given in Figure 4.1.

![Figure 4.1: Physiological effects of acute (effortful) psychological stress.](image)

As shown in Figure 4.1, increased heart rate is one of the hemodynamic responses caused by the activation of the SNS system. It has been used by a number of studies to demonstrate the effect
of exposures to acute mental stress. Thus, the association between increased heart rate and acute stress is considered in this subsection.

**Energy expenditure and heart rate (HR)**

![Characteristic curve of heart rate vs. oxygen consumption of a male subject and a female subject](image)

Several attempts have been made to assess the relation between daily energy expenditure and hemodynamic responses such as heart rate changes. In a study conducted by Spurr *et al.* [7], it was shown that there is a linear relationship between oxygen consumption and heart rate, as shown in Figure 4.2.

As described by Equation (4.1), as the volume of oxygen consumption increases, the energy expended also increases. Thus, in most studies, energy expenditure and oxygen consumption are used interchangeably. This association enables indirect predictions of energy expenditure during activities based on heart rate.

It has been shown that during mental stress, the sympathetic nervous system is stimulated and insulin-induced glucose utilisation is acutely enhanced. The activation of SNS is well known to have several effects on metabolic response (shown in Figure 4.1). In a study conducted by Seematter *et al.* [8], the effect of mental stress on energy expenditure was investigated. Seematter *et al.*, showed that the stimulation of SNS by mental stress effectively increases oxygen consumption, and consequently, energy expenditure.

The energy requirement for any activity can be approximately calculated using a simple system that depends on the basal metabolic rate, muscle activity and stress. Where stress is mental only,
an individual’s physical activity can be assumed to be low. As shown in Figure 2.1, at rest, approximately forty percent of the energy requirement is derived from blood glucose. Therefore, it is hypothesised that an equivalent percentage of the total energy expenditure or larger will be derived from the utilisation of blood glucose during acute mental stress.

Academic examinations have been shown to produce prominent hemodynamic responses. For various reasons, students undergo tremendous emotional stress before and during examination. In the case of a prolonged period of examination, the effect of stress persists for several days after the examination.

Under conditions of mental stress that require effort, the brain activity increases tremendously. This increased mental activity requires a higher rate of brain metabolism. Glucose has been shown to be the almost exclusive fuel substrate utilised by the brain. At rest, the energy requirement of the brain accounts for approximately 20% of the total energy consumption (which amounts to approximately 55% of the total carbohydrate metabolism). In spite of its high rate of glucose utilisation, the energy stores in the brain are tremendously small [9].

When the mental activity is high, the metabolically active regions of the brain often tend to be deprived of glucose. Preventing the decline in glucose levels by injecting glucose has been shown to enhance performance. Research has shown that the adverse effect of glucose deprivation on memory performance could be reversed by providing a glucose-containing drink [10].

Investigators showed that when a person is exposed to moderate mental stress, oxygen consumption is increased from 192 to 229 ml/min [8]. At rest, the respiratory quotient is about 0.8. The carbon dioxide outputs VCO₂ of 153.6 ml/min and 183.2 ml/l were calculated for an individual at rest and under mental stress respectively. Using Equation (4.1), the energy expenditure of 55.18 kCal/h and 65.815 kCal/h was calculated for an individual at rest and under mental stress respectively. It was shown that the total glucose utilisation due to mental stress was approximately 6.43 kCal/hour [8]. This indicates that about 60% of energy expenditure due to activities (i.e. mental stress) can be attributed to glucose metabolism. Using the results derived, the amount of glucose energy required during mental stress \( EE_{CHO,mental\ stress} \) can be expressed as,

\[
EE_{CHO,mental\ stress} = 60\% \times (TEE - BEE) \quad [kCal]
\] (4.4)
where $TEE$ is the total energy expended during activity and $BEE$ is the basal energy expenditure. $TEE$ can be approximated with Equation (4.1). $BEE$ is the minimum amount of energy that is required for maintaining bodily function. It is affected by the body size, age, sex and several other factors. Empirically derived equations for $BEE$ in an age group ranging from 18-30 can be described as [11]

\[
\begin{align*}
\text{males: } & \quad BEE = 15.3 \cdot W + 679 \quad [\text{kCal/day}] \\
\text{females: } & \quad BEE = 14.7 \cdot W + 496
\end{align*}
\]

where $W$ is body weight in kg.

The link between blood glucose expended during mental stress and the user-friendly unit (ets), is formulated below.

In human energy systems, the fuel substrates for energy expenditure are simply derived from food ingested or from bodily storage. Carbohydrate, fat and protein are the primary fuels obtained from our daily diet. However, carbohydrate is the only fuel substrate involved in blood glucose metabolism. In the endogenous blood glucose metabolism system, the liver is the only organ that controls the release of glucose through glycolysis via the interactions of endocrine hormones. Therefore, combining the two major fuel factors, the energy expenditure from blood glucose utilisation can be formulated as [6]

\[
EE_{CHO} = \%E_{\text{blood glucose}} \times EE = f_{CHO}E_{CHO} + f_{liver}E_{liver}
\]

where $f_{CHO}$ is the individual extraction factor for energy extraction from ingested carbohydrate with a certain amount of energy ($E_{CHO}$). Typical values of $f_{CHO}$ are shown to be between 0.8 and 0.9. $f_{liver}$ is the retrieving factor describing an individual’s ability to convert glycogen in the liver into blood glucose. If the amount of energy extracted from the ingested food is sufficient to cover energy expenditure required during activity, then energy retrieved from the liver becomes insignificant [6] and Equation (4.6) becomes,

\[
EE_{CHO} = \%E_{\text{blood glucose}} \times EE \approx f_{CHO}E_{CHO}
\]

The effective CHO energy derived from different foods with different compounds varies considerably. Taking mixed meal and GI effects into account, the description of the effective CHO energy can be used to describe ets. The unit, ets, can be defined as $E_{CHO}$ normalised by the amount of energy contained in one teaspoon of sugar. It is described by Equation (4.8) [12],

\[
\]
\[ ets = \frac{E_{CHO}}{E_{ets}} \] (4.8)

One teaspoon of sugar has a GI of 65 and weighs approximately 5 g \( (m_{CHO} = 5 \text{ g}) \). It was shown that every gram of carbohydrate yields about 4 kCal of energy \( (k_{CHO} = 4 \text{ kCal}) \). Therefore, the energy extracted from one teaspoonful of cane sugar is [12],

\[ E_{ets} = GI_{\text{teaspoon sugar}} \cdot m_{\text{teaspoon sugar}} \cdot k_{CHO} \approx 13 \text{ kCal} \] (4.9)

From Equations (4.8) and (4.9), the effective CHO energy can be expressed as

\[ E_{CHO} = 13 \cdot ets \quad \text{[kCal]} \] (4.10)

Thus, the energy expenditure can be formulated as [12],

\[ E_{ECHO} = 13 \cdot f_{CHO} \cdot ets \] (4.11)

**Application of the equations**

**Mental stress**

An academic examination has been shown to have inconsistent effects on cortisol response. However, during an examination, catecholamine levels were shown to increase significantly. Moreover, both the epinephrine and norepinephrine responses correlated significantly with tasks. These results suggested that mental stress that requires effort, activates primarily the SAM system. This is in agreement with a large body of literature [13][14][15].

In addition, during examination, epinephrine excretion was higher in male students than in female students. However, it was suggested that this could be associated with the differential effect of different emotions perceived by different genders. Generally, male students commonly display feelings of success and confidence. Discomfort was shown to be associated with poor performance in males. It was, however, correlated with good performance in females. Researchers concluded that the different levels of epinephrine increases could be attributed to different coping styles and different levels of perceived stress [16].

Yumatov *et al.* [17] have investigated the effect of the degree of self-discipline with regard to examination stress on heart rate responses. In the investigation, the level of knowledge and
preparedness of the student was correlated to and determined by the examination marks. It was shown that the level situational anxiety was correlated to heart rate before the examination.

The unprepared students exhibited minimal situational anxiety that corresponds to a minimal increase in heart rate. The excellent students tended to show a significant increase in situational anxiety accompanied by high levels of hemodynamic activation. Interestingly, the intermediate subgroups exhibited physiological responses similar to those experienced by excellent students [17]. Unfortunately, only the average hemodynamic responses after the examination were reported. In the analysis, constant rates of change of physiological responses during the examination were assumed.

According to the hypothesis, the physiological responses of students during the academic examination are shown in Table 4.2. It is assumed that male students had an average weight of 70 kg and female students weighed 60 kg on average. Using Equation (4.5), the average BEE is approximately 1564 kCal/day. For a three-hour examination and with the BEE calculated, the corresponding number of ets consumed due to stress are derived using Equations (4.10) and (4.4).

<table>
<thead>
<tr>
<th>Stress intensity (level of knowledge and preparedness)</th>
<th>Average HR [beats/min]</th>
<th>Average VO₂ [ml/min]</th>
<th>Total EE [kCal]</th>
<th>ets [ets/h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>93.5</td>
<td>613.07</td>
<td>528.59</td>
<td>5.7</td>
</tr>
<tr>
<td>Mild</td>
<td>101</td>
<td>952.14</td>
<td>820.93</td>
<td>10.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>101.5</td>
<td>962.65</td>
<td>830</td>
<td>10.8</td>
</tr>
<tr>
<td>High</td>
<td>103.5</td>
<td>1004.72</td>
<td>866.27</td>
<td>11.4</td>
</tr>
</tbody>
</table>

As shown in the table, the energy consumption (ets) increases as the intensity of mental effort increases.

As discussed, glucose is the major fuel substrate for the brain and is essential for the normal functioning of the central nervous system. Only a relatively small amount of glucose can be stored in the brain, it is reliant on a continuous supply of glucose. Due to the requirement of energy fuel during mental stress, it was shown that administration of glucose either peripherally or directly into the brain can produce significant positive dose-dependent effects on cognition in a range of tasks [18][19].
Research showed that intellectual performance is improved following the intake of glucose load or CHO rich food. Demanding mental tasks are mostly improved. While performing cognitive tasks, glucose acts as immediate provision of additional energy, and provision of additional substrate for neurotransmitters. Administration of glucose increases the availability of extracellular glucose in the brain. In the absence of exogenous glucose administration, neuronal enzymes involved in the metabolism of glucose are already maximally active. It was suggested that administration of glucose acts to reverse a reduction in available glucose caused by increased demand rather than to elevate the baseline extra-cellular concentration [18].

