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Pathogenetic Mechanisms of Exercise-Associated Hypoglycemia: Permanent and Reversible Counterregulatory Failure

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1. Introduction

These are times when health awareness has become part of everyday life to an extent that may have never been true before. We see health related articles and advertisement numerous times every day on newspapers, TV programs, and of course the internet and all related forms of novel electronic media. We are told repeatedly what is best for us, what we should or should not do, why we have been wrong in the past and how we can improve in the future. Unfortunately, these messages often comes to us in a very confusing and inconsistent manner, making it very hard to filter out what is backed by sound, proven scientific principles, and what is just the "in" new trend that may fade away in a few weeks or months. Among the many messages that are more systematically thrown at us, however, is that we should definitely try to incorporate at least some form of exercise in our daily routine. This is nothing new in general, as going back in history, looking at most ancient civilizations, from the Chinese to the Romans or Greeks, they all seemed to value and implement forms of structured physical exercise. And in fact in our society, if one were to ask anybody, even people who are not health professionals, whether they think that exercise is "good" for you, in the overwhelming majority of cases they would respond that yes, of course it is. And if you were to be more specific, and ask if exercise were "good" for people with diabetes, they would also most likely answer "yes, of course it is going to be good for them". And common sense indicate that would be right. Now, if you were to ask why exercise is "good", both for the general population and for patients with diabetes, you would probably get a variety of responses, (mostly "I am not sure"), with some mixture of truth, speculation and traditional lore. In reality, even among exercise and metabolism professionals, as well as health care professionals, a complete answer to this question is still far from clear. We certainly do know that a number of positive things happen if people exercise regularly, and we have in past decades rather quantified what these beneficial effects are, but we still not know in detail why they occur.

Nevertheless, abundant empirical evidence indicates that, while we may not be sure about the underlying mechanisms, a lot of positive health effects are associated with regular exercise, and are especially important for patients with T1DM (Berenson *et al.* 1998; Hannon *et al.* 2005; Laaksonen *et al.* 2000; Lakka *et al.* 1994; Larson *et al.* 2006). In these patients, in fact, exercise is advocated as a necessary preventive measure against their increased risk of

vascular-related diseases, protecting against both micro- and macro-vascular complications such as diabetic retinopathy, nephropathy, neuropathy, and cardio- and cerebro-vascular diseases (Anonymous 1993b; Anonymous 2002; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. 2005; Hambrecht *et al.* 2000; The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group 2000; White *et al.* 2001). Exercise also improves insulin sensitivity (Pedersen *et al.* 1980), helps to control body weight, and exerts positive intracellular molecular effects such as activation of the peroxisome proliferator-activated receptors (PPARs) target genes, coding for anti-inflammatory cytokines and other novel protective candidate targets, and enhancing cellular metabolism and insulin sensing pathways (Nieman *et al.* 2005b; Smith & Muscat 2005; Teran-Garcia *et al.* 2005). In children, there is also the added issue of regulation of physiological growth and development. It is therefore in fact now very well established that during their schools years, children must perform multiple bouts of moderate to vigorous exercise every day, in order to achieve proper development of their musculoskeletal and cardiovascular systems, as well as an appropriate psychomotor and behavioral equilibrium. Different authors have suggested different amounts of minimum necessary duration of daily physical activity, but in general the recommendation of at least 60 minutes of exercise per day is considered appropriate, and supported by a recent revision of several hundred scientific articles published on the topic (Strong *et al.* 2005).

As we stated above, despite this broad consensus on the vague concept that "exercise is good", many of the detailed biochemical mechanisms by which exercise actually induces its health effects remain incompletely elucidated. This is due in part to the simple fact that the number of interwoven mechanisms that are trigger by exercise is enormous, and probably included several additional still un-identified components. Among the most typical responses to exercise are those aimed at maintaining constant circulating level of glucose, and at making sure that sufficient amounts of energy substrates, such as glucose and lipids, are made available to the exercising muscle, whose metabolic need may have increased by several fold. These responses are collectively defined as counterregulatory responses, and include secretion of hormones such as catecholamines, cortisol, glucagon, growth hormone (GH), with stimulation of both hepatic glycogenolysis and gluconeogenesis, as well as lipolysis. In addition to its glucoregulatory effects, GH is also part of the GH→ insulin-like growth factor I (GH→IGF-I) axis (Nemet *et al.* 2002), which modulates growth and development, and ins therefore especially relevant for subjects of pediatric age. Another series of adaptive response to exercise includes the production of reactive oxygen species, (ROS), the causing agents of oxidative stress, that can be acutely increased by strenuous exercise, as well as mitigated by appropriate antioxidant mechanisms (Nikolaidis *et al.* 2007; Urso & Clarkson 2003). Also, exercise can exert a strong effect on immunologic and inflammatory status, by inducing substantial changes in circulating concentrations of leukocytes (WBC), as well as their level of secretion of cytokines, chemokines, colony-stimulating factors, adhesion molecules and other inflammatory markers (Cryer 1993; Galassetti *et al.* 2006a). Inflammatory and oxidative stress pathways, as well as other critical homeostatic pathways, are also stimulated by exercise at the level of gene expression; in fact hundreds of genes in all subtypes of WBCs (Nemet *et al.* 2004), skeletal muscle (Nieman *et al.* 2005a) and other tissues undergo either up-or down-regulation, as well as post-translational epigenetic regulation especially during physical exertions of considerable intensity (Cooper

et al. 2004). This chapter is focused on hypoglycemia and exercise, and therefore, among the many adaptive response listed above, counterregulatory functions are the most relevant. However, this broader context of multiple, simultaneous and coordinated adaptive response to exercise had been presented to make the point that hypoglycemic counterregulation does not occur as an isolated set of events, but together with the stimulation or suppression of numerous other systems with which it interacts and by which it can be regulated. Along this line of thought, it is important to remember that in diabetes management, one must constantly evaluate the reciprocal balance of all components of glycemic responses; as specifically related to exercise, it is necessary to determine if all physiological exercise response are preserved, and if alterations are present, whether these are permanent or reversible, and what factors may have affected them (Cooper *et al.* 2007). It is in fact now amply established that many components the comprehensive exercise response to exercise may indeed become altered. Several glucoregulatory responses to exercise can become attenuated permanently (for instance when diabetic autonomic neuropathy develops, typically after years of poor glycemic control), or acutely and reversibly, which may occur even in well controlled patients, in whom diabetic tissue complications have not yet developed.

In this chapter we will therefore review in detail the key known physiologic molecular mechanisms that during exercise maintain glucose homeostasis, and how their potential alterations in T1DM may result in increased incidence of hypoglycemia both during the performance of physical activity, in the first several hours after exercise cessation, and during the following night or even several days.

2. Glucose homeostasis during exercise of varying intensity in type 1 diabtes

The concentration of glucose in plasma is one of the most tightly controlled variables in overall human homeostasis. The range of values within which plasma glucose levels physiologically fluctuate is in fact very narrow, and any changes below or above this range are rapidly corrected by a series of extremely effective adaptive mechanisms. A number of sensors for glucose concentrations are in fact located at critical sites, both within the central nervous system (hypothalamus)(Biggers *et al.* 1989) and in peripheral tissues (walls of the portal vein to detect differences in arterial vs. venous blood, pancreatic islets to directly affect beta- and alpha cells' output of insulin an glucagon, respectively, etc.)(Cherrington 1994; Donovan *et al.* 1994; Hamilton-Wessler *et al.* 1994; Pagliassotti *et al.* 1991). As soon as changes in glucose levels are perceived, corrective actions are immediately undertaken. With increasing glucose concentration insulin is released and counterregulatory hormone secretion is suppressed. I glucose levels are dropping, hormones such as cortisol, glucagon, epinephrine, norepinephrine and growth hormone are released, rapidly activating glycogenolysis an gluconeogenesis in the liver and, to a lesser extent, in other tissues such as the kidney and some areas of the gut. Exercise imposes an additional layer of stress upon these mechanisms, by causing very rapid changes in the skeletal muscle requirement of energy substrates (both carbohydrates and lipids) paralleled by acute increases in insulin sensitivity.

As in T1DM the very hallmark of the disease is an impairment of insulin availability, not surprisingly, in these patients major disruptions of this complex equilibrium are often present. The number of possible events that may occur during exercise in T1DM is actually

very broad, but fundamentally most glycemic alterations derive from the combination, in variable proportions, of two main homeostatic situations. First, T1DM patients are often unable to avoid hypoglycemia during exercise performance of in the hours following exercise cessation. This seems to happen more often if the exercise challenge was moderate in intensity but long in duration. Second, at the opposite end of the glycemic spectrum, when patients perfume very intense, albeit brief exercise formats, they can experience acute hyperglycemia, typically beginning during exercise and further increasing afterwards.