During periods of intense cognitive processing and without exogenous glucose administration, blood glucose would decline tremendously. Under this intensive stressful situation, it is necessary to maintain a minimum threshold level of blood glucose ensuring a sufficient energy supply. If it falls below the threshold, hypoglycaemia occurs. If the situation is not rectified quickly, coma and death may follow [20].

The technological changes of the modern world promote a switch from physically demanding tasks to knowledge-based work soliciting an enhanced cognitive demand. The impact of cognitively demanding tasks include potential effects on the control of appetite, food intake, and energy expenditure [21].

In humans, it is well known that stress promotes excess energy intake. McCann et al. showed that a high-energy intake and high percentage of energy from fat was associated with a high university workload [22]. In a study of high workload periods, it was shown that the associated high level of perceived stress was related to higher energy, saturated fat and sugar intakes [23].

Chaput et al. employed a laboratory test to evaluate the impact of knowledge-based work (KBW) on feeding behaviour [21]. A total number of 15 healthy female university students with a mean BMI of 24.0 ± 4.3 kg/m² participated in the study. It was found that during and after a 45 minutes cognitive task (reading a document and writing a summary of 350 words using a computer) with a medium level of stress intensity, both the heart rate and carbohydrate intake revealed significant changes (as depicted in Table 4.3).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control session</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>67.7 ± 9.6</td>
</tr>
<tr>
<td>Carbohydrate intake (kCal)</td>
<td>394 ± 29</td>
</tr>
<tr>
<td>Extra ets required during stress (ets/h)</td>
<td>---</td>
</tr>
</tbody>
</table>
From Chaput’s study, it illustrated that over-consumption of foods generally happens when activities require a significant cognitive demand [21]. The amount of extra glucose required during mental stress showed in Table 4.3 is in the same range as that calculated using the changes of heart rate under the examination stress.

4.4 Acute stress and neuroendocrines

Emotions are important for everyday life. They play a major role in preparing an organism to respond to threat quickly, for human interaction, and memory formulation and retrieval. However, they may become adaptive in most areas and have a detrimental effect on physical well-being [24].

The majority of studies have concentrated on the role of negative emotions. The study outcomes have led researchers to draw the conclusion that there is a strong association between negative emotions and morbidity and mortality with most chronic diseases [24].

Emotions are complex processes. They involve an interaction between physiological arousals and behavioural displays and can be described using an emotion model (as shown in Figure 4.3). As depicted by Figure 4.3, depending on the type of emotion, different emotions may have different degrees of arousal and in the degree to which they are experienced as negative. Due to these differential reactions (i.e. different interactions between physiological arousals and behaviours), it has been found that several negative emotions have unique patterns of activation. As mentioned in the previous section, high-arousal negative emotions would result in the activation of the SNS axis, whereas the low-arousal negative emotions would stimulate the activation of the HPA axis [24].

![Figure 4.3: Emotion model.](image)
The activation of the SNS system will generally cause an increase in heart rate. The effect of changes in heart rate on glucose utilisation was discussed in Section 4.3. In this subsection, the association between the blood glucose increase and low-arousal negative emotions is developed. When exposed to low-arousal negative emotions or effortless stress, the HPA axis is activated and stimulates the release of cortisol (as shown in Figure 4.4). An increase in cortisol concentrations would generally cause a cascade of physiological responses. Some of the responses are shown in Figure 4.4. As one can expect, if some or all of these physiological responses are stimulated chronically, the body would stop responding to the invading virus, the risk for heart disease increases, and the probability of developing various types of mental disorders may also increase.

![Figure 4.4: Physiological effects of acute (non-effortful) psychological stress.](image)

In most of the studies, cortisol has been used to characterise the effect of exposure to low-arousal stress. Thus, it is used here for characterising this type of stress.

### Derivation of the link between acute stress and ects

De Vries et al. [25] used exercise as physical stressor and investigated the effect of graded exercise on the hormonal responses. Table 4.4 shows the plasma hormonal concentrations in relation to workload. The maximum power output is $VO_{2,max} = 5.0 \pm 0.5$ W/kg.

In the study [25], results showed that increases in plasma epinephrine are related to the intensity of exercise-induced stress. However, plasma cortisol levels remained relatively unaffected at different exercise intensities. It has been shown that cortisol concentration peaks in the early morning and its clearance rate is high in the first few hours after awakening. In the study, the experiment was carried out early in the morning and only the pre-exercise basal cortisol level was measured. Measuring the cortisol concentrations with respect to pre-exercise basal cortisol levels, especially in the morning, cannot reflect the cortisol response to stressors.
Table 4.4: Plasma hormonal responses in relation to the relative work load [25].

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oxygen consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Total epinephrine increase (nmol/l)</td>
<td>0.6</td>
</tr>
<tr>
<td>Total blood glucose increase (mmol/l)</td>
<td>2.317</td>
</tr>
</tbody>
</table>

Recently, Ronsen et al. [26] demonstrated the increase of hormones in response to a cycle ergometer exercise bout. In the study, it showed that there is a functional link between the nervous and endocrine systems. Consequently, an increase in the plasma cortisol level is associated with an increase in the plasma epinephrine level as shown in Figure 4.5 [26].

![Figure 4.5: Dependency of plasma cortisol increase and plasma EPI increase.](image)

With the relation between plasma EPI increase and plasma cortisol increase drawn, the dependency of variations of glucose concentration or ets on the fluctuation of cortisol levels can be formulated and is shown in Equation 4.12.

\[
\Delta \text{AUC}_{BG} (\text{mmol/l}) = 0.0229 \cdot \Delta \text{AUC}_{CORT} (\mu\text{g/dl}) + 3.15 \tag{4.12}
\]

where \( \Delta \text{AUC}_{BG} \) is the relative change of total blood glucose concentration within the response time and \( \Delta \text{AUC}_{CORT} \) is the relative change of total plasma cortisol concentration within the response time.

In order to facilitate user-friendly methodology, it is necessary to convert the change of blood glucose into virtual ets. It has been shown that the atomic weight of one glucose molecule is 342
and 1 ets contains about 14.6 mmol of glucose. Let the ets-glucose conversion factor be $K = 14.6$ mmol/ets, then, the ets-glucose relation can be set to [12]

$$G_{\text{blood}}(t) = BG(t) \cdot \frac{V_{\text{blood}}}{K}$$

where $G_{\text{blood}}(t)$ is the glucose utilised in term of ets and $V_{\text{blood}}$ represents an individual’s blood volume.

**Application of the equations**

**Sleep deprivation**

Emotional stress in middle-age has been previously reported to be the most frequent underlying cause of insomnia complaints [27]. Most patients with chronic medical conditions also exhibit some degree of insomnia leading to increased rates of hospitalisation [28].

Sleep deprivation is becoming increasingly prevalent. During the second half of the 20th century, sleep duration was decreased by one to two hours. Concurrently, the incidence of obesity has nearly doubled. A significant association has been found between sleep duration and BMI [29][30].

If sleep deprivation is sufficiently prolonged, it may affect many processes including energy metabolism, immune system function, learning/memory, appetite regulation and gene expression [31].

In 2001, sleep researchers showed that inadequate sleep might promote development of insulin resistance. It was found that short-term sleepers (averaging less than 6.5 hours of sleep per night) secreted 50 percent more insulin and were 40 percent less sensitive to the effects of insulin compared to the normal sleepers. Evening cortisol concentrations were significantly elevated and activity of the sympathetic nervous system was increased in the sleep-debt condition [32].

In particular, sleep restriction is accompanied by increased cortisol levels in the afternoon and early evening. These alterations could lead to glucocorticoid excess and result in memory deficits. It was also shown that sleep restriction is also associated with an impairment of carbohydrate tolerance. Sleep deprivation may therefore increase the risk for diabetes [33].
Studies have found increased mortality associated with usual sleep times of less than seven or more than eight hours per night. Gottlieb [34] demonstrated that sleep duration of six hours or less or nine hours or more is associated with increased prevalence of diabetes and impaired glucose tolerance. It suggests a causal association between short sleep and impaired glucose regulation. Six nights' 4-h short sleep time was shown to cause IGT in healthy young adults, which was resolved after one week of increased sleep duration [32].

Diabetes carries a high risk for cardiovascular-related mortality, the impact of sleep deprivation on glucose regulation therefore suggests a mechanism whereby restricted sleep time might increase mortality.

In a cancer prevention study of more than 1.1 million men and women, it was reported that there was an increase in mortality hazard of more than 15% for participants who reported more than 8.5 hours or less than 3.5 or 4.5 hours sleep [35].

The association between long sleep time and impaired glucose regulation or mortality is speculative [34]. However, it was reported that subjects who sleep 9 hours or more per night were 15% less physically active per week than those sleeping 7 to 8 hours per night [36]. These effects of inactivity might be the cause that led to impaired glucose regulation [37].

Studies showed that the evening cortisol secretion before bedtime is significantly correlated with the number of nocturnal awakenings during the following sleep period. The parameters of sleep deprivation and cortisol output during the first half of the night are only marginally correlated for healthy subjects but significantly associated in patients with severe primary insomnia. Unfortunately, the data set for the evening cortisol secretion and the parameters of impaired sleep is not included in the study. However, the area under the curve (AUC) of the increase in plasma cortisol concentrations and the number of hours of sleep deprivation is shown in Table 4.5 [38]. The corresponding ets/h secreted due to different periods of sleep deprivation were also calculated and are provided in Table 4.6.

<table>
<thead>
<tr>
<th>Number of hours of sleep deprivation</th>
<th>AUC of plasma cortisol concentration (ng/ml per 4h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with primary insomnia</td>
</tr>
<tr>
<td>1.4 h of bedtime</td>
<td>21.02</td>
</tr>
<tr>
<td>2.4 h of bedtime</td>
<td>58.92</td>
</tr>
<tr>
<td>Total night (8 h)</td>
<td>79.94</td>
</tr>
</tbody>
</table>
**Table 4.6: Relation between ets expended and sleep deprivation.**

<table>
<thead>
<tr>
<th>Number of hours of sleep deprivation</th>
<th>ets expended per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with primary insomnia</td>
</tr>
<tr>
<td>1.4 h of bedtime</td>
<td>0.35</td>
</tr>
<tr>
<td>2.4 h of bedtime</td>
<td>0.25</td>
</tr>
<tr>
<td>Total night (8 h)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Despite the fact that Table 4.5 and Table 4.6 do not show significant increases in glucose expenditure, the metabolic consequences of sleep deprivation cannot be neglected. In an experimental study conducted by Spiegel *et al.* [32], it was shown that in sleep-debt conditions, the metabolic and endocrine alterations closely mimic some of the hallmarks of ageing. It suggests that chronic sleep deprivation could promote the development or the severity of age-related pathologies.

**Negative affects**

It is well known that negative emotions cause some degree of alteration in physiological indicators. However, the degree of physiological response to negative emotions is usually small. Furthermore, negative emotions are difficult to induce in laboratory and the measurement may be influenced by the high degree of individual variability. The onset and cessation of a psychological stress is also unjustified. In particular, extreme negative emotions have been avoided in the laboratory investigation. An extreme case of psychological stress may induce the onset of potential adverse physiological outcomes.

Sobrinho *et al.* [39] investigated cortisol responses to emotions during a hypnodial state. They showed that the AUC of the cortisol surge response appears to respond to specific emotions. Table 4.7 shows the relation between the intensity of the cortisol surges in approximately 75 minutes and the type of the preceding emotions.

To convert the conventional cortisol unit (μg/dl) to the standard international (SI) unit (nmol/l) a conversion factor is applied:

\[ \Delta \text{AUC}_{\text{CORT}}(\text{nmol/l}) = 27.59 \cdot \Delta \text{AUC}_{\text{CORT}}(\mu g/dl) \]

(4.14)

Together with Equation (4.14) and the linear link between changes in plasma cortisol concentration and glucose (Equation (4.12)), the effects of psychological stress on blood glucose levels are approximated and provided in the table below. For a person with a blood volume of
about 4.5 litres, using Equation (4.13) the corresponding additional ets/h secreted due to negative emotions is also shown in Table 4.7.

Table 4.7: Cortisol and blood glucose responses to different type of negative emotions [39].

<table>
<thead>
<tr>
<th>Variables</th>
<th>Negative emotions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intimidation</td>
</tr>
<tr>
<td>ΔAUC of plasma cortisol response (µmol/l)</td>
<td>12.4</td>
</tr>
<tr>
<td>ΔAUC of blood glucose response (mmol/l)</td>
<td>13.42</td>
</tr>
<tr>
<td>ets/h secreted</td>
<td>4.14</td>
</tr>
</tbody>
</table>

The HPA axis has been shown to be the most important endocrine system in stress responses. As mentioned, academic examinations have been perceived as stressful challenges to many students. Seeing that examinations can be categorised as a classical psychological stress, it has also been widely accepted that cortisol concentrations increase in response to the exposure to examination stress.

Martinek et al. [40] investigated the cortisol response to different degrees of difficulty of examination stressors. It was shown that the cortisol concentration was significantly higher before an anticipated examination compared to that on control days. Furthermore, cortisol level increases with the increase of stressors that are due to a higher degree of difficulty. Table 4.8 shows the cortisol levels just before and after different examinations. Basal cortisol levels which were measured at similar time points are also indicated.

Table 4.8: Cortisol response to different level of difficulty of examination stress [40].

<table>
<thead>
<tr>
<th>Stressors</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mildly stressful</td>
</tr>
<tr>
<td>Baseline</td>
<td>3.8</td>
</tr>
<tr>
<td>Before exam</td>
<td>5.1</td>
</tr>
<tr>
<td>After exam</td>
<td>3.1</td>
</tr>
<tr>
<td>ΔAUC cortisol (nmol/l)</td>
<td>66.64</td>
</tr>
<tr>
<td>ets/h expended</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Unfortunately, the basal cortisol levels were only assessed at a pre-stressed point. Furthermore, the duration of examinations and the neurohormonal response during stress were not given and assessed. It is difficult to determine whether the cortisol levels returned to the basal value directly following examinations or whether the concentrations represent a prolonged hormonal
response. However, on the assumption that cortisol levels returned to the basal levels, using Equations (4.13) and (4.12), the amount of ets secreted over the total response time is shown in Table 4.8.

When comparing the results shown in Table 4.8 to the results calculated with SNS responses given in Table 4.2, it is clear that the glycaemic response to mental stress that requires effort is greatly underestimated when using the cortisol response as the biomarker.

4.5 Chronic stress and cardiovascular disease

Chronic distress

Cortisol is the primary glucocorticoid secreted in humans. It is secreted by the adrenal cortex in a diurnal pattern. However, the amount of the cortisol secreted is dramatically influenced by the presence of physiological and psychological stressors. Both cortisol deficiency and excess can result in adverse health conditions.

The release of cortisol in stressful situations also facilitate the metabolic effects of other stress hormones, such as catecholamines. The release of adrenaline simulates cardiovascular activity and increases blood pressure. As a result, the cardiovascular system may be impaired.

In humans, chronic stress can increase the risk of several diseases or enhance the severity of pre-existing diseases. On an almost daily basis, humans face social stress to varying degrees. Social stress derived from interactions between people and on an individual’s position in society can be one of the most important sources of stress in human life. It may play a critical role in the development of stress-related diseases. Psychosocial challenges have been associated with increased cortisol secretion followed by increased risk factors for disease [41][42].

Stress is believed to accelerate the development of atherosclerosis by increasing the secretion of stress hormones and therefore raising the level of serum lipids.

Psychological stress has been frequently related to cardiovascular disease. Scientists showed that frequent sympathoadrenal activation in response to psychosocial stress is central to the development of pathophysiology of cardiovascular disease.

Blood glucose control is vitally important for the prevention of heart disease. It improves the elasticity of the walls of arteries, body fats and clotting factors, and maintains desirable levels of high-density lipoproteins (HDL).
In today’s fast-paced and challenging society, everyday living is stressful. However, the intensity of stress an individual experiences is not easy to assess. Many individuals handle daily stress without any significant physiological responses. In 1967, Drs Holmes and Rahe interviewed thousands of patients and developed a list of 43 stressful life events commonly experienced by the public. Each event is assigned relative points, ranging from 0 to 100, according to their stressfulness. After years of follow-up, it has been concluded that an accumulation of 150 stress points or more in any one year significantly increases the risk of major illness. The effect is probably due to the resulting chronic activation of the HPA response [43].

A few studies have investigated the effects of different levels of job strain on the bodily physiology based on cortisol diurnal secretion. However, cortisol levels in high work-stressed individuals did not differ significantly from the low work-stressed group. Only in the first hour after awakening, the high stress group exhibited higher cortisol secretion than the low stress group. The difference was explained by arguing that it might be that the high work stress group generally experienced greater job demands in the morning than the low work stress individuals.

It was suggested that chronically high stress significantly increases the adverse health outcomes. Diurnal cortisol secretions in relation to work stress under investigation led to speculations. The non-significant differences exhibited by the stressed groups might be due to the fact that the selected individuals or groups were not significantly differentially exposed to work stress. It was further suggested that they were not exposed to the respective levels of stress long enough to provide a meaningful investigation of the effect of work stress on physiological changes.

In spite of the lack of association between cortisol and work stress, Kivimaki et al. [44] showed that the degree of work stress experienced was significantly associated with the relative CVD risk factors, as indicated in Table 4.9. As a person experiences an unnecessary physiological response, an increased turbulence in the bloodstream occurs. As a result, circulating stress hormones may damage the lining of arteries.

<table>
<thead>
<tr>
<th>Job stress characteristic</th>
<th>CVD risk factor</th>
<th>Total equivalent ets secretion per hour (ets/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
<td>1.667</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.58 (0.84 to 2.95)</td>
<td>2.05</td>
</tr>
<tr>
<td>High</td>
<td>2.35 (1.22 to 4.52)</td>
<td>2.567</td>
</tr>
</tbody>
</table>

Table 4.9: The influence of work stress on CVD risk factor (adapted from [44]).
It has been shown that there is a positive correlation between ets and the risk of CHD or CVD [45]. Laubscher showed that if the ets intake per day exceeds 40 ets, the risk of CHD increases, as shown in Table 4.9. From the data the risk for CHD and ets intake per hour can be described as:

\[
\text{CHD/CVD risk} = 1, \quad \text{if } \text{ets} < 1.667 \text{ ets/h} \\
= 1.5 \text{ ets} - 1.5, \quad \text{if } \text{ets} \geq 1.667 \text{ ets/h} \quad (4.15)
\]

Since several types of chronic stress have been related to chronic diseases, especially CVD, several other chronic stressors may be quantified using this measure.

When the relative risk factor is greater than 1, the extra amount of ets secreted per hour is obtained with Equation (4.16) (which is obtained by re-writing Equation (4.15)),

\[
\text{extra ets secreted/h} = \left( \frac{(RR_{CVD} + 1.5)}{1.5} \right) - 1.667 \quad (4.16)
\]

Over the past decade, psychological distress, in particular depressive features, has been recognised as a potentially important cardiovascular risk factor [46]. A cohort study of middle-aged adults in the US showed that long-term psychological stress is associated with development of CHD or CHD death for persons with pre-hypertension [47]. The stress measure was also associated with increased myocardial infarction risk as well as an association with nonfatal myocardial infarction [48].

Studies showed that long-term effects of depression might lead to the development of atherosclerotic plaques [49][50]. This association is not affected by adjusting for conventional CHD risk factors. Alternative studies reported that emotional distress serves to accelerate the progression of, rather than to promote, underlying diseases [51]. However, this model has not been examined by stratifying the population at risk and requires further exploration.

A third model suggests that the association between distress and heart disease is attributable to the presence of undetected cardiac disease leading to distress. Studies have found that recent or increased psychological symptoms may be stimulated by undiagnosed CHD. It suggests the reversibility of the causality [52].

CHD affects approximately 13 million persons in the United States, and accounted for one-fifth of all deaths in the United States in 2002 [47]. Despite the cause-effect cycle, studies showed the
importance of managing chronic psychological stress in order to minimise the likelihood of developing CHD.