A healthy person of average body size, in resting conditions and at least 2-3 hours after the last meal, (i.e. not actively absorbing carbohydrates), "burns" every minute about 2 mg of glucose per Kg of body weight. This is referred to as glucose rate of disposal, or glucose Rd, and is a measure of all the glucose that at any given time is taken up cumulatively by all cells in the body. In these conditions, the movement of glucose into human cells is mediated by baseline systemic insulin concentration ranging between ~ 5 and 10 □U/ml.

If glucose were gradually take up from the bloodstream without replacement, glycemia would progressively decreases over time; this is prevented, however, by endogenous glucose sources, which simultaneously release into the bloodstream an amount of glucose exactly matching the amount that is being taken up. This occurs via breakdown of existing glycogen stores (glycogenolysis) and *de novo* synthesis of glucose molecules (gluconeogenesis). Interestingly, while the body's greatest glycogen stores are contained in the skeletal muscle, muscle glycogen cannot be used to sustain systemic glycemia, as muscle does not express glucose-6-phospahtae, an enzyme necessary to "free" glucose molecules before they are released into the bloodstream. Muscle glycogen can therefore only be used for energy production within the muscle cell. For exercise to be sustained for prolonged periods of time, it must be at a "sub-maximal" level, i.e. at a workload below the anaerobic (or lactate) threshold (normally occurring at 50-60% of individual maximal aerobic capacity). With this type of exercise, glucose Rd typically increases by two- or three- fold, due to the increased metabolic needs of contracting skeletal muscle. This increase in uptake, however, results in only minimal or no decrease in glycemia by the combined effects of two key mechanisms: a) a quick compensatory increase in endogenous glucose production, and b) a parallel decrease in the amount of insulin secreted by the pancreatic beta cells, which is induce by an acute increase in autonomic nervous system efferent stimulation of the pancreas through alpha-adrenergic fibers. This reduction in insulin levels is critical, because during exercise not only insulin sensitivity is markedly enhanced, resulting in increased glucose disposal for the same concentration of insulin, but the is also a simultaneous activation of non-insulin dependent glucose transport across the sarcolemmal membrane, mediated by the increase intracellular calcium release associated with exercise. As a result, if baseline insulin levels do not decrease, the amount of glucose transported into the skeletal muscle cells would actually be excessive, and glycemia in the bloodstream would drop.

It is then evident how this situation can become problematic in T1DM subjects, who can't any longer regulate endogenous insulin release. Preventing the onset of hypoglycemia during exercise then becomes a matter of how accurately patients can reproduce the physiological profile of insulin secretion. If they are using an insulin-infusion pump, they can try and decrease, or even completely stop insulin infusion (many prefer to do so even if this may result in mild hyperglycemia). Conversely, subjects who administer insulin via multiple insulin injections cannot reduce their baseline insulin level, and may find themselves in a state of relative hyperinsulinemia. In fact, sometimes even the opposite may

occur, i.e. they may experience an acute increase in insulin release. This may happen if the last insulin injection before exercise was performed close to a muscle mass likely to be mobilized during exercise, such as the side of the thigh; part of the injected fluid, in fact, may occasionally be trapped in a subcutaneous pocket, and be acutely released into the bloodstream when exercise in started, which is practically equivalent to a small additional insulin shot. The added amount of insulin will then not only cause an exaggerated uptake of glucose by the skeletal muscle, but will also suppress endogenous glucose production. These two effects combined markedly enhance the likelihood of the development of an acute hypoglycemic episode.

Conversely, if the type of exercise is very intense, i.e. well above the anaerobic threshold and closer to individual maximal aerobic capacity, a series of drastically different adaptive event are likely to take place. This type of exercise can only be sustained for a much shorter time - rarely more than 20 to 30 min-, and induces a very strong whole-body activation of adrenergic efferents. The main purpose of this response is to generate a sufficiently strong up-regulation of cardiovascular function to match the now extremely increased systemic metabolic needs. The increase in endogenous glucose production resulting from this level of adrenergic activation actually exceeds required by peripheral tissues, resulting in a state transient hyperglycemia of moderate magnitude (typically under 140 mg/dl), which spontaneously subsides shortly after exercise ends, in response to a prompt insulin response (in fact, in the immediate post-exercise state the combination of this insulin secretion with increased insulin sensitivity often induce brief, mild hypoglycemia). In T1DM the initial hypoglycemic response is similar, but at exercise cessation, as the diabetic cannot produce the expected insulin response, the magnitude of hyperglycemia often continues to increase, sometimes up to very elevated levels.