Mental factors such as stress and depression have been shown to affect the HPA and functioning of the immune system. Exposure to a hurricane experiment showed that stressful experience variables induced with perceived loss being the highest correlate, were associated with decreased natural killer cell activity. Significantly increased depression has been reported for parents who have experienced sudden death of a formerly healthy child.

The importance of hope or optimism has long been recognised. A lack of hope is generally believed to have a negative impact on psychological well being and physical health. Evidence suggested that hopelessness is associated with greater disease progression and earlier death among cancer patients [53].

Hopelessness has been importantly related to various psychopathological conditions such as suicide and most commonly to depression. It should be noted that hopelessness and depression are not identical symptoms. Empirical evidence suggests that hopelessness may function independently from depression.

It was found that hopelessness may be sufficient, but is not necessary, to cause depression. Suicidal intent have been shown to be more consistently and strongly correlated with hopelessness than with depression. From the evidence, it is suggested that hopelessness is associated with adverse physical and psychological outcomes [53].

In a population based study of 2400 middle-aged men conducted by Everson et al. [53], it was found that hopelessness was significantly related to death from both cardiovascular (as shown in Table 4.10) and non-cardiovascular causes. High levels of hopelessness are consistently associated with increased morbidity and mortality. Several research studies have shown that emotional states are associated with distinct cardiovascular, immunological, and neuroendocrine patterns of activation.

From the data presented by Everson et al. [53], it is suggested that hopelessness appears to be a relatively distinct psychological symptom. It is not interchangeable with feelings of depression or isolation or a relation of illness.

Evidence showed that subjects experiencing depressed mood or clinical depression have an overall relative risk for the development of CHD of 1.64. Furthermore, in the Normative Aging Study, men who reported having more than two symptoms of anxiety at baseline on the Cornell
Medical Index, compared with men who reported no anxiety symptoms, had an increased risk of fatal CHD [54].

Todaro et al. [54] showed that negative emotion measured by the Minnesota multiphasic personality inventory (MMPI) Welsh A scale (which ranges from 0 to 35) significantly predicted the incidence of CHD. The study suggested that a 1-point increase in the negative emotion scores corresponded to a 6% increase in the risk of developing CHD during the 3-year follow-up.

The Northwick Park Heart Study, the Health Professionals Follow-up Study and the study performed by Kawachi et al. found a strong association between anxiety and fatal CHD, in particular sudden cardiac death [55][56]. Via clinical and electrophysiological studies, scientists have found that intense psychological stresses burdening daily life, and a proximate charge psychological event are two of the precursors to fatal ventricular arrhythmia and sudden cardiac death supporting a causal link between anxiety and risk of CHD [57] [58].

Prospective positive associations between coronary artery disease (CAD) and panic disorder and between CAD and worry have also been found [59]. A prospective study conducted by Kubzansky suggests that worry in different domains, such as financial worry, health worry and worry about social conditions, is associated with increased risk of CHD. In particular, worry about social conditions is associated with a 1.5-fold increase in risk of total CHD [60].

The authors [60] suggested that the associations between worry and risk of CHD appears to be somewhat specific to distinctive. However, further studies are necessary to confirm these associations.

Beem et al. showed that three months and seven months after bereavement, there was no significant difference found in NK cell concentration between a group of widows and non-widows. However, physical illness and mortality were found to be increased during the first two years of bereavement. This could attributed to the persistent activation of the adrenocortical axis [61].

Gerra et al. [61] investigated the delayed effect of an unpredictable emotional stress, such as the sudden death of a loved one, on healthy subjects. The authors showed that at 90 days after bereavement, it may be too late to detect early changes. Significant endocrine changes were evident at early stages after the stressful experience. Persistent activation of the HPA axis and a stable depressed mood were manifested at latter stages. This finding is persistent with the results shown by Kaprio [62].
Kaprio et al. [62] showed that in the entire cohort of 95,467 widowed persons studied, 44% of men and 49.2% of women died during the first week after bereavement. Some studies demonstrated that the high mortality rates during the early stage after bereavement is mainly due to coronary deaths. Excess mortality from heart disease may be related to grief and emotional distress.

During the first six months of widowhood, the study revealed an excess of death caused by accidents and suicides. The authors suggested that sleeplessness after bereavement may also be a precipitating factor in a reactive psychosis.

Cluster analysis of the study [61] showed significant inter-individual differences in the long-term persistence of endocrine changes associated with bereavement-related psychological stress.

In summary, the research outcomes derived by Everson [53], Kawachi [56], Kubzansky [60] and Kaprio [62] on the investigation on the effects of chronic hopelessness, anxiety, worry and bereavement on the relative risk factors for CVD or CHD are presented in Table 4.10 and Table 4.11. The corresponding glycaemic response due to each distress was also calculated and presented in the tables.

### Table 4.10: Extra ets secreted per hour due to different chronic psychological stress.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic worry about social conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR for CVD</td>
<td>1.4</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Extra insulin Units/day</td>
<td>5.3</td>
<td>15.98</td>
<td>37.2</td>
</tr>
<tr>
<td>Extra ets/h secreted</td>
<td>0.3</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Chronic anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR for CHD</td>
<td>1</td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>Extra insulin Units/day</td>
<td>0</td>
<td></td>
<td>30.7</td>
</tr>
<tr>
<td>Extra ets/h secreted</td>
<td>0</td>
<td></td>
<td>1.73</td>
</tr>
<tr>
<td><strong>Hopelessness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR for CVD</td>
<td>1</td>
<td>1.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Extra insulin Units/day</td>
<td>0</td>
<td>7.1</td>
<td>15.98</td>
</tr>
<tr>
<td>Extra ets/h secreted</td>
<td>0</td>
<td>0.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

### Table 4.11: Extra ets secreted per hour due to chronic stress caused by bereavement.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-7 d</td>
</tr>
<tr>
<td>Men: RR for CHD</td>
<td>2.3</td>
</tr>
<tr>
<td>Extra insulin Units/day</td>
<td>15.98</td>
</tr>
<tr>
<td>Extra ets/h secreted</td>
<td>0.9</td>
</tr>
<tr>
<td>Women: RR for CHD</td>
<td>3.49</td>
</tr>
<tr>
<td>Insulin Units/day</td>
<td>29.48</td>
</tr>
<tr>
<td>Extra ets/h secreted</td>
<td>1.66</td>
</tr>
</tbody>
</table>
Within the first few days after bereavement of a closely-related partner, the psychological stress level is believed to be intense and severe. This stress level is alleviated as time progresses. The effect of the severity of stress on glucose levels (correspondingly, ets/h) can be seen in Table 4.11. The number of extra ets/h secreted after bereavement is a function of time.

Extra insulin is required from the pancreas (healthy person) or from injection (type 1 diabetic person) to counter the elevated glucose levels. Assuming an averaged sized person weighing 65 kg with a typical $f_i$ value of 0.74, the extra insulin requirements ($0.74 \times (\text{ets/day})$) are also computed and shown in the two tables (Table 4.10 and Table 4.11).

Within the first week after bereavement, the additional number of ets secreted agrees with the amount secreted when stress experienced by an individual is high. When the period is greater than two months, the psychological burden is lessened. The resulting ±0.11 ets/h secreted corresponds to the number of ets/h secreted, observed in a mildly stressed individual.

**Sleep deprivation**

As discussed, sleep also plays an important role in energy balance. Emerging scientific evidence indicates that insufficient sleep may have deleterious effects on health. Several studies have linked inadequate sleep with increased risk or major illness, and showed a number of clinically significant associations.

Partial sleep deprivation was found to be associated with a decrease in plasma levels of leptin and a concomitant increase in plasma levels of ghrelin. Sleep duration may be an important regulator of body weight and metabolism. It appears to influence the neuroendocrine regulation of appetite and food intake. Subsequently, it may favour the development of obesity. Researchers showed that adults who sleep less than seven hours per night have a significantly higher risk of obesity [33][63][64].

To determine the effect of sleep restriction, Spiegel et al. conducted a 2-day sleep restriction test on 12 healthy men (mean age [± SD], 22 ± 2 years; mean body mass index [± SD], 23.6 ± 2.0 kg/m²). After 2 days of 4-h sleep time, there were increases in hunger (increase, 24%) and appetite (increase, 23%), especially for calorie-dense foods with high carbohydrate content (increase, 33% to 45%) [63].

Authors [64] suggested that the inhibition of leptin release due to increased sympathetic nervous outflow is a possible mechanism underlying the decrease of leptin levels during chronic partial
sleep loss. Experimental or pathological sleep loss has been consistently shown to be associated with increases in markers of sympathetic nervous activity.

Speigel et al. [64] indicated that it is not known whether sleep loss induces a commensurate increase in sympathetic activity at all peripheral sites. The relationship between elevated sympathovagal balance at the level of the heart and sympathetic outflow to adipose tissue is uncertain. However, the demonstration of increased cardiac sympathovagal balance in healthy young individuals submitted to semi chronic partial sleep restriction suggests that sleep loss has an adverse impact on cardiovascular function.

The possible adverse impact of sleep deprivation was also shown by Tochikubo et al. [65]. Throughout a day following insufficient sleep (mean period of sleep, 3.6 hours), heart rate was significantly higher than in a normal workday (81 ± 11 versus 76 ± 8 beats per minute).

It was suggested that sustained partial sleep duration could lead to adverse cardiovascular consequences. To test the hypothesis, Ayas et al. [66] conducted a study to investigate the association between reported sleep duration and the incidence of major coronary heart disease related events.

A cohort of 71 671 US females (aged 45-65 years) without reported coronary heart disease at baseline was studied [66] over 10 years of follow up. It was found that sleeping five or fewer hours per night was associated with a 39% increase in risk of CHD, and 6 hours per night with an increase of 18%, compared with sleeping 8 hours per night.

Data suggests that insufficient duration of sleep may increase CHD risk. Table 4.12 shows the relative risk factor for CHD (after adjusting for snoring, body mass index, and smoking) for individuals with different sleep durations. Using Equation (4.14), the corresponding extra ets secreted per hour is computed and given in the table below.

<table>
<thead>
<tr>
<th>Table 4.12: The relative risk factors of CHD according to different sleep duration at baseline.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
</tr>
<tr>
<td>RR</td>
</tr>
<tr>
<td>ets/h</td>
</tr>
</tbody>
</table>
In spite of a clear association between the relative risk factor for CHD and sleep duration, it was found that the association of sleep duration to glucose metabolism is mild. However, the results obtained in Table 4.12 are similar to those calculated in Table 4.6.

4.6 Stress and insulin-dependent diabetes (IDDM)

As mentioned earlier, the major effect of elevated blood concentrations of cortisol is increased blood glucose concentration through the facilitation glucose formation and anti-insulin actions. One would expect diabetes to be the most obvious disease affected by large amounts of cortisol.

It has been reported that the activation of the HPA axis and the sympathetic nervous system are responsible for developing endocrine abnormalities. The permissive effect of cortisol on functions and production of other stress hormones is diabetogenic.

Insulin-dependent diabetes mellitus is accompanied by long-term micro vascular, macro vascular and neurological complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease. The spectre of metabolic decomposition and long-term complications has caused the most morbidity and mortality [67]. As a result, diabetes has been recognised as an independent risk factor of morbidity and mortality in patients admitted to the hospital [68][69].

A recent report showed that the incidence of type 1 diabetes is rising by about 3% per year [70]. Individuals with type 1 diabetes face a lifetime of inconvenience and frequently experience depression which often worsens glycaemic control. It significantly elevates mortality among individuals with diabetes [71]. It is ultimately important for these individuals to maintain a near-normal blood glucose level to reduce the threat of long-term complications while avoiding the short-term hypoglycaemia. The beneficial effect of blood glucose management has been demonstrated in several studies [67][72].

From a study of a total of 1441 patients with IDDM performed by the diabetes control and complications trial research group [67], it was found that intensive therapy of IDDM patients delayed the onset and slowed the progression of clinically important retinopathy by a range of 35 to more than 70 percent. Furthermore, it also reduced the risk of albuminuria and microalbuminuria by 54 percent and 39 percent, respectively.

Diabetes mellitus has recently been designated as a major risk factor for heart disease. A marked increase in cardiovascular disease in diabetic patients has been noted. It is therefore increasingly critical to protect or improve people who have or are in the process of developing disease.
Hyperglycaemia is advantageous for the colonisation and growth of a variety of organisms. The adaptation of the body to an intense or prolonged stress may also increase the susceptibility to infection, cancer, and chronic fatigue [73]. These abnormalities improve with glycaemic control and when blood glucose levels are reduced below 11 mmol/l [74].

Several studies reported that patients with diabetes generally show lower psychological well-being. Diabetic patients frequently experience cardiac and other complications, which have a tendency of deteriorating their well-being. Positive feelings such as calmness, cheerfulness and life satisfaction show only a weak relationship with diabetes [75].

The ultimate goal of patients with diabetes is the control of blood glucose. It is important for patients to follow strict daily dietary and exercise regimens. Successful management depends on individuals’ behaviour and psychological factors [76].

The thesis of the contribution of stress to diabetes mellitus was first put forth in 1689. By the nineteen century, this doctrine was firmly established and the effects of stress management on diabetes were emphasised. William Osler stated that “In true diabetes, instances of cure are rare. On the other hand, the transient or intermittent glycosuria met with in stout over-feeders, or in persons who have undergone a severe mental strain, is very amendable to treatment” [77].

Studies showed that approximately 14% to 32% of diabetes patients suffer from major depression [78]. Van Tilburg et al. [76] showed that there is a significant relationship between depression and glycaemic control in type 1 diabetes. In the study, the glycaemic control was measured in terms of HbA1c levels. The Beck Depression Inventory (BDI) scores revealed a positive relationship with HbA1c levels. The BDI is the tool that has been used extensively to measure the depressive symptomatology. Scores of higher than 16 imply possible clinical depression. The observed relationship is not restricted to scores associated with clinical depression.

In the study, it was shown that there is a positive correlation between BDI scores and HbA1c levels. Characteristics of type 1 diabetes patients included for this study are shown in Table 4.13. The relationship between the BDI scores and HbA1c levels is illustrated in Figure 4.6 [76].

<table>
<thead>
<tr>
<th>BDI</th>
<th>HbA1c (%)</th>
<th>Age in years</th>
<th>Duration of illness</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4 ± 5.4</td>
<td>8.3 ± 1.2</td>
<td>40.7 ± 14.7</td>
<td>19.3 ± 12.5</td>
<td>24.6 ± 4.8</td>
</tr>
</tbody>
</table>
Glycated haemoglobin (haemoglobin A1c) is used primarily to identify blood glucose over time. It is formed when blood glucose molecules bond with haemoglobin in the 120-day life cycle of a red blood cell. The accumulated glycated haemoglobin level within the red blood cell correlates to the average blood glucose level (ABG) over the previous four to 12 months. The relation is illustrated in the figure below. An HbA1c goal of less than 7.0% is recommended for diabetes [79].

From Figure 4.7, the association between the two can be described as,

\[
ABG = 1.943 \times \%HbA_{1c} - 4.163 \quad [\text{mmol/l}] \\
\]

(4.17)

where \(ABG\) is the average blood glucose.
As shown, in order for type 1 diabetes to be free of depressive symptoms, it is necessary to keep the blood glucose level below 10.4 mmol/l.

A patient with a BDI score of 12.4 is diagnosed as highly depressive. BDI scores of 7.5 and 3.6 indicate moderate and low depression, respectively [80]. Together with the scores and the blood glucose-HbA1C relation, the extra ets secreted due to depression at different depressive levels is derived and given in Table 4.14.

It is known that type 1 diabetics have no or negligible insulin. In the absence of insulin, excess blood glucose cannot be utilised by or stored in the tissue cells. Thus, the level to which the diabetics' blood glucose levels rise should provide a good measure of glucose response due to stress [12]. For an average individual with a weight of 65 kg and blood volume of 4.5 litres, the extra ets secreted due to depression is also computed and given in Table 4.14.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>BDI scores</td>
<td>3.6</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.86</td>
</tr>
<tr>
<td>Average blood glucose [mmol/l]</td>
<td>11.1</td>
</tr>
<tr>
<td>Extra ets secreted (ets/h)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

In another study, it was shown that when the HbA1C level is less than 5% the relative risk for CVD is 1 [81]. The relative risk of CVD increased 1.15-fold for a 1% increase in HbA1C (e.g. for HbA1C from 5 to 6%) [82].

Using the relation between the relative risk of CVD and HbA1C levels, the relative risks of CVD for the low, medium and high depressive levels are calculated and given in Table 4.15. The additional ets secreted due to different intensities of depressive symptoms are also computed (using Equation (4.18)) and provided in Table 4.15.

The results (as given in Table 4.15) derived using the CVD relative risk factors reveal a strong agreement with the response predicted using the average blood glucose levels (as given in Table 4.14). The strong association that exists between the two methods indicates the validity of the response predicted using the average blood glucose level for depression.
Table 4.15: Relationship between depressive symptoms and blood glucose levels in patients with type 1 diabetes predicted using the RR factors of CVD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>BDI scores</td>
<td>3.6</td>
</tr>
<tr>
<td>RR of CVD</td>
<td>3.26</td>
</tr>
<tr>
<td>Extra ets secreted (ets/h)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

The risk of diabetic patients has also been shown to increase by 17% for every 1 mmol/l increase in average blood glucose level greater than 6.1 mmol/l [83]. Malmberg et al. [84] showed that diabetic patients with intensive glycaemic control had a significant relative risk reduction in 1-year mortality after myocardial infarction.

Researchers have suggested that psychological factors contribute significantly to the pathogenesis of medical illnesses. People with type 1 diabetes under psychological stress may experience blood glucose increases and behavioural changes. Such changes may lead to increased food intake and reduced exercise. Overall, it can result in disruptions in metabolic control.

Studies showed that psychosocial stress is a significant risk factor for medical adjustment in diabetes patients. Diabetics with poor metabolic control continuously experienced high levels of stress, which may result in psychological mal-adaptation and further deteriorate metabolism. In contrast, patients with good metabolic control showed low amounts of minor stressors, improved attention and active coping with these stressful events [85]. A strong link between medical and psychosocial adaptations was revealed.

Medical adaptation in type 1 diabetes can be clearly ascertained through metabolic control. The quality of blood glucose control is directly linked to hyperglycaemia or diabetic coma. Continuous poor metabolic control may lead to problem behaviour and long-term medical complications.

Warren et al. [86] reported that when diabetics experience elevated blood glucose levels, individuals frequently experience irritability and agitation. Another study showed that the rate of problem behaviour was higher when an individual is in a hyperglycaemic state than in the normoglycaemic condition [87]. Physical symptoms along with greater negative affect were found to be associated with poorer physical health [88].
Stress has been associated with an increase in stress hormones. Studies showed that tissue insulin resistance is heightened with elevated glucocorticoid levels. This effect would most likely be amplified in diabetic individuals. Animal studies showed that diabetics exhibited an increased susceptibility to acute stress. It suggested an increased requirement of insulin [89].

Scientists [73][90] have reported that psychical stress significantly increased the blood glucose levels in both nondiabetic and diabetic rats. However, the relative increase of the glucose level was significantly higher in nondiabetic rats [90]. The stressed nondiabetic rats had an increase of approximately 23.74% in the blood glucose level, whereas the stressed diabetic rats experienced an increase of 16.4% in blood glucose level. This could be attributed to the high basal blood glucose levels in diabetic rats. Unfortunately, only single glucose level was measured, the result in the article is disputable. Moreover, it was unclear whether the measurements among different groups of rats were taken at the same time of the day.

Forst et al. [91] demonstrated that a short, mild mental stress significantly increased the plasma epinephrine levels in both diabetic patients and healthy individuals. The absolute change of the epinephrine concentration levels over the response time was approximately 20% lower for the diabetic patients, as shown in the table below. However, the corresponding glycaemic responses (Table 4.17) are not significantly different between the two groups.

| Table 4.16: Absolute change in plasma epinephrine concentration following 7-minute mental stress [91]. |

<table>
<thead>
<tr>
<th>Change of plasma epinephrine concentration [(pmol/l).14minutes]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>Diabetic patients</td>
</tr>
</tbody>
</table>

From Table 4.4, the relation between the change of blood glucose concentration ($\Delta BG$) and the change of plasma epinephrine ($\Delta EPI$) can be expressed as,

$$\Delta BG [mmol/l] = 0.1756 \times \Delta EPI [nmol/l] + 3$$  \hspace{1cm} (4.18)

| Table 4.17: Equivalent ets/h secreted during low intensity mental stress. |

<table>
<thead>
<tr>
<th>ents/h secreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>Diabetic patients</td>
</tr>
</tbody>
</table>

To determine the glycaemic response to epinephrine in type 1 diabetes and healthy individuals, Berk et al. [92] conducted two studies. In both studies, epinephrine was infused at increment rates in both type 1 diabetes and nondiabetic subjects. However, in one study (control study),
insulin and glucagon were free to change. In the second study (islet clamp study), insulin and glucagon were held constant.