Exercise in real life is almost never exclusively moderate and prolonged, or brief and intense, but most commonly a combination of the two in various proportions. The actual glycemic fluctuations that can be experience in the presence of any given specific exercise format, therefore, could fall anywhere across this broad range. In fact, moderate and intense exercise, performed within the same exercise session, could exert opposite hypo- and hyper-glycemic effects that could, to some effect, cancel each other out. Used in a controlled manner, this principle could conceptually result in optimal glycemic control without additional interventions, and its use has indeed be explored in a series of controlled studies on a group of diabetic Australian youth (Bussau *et al.* 2007a).

3. Altered counterregulatory mechanisms in t1dm

Unfortunately even in T1DM patients who manage to administer themselves an ideal amount of exogenous insulin, and indeed reproduce as closely as possible the physiological profile of endogenous insulin secretion, a variable degree of counterregulatory impairment may still occur, although the underlying mechanisms to date are not understood in full (Tansey *et al.* 2006a). Evidence derived from several studies indicates that the exercise response of major counterregulatory hormones is in general decreased in T1DM when compared to healthy controls (Galassetti *et al.* 2006b; Tansey *et al.* 2006b; Wanke *et al.* 1996).

The issue of counterregulation is very complex, and extends to a number of conditions other than exercise. Of these, the best studied is hypoglycemia itself. The possible blunting of counterregulatory response to exercise, in fact, is very similar to what occurs when

counterregulatory responses to hypoglycemia (occurring independent of exercise) become impaired (Bjorgaas *et al.* 1997; Hoffman *et al.* 1991), (the response to hypoglycemia also include associated neurogenic symptoms-hunger, sense of anxiety, sweating, palpitations) caused by the sympathoadrenal effects of epinephrine (Hoffman *et al.* 1991).

This parallelism between altered adaptation to exercise and hypoglycemia is important, as most involved hormones and autonomic pathways are shared by the two conditions. A notable exception, however, is glucagon. Patients with T1DM, in fact, within the first two years after having been diagnosed with the disease, become completely unable to secrete glucagon during a hypoglycemic episode (this was demonstrated by Dr. Gerich and co-authors in a classic study appeared in the journal Science in 1973, (Gerich *et al.* 1973) and confirmed in numerous subsequent studies in both adult and pediatric patients, in which hypoglycemia of varying depth, duration and onset kinetics was induced, always with glucagon concentrations remaining unchanged as compared to baseline values (Ross *et al.* 2005). Interestingly, it appears that pancreatic α-cells in these patients are not unable to secrete glucagon (in fact basal levels are normal), but rather are incapable of increasing glucagon secretion when hypoglycemia is induced artificially via elevated levels of exogenous insulin, which is by far the most common way in which hypoglycemia occurs in T1DM. In animal models of T1DM, however, it was observed that if hypoglycemia was induced by other means, (i.e. via administration of agents such as AICAR and phlorizin, (Banarer *et al.* 2002; McCrimmon *et al.* 2002), the glucagon response was restored. Similarly, and pertinent to the focus of this chapter, the □-cells of patients with T1DM retain the full ability to secrete glucagon in response to other stimuli, including physical exercise (Marliss & Vranic 2002).

Before we further advance in our discussion of altered adaptive mechanisms to exercise, we should now clearly delineate the distinction between those alterations in counterregulatory responses to exercise in diabetes that are permanent (irreversible) and those that are transient (reversible). This is not just and academic distinction, but has a series of obvious practical implications that affect the way a patient may approach exercise. Permanently lost responses, in fact will require alternative ways to substitute lost mechanisms; dealing with reversible alterations, on the other hand, will instead imply focusing on prevention of the causes inducing the temporary impairment.

The two counterregulatory hormones that are commonly defined as the "first line" intervention against hypoglycemia are epinephrine and glucagon; quantitatively, they account for large majority of counterregulatory function during the first hour or so hypoglycemia or exercise have started. In T1DM, with long lasting, poorly controlled diabetes, the characteristic tissue complications of the disease start appearing, including diabetic neuropathy. As part of this condition, the catecholamine response to stress is gradually attenuated until, in the most advanced stages of the disease, may become completely suppressed (Cryer *et al.* 2003) (it should be noted that these complications are not a mandatory part of being diabetic, but can be virtually completely prevented with continuous optimal glycemic control) (Karavanaki & Baum 2003).