It was shown that diabetic patients have enhanced glycaemic responsiveness to epinephrine. This effect is the result of patients' inability to augment insulin secretion. Data from the islet clamp suggested similar glucose responses to epinephrine infusions in both diabetics and nondiabetic subjects. This may explain the result seen in Table 4.17.

One study [93] in type 1 diabetes showed no effect on glucose response to acute psychological stress in the fasting state. However, in a fed state, a standard 15-minute TSST test delayed the decrease of glucose concentrations by 30 minutes. The delay of the decrease of glucose levels was possibly caused by an impaired insulin sensitivity following stress.

During mental stress, the authors [93] showed that there were significant increases in heart rate, blood pressure and salivary cortisol in both the fasting state and fed state. It suggested a potential increase of glucose levels in response to the release of cortisol and catecholamines.

In the study [93], it appeared that mental stress does not cause apparent glucose excursions. However, Kirschbaum et al. [94] reported that the TSST test caused a more significant cortisol secretion when following glucose intake. One may conclude that in a fasting state, the immediate glucose is mostly depleted, which would result in a nonsignificant glucose response during acute mental stress.

Long-term stress in diabetes has been associated with higher glycosylated haemoglobin levels. Lloyd et al. [95] showed that recent severe personal stressors (SPS) are associated with poorer glycaemic control. Whereas individuals with fair or improved glycaemic control tend to experience positive life events. A SPS event includes any relationship problems, disturbed behaviour or death of a close relative.

The study [95] found that glycaemic control in individuals who experienced severe personal stressor events within the past 3 months had deteriorated or remained poor. However, life events and difficulties occurring more than 3 months prior were not significantly associated with alterations in glycaemic control. The demographic factors and changes in glycaemic control are shown in Table 4.18. Diabetic patients included in the study had a fair HbA1c level of 7.5%.
It is well known that a link between stress and diabetes exists. However, the complexities of this relationship have not been well researched. Nevertheless, there has been some study of the extra-laboratory generality of stress effects on diabetic metabolism. Researchers have shown a potential influence of stressful experiences on diabetes control. Studies showed significant positive associations between stress and blood glucose levels [96].

The prevalence of depression is twice as high in patients with diabetes as in the general population. It is generally regarded as a consequence of chronic diseases such as diabetes and has contributed to the high economic burden of health care costs. A number of studies have shown that depression predicts subsequent morbidity and mortality. The risk of complications increases with the degree of hyperglycaemia [97]. It is demonstrated that the combined effects of diabetes and depression are synergistic rather than additive.

The effect of depression seems to be an important problem in patients with diabetes. In most studies depression is linked with hyperglycaemia [98]. It is shown that measures of diabetes self-care did not appear to mediate the adverse effect of depression. It is evident that diabetic patients with depression are associated with poor metabolic control and decreased quality of life [99][100][101]. Clinical studies show that relief of depression can be accompanied by parallel improvements in glycaemic control and insulin resistance [102].

The research findings emphasise the importance of achieving optimal glycaemic control in patients with diabetes in order to minimise long-term complications. Glycaemic control is
subject to intervention. Several studies suggest that better control may decrease hospitalisation among people with diabetes [103].

An empirical study shows that illness severity determines the immediate management of the IDDM patient. Only about 10% to 20% of newly diagnosed youngsters are affected by diabetic ketoacidosis (DKA), which is believed to represent severe illness. The decrease in the prevalence of DKA was possibly due to earlier treatment of the illness [104].

In the study conducted by Charron-Prochownik et al., 95 IDDM children with a mean age of 11 years were examined for the investigation of the distribution of illness severity. Illness levels were evaluated with illness severity scores ranged from 0 to 10. It was found that children in the different degrees of illness severity groups have significantly different %HbA1c and mean insulin doses, as shown in Table 4.19, at discharge [104].

It was shown that the typical value of the insulin response / ets relationship efficiency factor, $f_i$, is 0.74. For an average sized person the recommended daily allowance ets ($ets_{RDA}$) value is approximately 30 ets. Assuming an average sized person weighing 65 kg, the extra insulin injection required is shown in Table 4.19. Using the $f_i = 0.74$ and $ets_{RDA}$ values, extra ets secreted can be calculated from additional insulin required. The calculated amounts are shown in Table 4.19.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Variables} & \textbf{Illness Severity} \\
 & \textbf{Mild (n = 45)} & \textbf{Moderate (n = 24)} & \textbf{Severe (n = 20)} \\
\hline
Insulin dose at discharge & \multicolumn{3}{c|}{\text{Units/kg/day [mean ± standard deviation]}} \\
 & 0.7 ± 0.23 & 0.95 ± 0.2 & 1.02 ± 0.21 \\
\hline
Extra insulin injection & 18.13 & 34.3 & 38.9 \\
Units/day \\
\hline
Extra ets secreted/hour & \textbf{1.03} & \textbf{1.93} & \textbf{2.19} \\
\hline
\end{tabular}
\caption{Characteristics of IDDM patients according to level of illness severity.}
\end{table}

The amounts of ets secreted are similar to those shown in Table 4.14.

### 4.7 Time effect

The activity of the pituitary-adrenocortical system shows a cyclic diurnal effect, which is manifested by variations of the plasma cortisol concentration. This circadian periodicity shows high cortisol concentrations in the morning in diurnal species like humans and pigs.
Cortisol and insulin are antagonists in regulating carbohydrate and protein metabolism. This implies that an interaction may exist between cortisol and insulin. It is speculated that the plasma insulin concentration is in proportion to the consumed meal but also in proportion to counteract the catabolic pressure of cortisol on metabolism.

It was shown in a pig study [105] that the postprandial diurnal rhythm in plasma insulin response is greater in the morning compared to the evening. In contrast to the response of insulin, the postprandial cortisol response over pre-prandial concentration is similar in the morning compared to the evening. It suggests that the postprandial diurnal rhythm in plasma cortisol concentrations is not affected by the time of feed intake.

In the pre-prandial phase, plasma cortisol exhibits high concentrations in the morning and plasma insulin shows normal basal concentration levels. However, in the postprandial phase, high morning plasma cortisol concentrations are paralleled by high cortisol concentrations. Extra insulin secretion is necessary to counteract the catabolic effects of high plasma cortisol concentrations during feeding [105].

Cortisol and insulin are antagonists in regulating carbohydrate. However, from the study performed by Koopmans et al. [105], this antagonism exists only in the postprandial phase and not in the preprandial phase. Furthermore, there is no timing effect on the cortisol response.

A timing effect of stressors was conducted by Klemcke et al. [106] to study the cortisol response in castrated male pigs (barrows). 14 barrows were bled at 6-hour intervals for 24 hours. The response-associated parameters (maximum incremental concentrations and integrated response) for cortisol did not differ between the morning and the evening stressors. The response of plasma norepinephrine and epinephrine also did not differ at different times. The study indicates that the responsiveness of the HPA axis to a stressor did not exhibit quantitative diurnal changes at the time periods measured.

In the study of glucose facilitation of cognitive performance [19], Sünram-Lea et al. found that resting blood glucose levels did not generally influence cognitive performance after administration of the glucose drink. Their findings showed that the actual resting blood glucose level or time of day may not be critical for the effect of glucose on facilitating memory performance. The authors suggested that the effect of cognitive performance rather depends on the actual rise in blood glucose levels following administration of the glucose drink.
4.8 References


Chapter 4

Stress Quantification


[63] Spiegel, K., Tasali, E., Penev, P., and van Cauter, E., Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite, Annals Internal Medicine, Volume 141, Number 11, 846-850 (2004).


Koopmans, S.J., van der Meulen, J., Dekker, R., Corbijn, H., Mroz, Z., and Wageningen UR Animal Sciences Group, Diurnal rhythms in plasma cortisol, insulin, glucose, lactate

Chapter 5 Verification

5.1 Introduction

In the previous chapter, the links between the ets concept and stress were derived. Results under different stressful conditions were computed and presented. However, the feasibility of the model is dependent on the accuracy of the predicted results. For evaluation purposes, the results derived from the model were compared to the measurement data.

The first part of this chapter consists of a description of the measurement procedures. The comparison of the measured data with the predicted glucose response due to exposures to different stress conditions is given in the second part of the chapter.

5.2 Measurements

Test subjects

In this test, a total of 18 normal healthy volunteers were studied for a period of three years. All volunteers were nonobese and in a good physical condition and had no personal history of endocrine or metabolic illness. The subjects consisted of people with varying ages and body mass indexes (BMI). The characteristics of the volunteers are shown in Table 5.1.

<table>
<thead>
<tr>
<th>Number</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27</td>
<td>9 to 58</td>
</tr>
<tr>
<td>Length (m)</td>
<td>1.74</td>
<td>1.0 to 1.98</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9</td>
<td>19.6 to 30.8</td>
</tr>
</tbody>
</table>

Table 5.1: Characteristics of the group of healthy volunteers [1].

Methods

In the trials, the test periods ranged from one day up to several days. During the test, all test subjects were asked to log their behaviour over long periods. The volunteers had to keep track of their stress and illness levels. The corresponding blood glucose measurements were recorded.

For the sake of simplicity, only high, medium or low stress levels were used to distinguish between different stressful conditions. The test subjects were requested to record their blood glucose levels with a glucose monitor throughout the trials. The exact time of measurements was recorded and was necessary for accurate verification.
Measurement data was collected over a series of separate trials. Blood glucose levels of the test subjects of all the trials performed were monitored under different situations. The normal invasive method of estimation by impedance was employed for the measurements of blood glucose concentrations [1].

A short summary of the measurement results is discussed below.

### 5.3 Results and verification

The test data was collected during each separate trial as explained in Section 5.2. The ets response due to different stress responses is shown in Table 5.2.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Example</th>
<th>Amount of ets secreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mental stress (medium-duration)</td>
<td>Examination</td>
<td>Up to 10 ets/h</td>
</tr>
<tr>
<td>Chronic stress (long-term)</td>
<td>Great illness</td>
<td>Up to 2 ets/h</td>
</tr>
</tbody>
</table>

An average sized person can store about 30 ets of glucose energy in the liver. As shown in Table 5.2, when an individual is under extreme stress, the individual is capable of coping with stressful situations for less than 3 hours and may experience hypoglycaemia afterwards.

Due to the lack of clinically accepted assessment or rating of stress levels, the ratings were greatly influenced by subjective feelings. As a result, no clear crossover points could be distinguished from the measured data. For this reason, only the maximum amount of ets secreted during acute or chronic stress was used for comparison.

Table 5.2 shows that for medium-term and long-term stressful conditions, an average sized person may utilise up to approximately 10 ets/h and 2 ets/h respectively.

It is clear that the experimental results of the ets response for medium-term and long-term stress were closely related to and agreed with the models derived in Chapter 4. The maximum deviations between the derived and experimental results for high stress are about 13% and 9% for acute and chronic stress, respectively, when maximum stress is experienced.

### 5.4 Correlation between different methods

As shown in Chapter 4, different types of stress were characterised using different methods. In this section, the comparisons of the derived quantifications are presented.
The types of stress involved in the comparison tests are acute mental stress, sleep deprivation and chronic stress.

**Acute mental stress**

![Acute mental stress chart]

*Figure 5.1: Comparison between derived and experimental results of ets secreted due to acute mental stress.*

Academic examination stress has been shown to provide a relatively good indication for assessing different stress intensities. Thus, examination stress is used here for the quantification of mental stress, and is compared with other types of mental stress (i.e. TSST experiments and measurements) characterised using different methods.

As discussed, TSST has been used most widely by the majority of the researchers for investigating the physiological responses of stress exposure. However, none of the experiments conducted with the TSST test thus far could provide a complete set of results for quantifying stress at different intensities. Thus, data obtained from different tests (origins) is used here for comparison with the results calculated (using energy expenditure) for examination stress. For low stress levels, the results obtained from TSST tests shown in Table 4.17 are used. For high and medium stress levels, results obtained and derived from Table 5.2 and Table 4.3 are taken. The test comparison is shown in Figure 5.1.

The comparison shows that at both low and medium stress levels, the results correlate moderately. However, at high stress levels the comparison between the academic stress and the measurement data reveals a strong association.
The data obtained from the academic stress was based on students' academic results. The academic scores may not accurately represent a student's stress level, and thus causes moderate deviations in different quantification methods.

**Sleep deprivation**

As mentioned in the previous chapter, due to our stressful environment, there is a trend to decrease the number of sleep hours every decade. Researchers showed that chronically depriving individuals of sleep hours would increase the risk for developing CVD (Table 4.12 and represented as the corresponding ets secretion in Figure 5.2).

In the absence of stress or illness, the stress hormone cortisol illustrates a general diurnal pattern. Researchers believe that deprivation of sleep hours will cause a disturbance of cortisol's diurnal pattern. If the disturbance occurs chronically, it may lead to adverse health conditions. The disturbance (measured in terms of cortisol increase) due to different hours of sleep deprivation was investigated by Rodenbeck (results were provided in Table 4.6). The associated virtual ets secreted due to an increase in cortisol concentrations in different sleep deprived conditions were computed and shown in Figure 5.2.

The comparison reveals that the results correlated remarkably well. It indicates that both the cortisol increase and the CVD risk factors are good indicators for stress intensity assessment for sleep deprivation.
Chronic stress

Chronic stress has often been associated with chronic disease, especially depression and cardiovascular disease. Researchers have found that exposure to different types of psychological stress or emotions may result in different physiological responses. This effect can also be seen in the risk factors for CVD/CHD associated with various psychological stressors (as shown in Table 4.10 and Table 4.11).

The results show that, depending on the dimension of the stressors, at different stress levels one stressor may have different risk factor compared to other stressors. For verification purposes, the stressors that result in the highest risk factors for CVD were chosen at each stress level. The corresponding risk factors were converted to extra ets secreted and presented in Figure 5.3.

It is generally believed that severe depression is caused by the modulation of brain cells. Researchers have shown that one of the main target organs for the stress hormone cortisol is the brain. This leads to a generalised theory that variations in cortisol concentrations have a direct effect on the development of depression. Although cortisol levels have not yet been linked to different degrees of depression, Van Tilburg et al. [4] have associated depressive intensities with HbA1c (as given in Table 4.14). The corresponding glucose responses caused by depression are depicted in Figure 5.3.

Severe illness is often referred to as chronic stress. During severe illness, the bodily metabolisms are increased to protect the body against invading viruses. The consequence of the increased
metabolisms is often increased blood glucose concentrations. To investigate the effect of severe illness on the glycaemic response, severe illness was also characterised.

Data (as depicted in Figure 5.3) showed that at the high stress level, there is a strong association between the results obtained from different models. However, as the stress level decreases and when subjective ratings are involved, the correlation also decreases. The worst correlation occurs when the stress level is low.

Despite the large deviations in the results shown in Figure 5.3 at the low stress level, one should note that when subjective ratings are required, individuals normally rate “no stress” as “low stress”. However, when stress levels can be assessed or measured methodologically, a low stress level often still refers to the presence of mild sickness. Thus, the deviations seen in Figure 5.3 may be the result of the two different definitions of “low stress” being utilised.

5.5 Statistical measure of the models

![Figure 5.4: Percentage errors for different types of stress at different stress intensities.](image)

To compare the degrees of correlation among different models mathematically, the following equation was used,

$$\text{Error} = \frac{\text{RMSE}}{\bar{x}} \times 100\% \quad [\%] \quad (5.1)$$

where $\text{RMSE}$ is the root-mean squared error and $\bar{x}$ is the average of the results obtained from different models at the respective stress levels.
The computed errors using the results given in Figure 5.1 to Figure 5.3 are illustrated in Figure 5.4. As shown in the figure, at the high stress level, all models used for different types of stress achieve an accuracy of better than 90%. The accuracy of the predictions decreases as the stress intensity decreases. The worst predictions occur at the low stress level with the worst accuracy of about 34% for chronic stress. However, if the subjective ratings are eliminated, the models can achieve an accuracy of about 70% or better for all cases.

5.6 References


6.1 Introduction

The objective of this study is to provide a scientific link between increased blood glucose and psychological stress. A summary of the important aspects of the study is given in the first section of the chapter. Recommendations for future work are provided in the second section.

6.2 Summary and conclusion

Via the literature study, various types of stress associated with blood glucose energy were obtained. The ets concept was shown to be valid and a user-friendly tool for quantifying blood glucose energy flow in the human energy system. Thus, stress-blood glucose energy associations were further linked with the ets concept.

Researchers showed that exposure to different types of stress would activate different physiological responses. It was, however, accepted by the majority of the researchers that when stress involves mental efforts or if it has a high level of arousal, the responses caused by the activation of the sympathetic nervous system would dominate the responses of those stimulated by the activation of the hypothalamo-pituitary-adrenocortical axis. However, if the stressor has low arousal or does not require mental effort, the response of the HPA axis would dominate.

Despite the different physiological systems being activated in different stressful situations, it was suggested that the amount of corresponding stress hormones stimulated (i.e. epinephrine for the SNS system and cortisol for the HPA system) was associated with stress intensities. Therefore, in this study, epinephrine or its corresponding hemodynamic response was utilised for quantifying effortful mental stress, low arousal stress or stress without mental effort was quantified with cortisol response.

It was shown that the brain almost exclusively uses blood glucose as its energy source. At rest, the brain consumes about 20% of the total energy expenditure (about 55% of the total carbohydrate metabolism) for sustaining its normal function. The total carbohydrate metabolism is about 40% at rest.

Mental stress has been suggested to have a direct influence on brain activities and can have a substantial influence on the amount of glucose energy required by the brain. It was shown that during effortful mental stress, the glucose energy contributed to about 60% of the energy
expended as the result of the mental activity. This result indicates the effect that mental stress may have on the blood glucose concentration.

In one study, the heart rate changes of students during an academic examination were investigated. The data obtained from the study showed that when the mental effort demanded during the stress is intensive, it results in high glucose energy expenditure (about 11.4 ets/h at the high stress level). This result correlated remarkably well with the result obtained via the measurements (with an accuracy of better than 93%). However, at the low and moderate stress levels, it only achieved an accuracy of about 75% when compared to the results obtained via CHO ingestion or via the epinephrine response.

In our modern society, there are increased responsibilities and stress at workplaces. This situation generally leads to a decreased number of sleep hours per night. It was suggested that chronic sleep deprivation could impair an individual's mental function and even contribute to disease development.

It was shown that when an individual suffered from high sleep deprivation (less than 1 hour of sleep per night), the cortisol level was significantly increased and produced about 1.5 additional ets/day. As mentioned, cortisol is one of the main factors that contribute to or promote the development of chronic disease, especially cardiovascular disease. The outcomes of the adverse health conditions caused by sleep deprivation are highly suggestive.

In another study, sleep deprivation was linked to the risk of CVD. The glycaemic response obtained via the risk factors of CVD revealed a strong association with the results obtained via the cortisol increase. An accuracy of better than 10% was achieved for both the high and low stress levels. This verifies the concept that the stimulation of the HPA axis is the dominant response during chronic or low arousal stress.

Patients with diabetes have often been associated with chronic depression. It was shown that the HbA1c percentage was associated with the severity of depression in type 1 diabetes. The HbA1c percentage has often been used as the representation of the average blood glucose level. Type 1 diabetics do not secrete insulin or can only secrete an insignificant amount of insulin. It was suggested that in the absence of insulin, the blood glucose level in type 1 diabetics could be used to represent the amount of virtual ets secreted. When this model was applied, it was found that at a high depressive level, the individuals' glycaemic response due to depression was about 2.1 ets/h.
In a meta-analysis, it was shown that for every 1% increase in the HbA₁C level, the relative risk of CVD was increased about 1.5-fold for type 1 diabetes. Using the link between the HbA₁C percentage and the risk factors of CVD, it was found that high depressive individuals would produce about 2.3 ets/h additionally. The result reveals a close relation with that calculated using the average blood glucose level.

Severe illness has often been referred to as chronic stress. Over the past decades, efforts have been invested in investigating the effects of insulin on the glycaemic metabolism. A consensus was reached based on those studies. In one study, data showed that at a high level of severe illness, a relatively large amount of insulin was required. Associations also exist between the insulin dosages and medium and low stress levels. The glycaemic responses at both medium and high levels showed a strong correlation between the results derived during the depressive intensity and the results derived using the illness intensities (an accuracy of better than 10% can be achieved). However, at low stress level, an accuracy of only about 70% can be achieved.

As mentioned, CVD is one of the major causes of death in the US, a majority of research studies have made tremendous efforts to investigate the effect of chronic distress or emotions on the risks of CVD. Effects of some emotions were characterised and provided in Chapter 4. It was shown that different emotions may result in different degrees of risks of CVD. However, when the maximum risk factors for each stress level were taken, the results for the high stress level correlated remarkably well with the results derived using either insulin dosage or HbA₁C percentage as a stress marker. However, at the medium and low stress levels, the results deviated greatly from the results derived using other methods.

One should note that the stress levels assigned for risks of CVD were based on subjective ratings. The low stress level for the risks of CVD often refers to no stress experienced. However, the stress levels for severe illness or depression were assigned based on clinically accepted assessments. At the low stress level during severe illness or depression, a moderate amount of stress is often still experienced by the patients. Thus, for comparison purposes, the medium stress level of the risks of CVD will be adjusted to the low stress level. After the adjustment, a moderate association can be obtained from the results derived using the three methods (the HbA₁C percentage, the insulin dosage and the risk factors of CVD).

In conclusion, this study showed that glucose metabolism is indeed one of the major mechanisms involved during stress. The established associations between the ets concept and stress provide a valuable insight into the effects that stress has on glucose utilisation.
6.3 Recommendations for further work

The link between psychological stress and blood glucose presented here may provide reasonable starting points for investigations of psychological factors in diabetes care and disease prevention. However, testing the full psychological model is a challenge.

The discordant results on the effects of stress in the literature on humans are partially due to the lack of control inherent in the related investigations. Patient characteristics often vary from study to study and there are difficulties in evocating real-life stress experimentally. Furthermore, psychological stress observed in humans cannot be derived from animal models.

The following recommendations that could further refine predictions of stress related blood glucose increases are presented:

- Most research only used a small number of test subjects. It is well known that interpersonal effects can vary largely. As a result, measured data obtained from the literature using small sample sizes could be significantly biased.

  Further, in most of the investigations, types of psychological distress were classified according to subjective opinions of each test individual. As known, several emotions may be inter-influential and produce unpredicted results. Therefore, to derive an unbiased model with high accuracy, large samples, and precisely defined assessments are required to measure different levels and types of psychological distress.

- The mechanism of blood glucose metabolism caused by stress may not be unique. The availability of multiple psychometrically sound measures is necessary to assess each potential model component.

- There is a debate on whether exposure to stress at different times of the day would result in different physiological responses. As it is known that hormonal diurnal patterns exist, time effects may be significant. Thus, to counter the differences, a well-designed experiment is necessary to characterise this effect.

- Collaborative research may be necessary for multidimensional tests to advance the understanding of psychological aspects of glucose metabolism.
6.4 Closure

In conclusion, an association between stress and glucose utilisation does exist. Stress was successfully quantified with a sound correlation achieved between the quantification methods and blood glucose metabolism. Incorporating this quantification with the ets concept, an individual could achieve better glycaemic management and prevent the development or the progression of diseases.
<table>
<thead>
<tr>
<th><strong>adrenal medulla</strong></th>
<th>endocrine gland located at the centre of the adrenal gland; secretes mainly epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adrenocorticotropic hormone</strong></td>
<td>polypeptide hormone secreted by the pituitary gland; stimulated by the hormone corticotrophin-releasing hormone released by the hypothalamus; stimulates the adrenal cortex and enhances cortisol release</td>
</tr>
<tr>
<td><strong>amino acids</strong></td>
<td>the molecular subunit of proteins</td>
</tr>
<tr>
<td><strong>basal metabolic rate</strong></td>
<td>metabolic rate when a person is at rest in a neutrally temperate environment</td>
</tr>
<tr>
<td><strong>body mass index</strong></td>
<td>a statistical measure for assessing degree of obesity; defined as the individual’s body weight in kilograms divided by square of their height in metres</td>
</tr>
<tr>
<td><strong>Beck depression inventory</strong></td>
<td>a 21-question multiple-choice self-report inventory for measuring the severity of depression</td>
</tr>
<tr>
<td><strong>catecholamine</strong></td>
<td>chemical compounds derived from the amino acid tyrosin; most abundant catecholamines are epinephrine, norepinephrine and dopamine</td>
</tr>
<tr>
<td><strong>cortisol</strong></td>
<td>the main glucocorticoid steroid hormone secreted by adrenal cortex; increases blood pressure, blood sugar levels and has an immunosuppressive effect; counteracts insulin by increasing glycogenolysis, and promotes lipolysis and gluconeogenesis</td>
</tr>
<tr>
<td><strong>effector</strong></td>
<td>cells of which a change in activity constitutes a response in a biological control system</td>
</tr>
<tr>
<td><strong>epinephrine</strong></td>
<td>“fight-or-flight” hormone secreted by the adrenal glands; elevates the blood glucose level by increasing glycogenolysis and promotes lipolysis; increases heart rate and stroke volume; constricts arterioles in the skin and gut while dilating arterioles in skeletal muscles</td>
</tr>
<tr>
<td><strong>glucagon</strong></td>
<td>peptide hormone secreted by the pancreas; important counter-regulatory action during hypoglycaemia; enhances glycogenolysis</td>
</tr>
<tr>
<td><strong>glucocorticoid</strong></td>
<td>steroid hormone secreted by the adrenal gland; cortisol is the major natural glucocorticoid in humans</td>
</tr>
<tr>
<td><strong>gluconeogenesis</strong></td>
<td>generation of glucose by the liver or kidneys from non-sugar substrate such as pyruvate, lactate, glycerol or amino acids</td>
</tr>
<tr>
<td><strong>glycerol</strong></td>
<td>serves as the backbone of triacylglycerol</td>
</tr>
<tr>
<td><strong>glycogen</strong></td>
<td>polysaccharide composed of glucose subunits; the main form of carbohydrate storage and can be quickly mobilised to meet a sudden need for glucose;</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>glycogenolysis</td>
<td>the breakdown of glycogen into glucose</td>
</tr>
<tr>
<td>glycolysis</td>
<td>the metabolic pathway that converts glucose into pyruvate or lactate</td>
</tr>
<tr>
<td>growth hormone</td>
<td>peptide hormone secreted by anterior pituitary; stimulates production of insulin-like growth factor I that has a stimulatory effect on protein synthesis which can promote bone growth</td>
</tr>
<tr>
<td>hyperglycaemia</td>
<td>high blood glucose concentration</td>
</tr>
<tr>
<td>hypoglycaemia</td>
<td>low blood glucose concentration</td>
</tr>
<tr>
<td>insulin</td>
<td>peptide hormone produced in the Islets of Langerhans in the pancreas; stimulates glucose and amino acid uptake by most cells; stimulates glycogen; fatty acid and protein synthesis</td>
</tr>
<tr>
<td>insulin-like growth factor</td>
<td>hormone that mediates mitosis-stimulating effect of growth hormone on bone and has anabolic effects in adults</td>
</tr>
<tr>
<td>Islet of Langerhans</td>
<td>a cluster of pancreatic endocrine cells; release glucagon, insulin, somatostatin and pancreatic polypeptide</td>
</tr>
<tr>
<td>Krebs cycle</td>
<td>a metabolic pathway that oxidises carbohydrates, fats and proteins to release usable energy</td>
</tr>
<tr>
<td>lactate</td>
<td>ionised form of lactic acid; mainly produced and used by the muscles</td>
</tr>
<tr>
<td>lactic acid</td>
<td>mainly produced in muscle cells and red blood cells; produced when the body breaks down carbohydrate to use for energy when the oxygen level is low and the rate of demand for energy is high</td>
</tr>
<tr>
<td>lipolysis</td>
<td>the breakdown of triacylglycerol</td>
</tr>
<tr>
<td>low-density lipoprotein</td>
<td>protein lipid that regulates cholesterol synthesis and transports cholesterol from the liver to peripheral tissues</td>
</tr>
<tr>
<td>lymphocyte</td>
<td>a type of white blood cell that is response for specific immune defences</td>
</tr>
<tr>
<td>natural killer cell</td>
<td>a type of lymphocyte that has a major role in destroying virus infected and cancer cells</td>
</tr>
<tr>
<td>neurotransmitter</td>
<td>a chemical messenger that amplifies and modulates signals between neurons or between a neuron and an effector</td>
</tr>
<tr>
<td>nicotinamide adenine dinucleotide phophase</td>
<td>a reducing agent used in anabolic paths such as lipid synthesis, cholesterol synthesis and fatty acid chain elongation</td>
</tr>
<tr>
<td>norepinephrine</td>
<td>a catecholamine released from the adrenal medulla as a hormone into the blood and as a neurotransmitter in the central nervous system</td>
</tr>
</tbody>
</table>
Appendix A

Glossary

normoglycaemia

normal blood glucose level

pyruvate

forms lactic acid anaerobically in the absence of oxygen or enters Krebs cycle in the presence of oxygen

relative risk

a ratio of the probability of the event occurring in a group of people exposed to a putative cause versus a group or population not exposed to the cause

respiratory quotient

the ratio of carbon dioxide produced and oxygen uptake during metabolism

somatostatin

a peptide hormone that inhibits the release of growth hormone and thyroid-stimulating hormone

thyroid-stimulating hormone

a hormone secreted by the anterior pituitary gland; stimulates the thyroid gland to secrete thyroid hormones

triglyceride

major energy store in the body and also known as triacylglycerol; composed of glycerol and three fatty acids; major components of very low density lipoprotein

triacylglycerol

see triglyceride