If autonomic neuropathy becomes established, however, it is typically irreversible. This means that among other related alterations, the epinephrine response to stress is lost; this essentially leaves the burden of counterregulation at the beginning of a stress event to glucagon alone. If the stress is a hypoglycemic episode, however, as stated above the glucagon response is lost, and very little resistance is offered against the rapid onset of

hypoglycemic episode. May of these patients in fact suffer form repeated severe hypoglycemia, often leading to serious accidents if occurring during driving or the operation of heavy machinery, with sometimes catastrophic consequences. If the stress is exercise, on the other hand, the glucagon response is still preserved, producing at least some of the expected counterregulation. This, at least, provided that one of the mechanisms inducing temporary blunting of counterregulatory response is not also present.
Independent of the presence of autonomic dysfunction, in fact, all major counterregulatory responses to stress may undergo a variable degree of reversible attenuation. In general, this occurs according to this general paradigm: a certain stimulus occurs, that is able to blunt the activity of the hypothalamus-pituitary-adrenal axis (that coordinates counterregulation), and for the following hours to days, if counterregulation is needed in response to an episode of stress (hypoglycemia, exercise or other), it can only occur to a reduced degree, or not at all.

Prior Blunting Stimulus → **↓ Responses to Subsequent Stress**

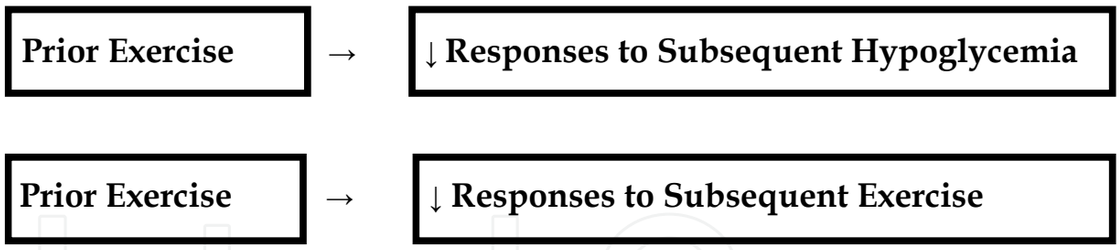
The best studied set of blunting stimulus/subsequent stress if repeated hypoglycemia, in which indeed hypoglycemia acts as both prior stimulus and subsequent stress. Therefore in this case the above paradigm can be re-written as:

Prior Hypoglycemia → **↓ Responses to Subsequent Hypoglycemia**

The scenario is unfortunately very common in T1DM, in which, even after a long period of optimal glycemic control, a hypoglycemic episode may be triggered by excessive insulin administration, insufficient carbohydrate ingestion, acute increase in insulin sensitivity, etc. Once this first episode occurs (during which counterregulatory responses may be normal)
For a number of hours to days the subject will be more susceptible to developing an additional hypoglycemic episode. This condition is now describe as Hypoglycemia-Associated Autonomic Failure (HAAF), and often results in more and more episodes of hypoglycemia, in which each episode acts as the blunting stimulus for the next, de facto starting a vicious cycle out of which it is very difficult for the patients to break. Paradoxically, this happens most commonly in those patients who put the greatest effort into tightly controlling their glycemia. By testing glycemia many times a day, and aggressively adjusting their insulin administration regimen in order to prevent any possible hyperglycemic episode, they in fact often inadvertently expose themselves repeatedly to situations of relative hyperinsulinemia, favoring the onset of hypoglycemia of variable depth and duration. It is unfortunately well documented that in these patients the incidence of hypoglycemic episodes is markedly higher that in patients with worse glycemic control(Amiel *et al.* 1987; Simonson *et al.* 1985). Now, as stated above, both hypoglycemia and exercise elicit similar responses; a logical development of this axiom should therefore be that these two situations could also reciprocally act as blunting stimuli. For instance, if an episode of hypoglycemia preceded an exercise challenge, the above paradigm could be hypothetically become:

Prior Hypoglycemia → **↓ Responses to Subsequent Exercise**

As it turns out, this was directly demonstrated in a recent study on sixteen young adults with T1DM (eight males and eight females) (Galassetti *et al.* 2003). These subjects participated in an experimental protocol that included biking on a stationary cycle for one hour and a half. If this exercise challenge was performed after several days of very tight glycemic control, i.e. with no episodes of hypoglycemia occurring, all response to exercise (including the expected increase in glucagon and epinephrine, cortisol, GH, endogenous glucose production and mobilization of free fatty acids), were the same as measured in age-matched, healthy control subjects. If, however, prolonged hypoglycemia was artificially induced on the day before the exercise challenge (four hours of glycemia at ~ 50 mg/dl, divided in two 2-hour blocks, morning and afternoon), the glucagon response to exercise was abolished, the epinephrine response was reduced by 50%, and other counterregulatory hormones, as well as tracer-determined endogenous glucose production and lipolysis, were all significantly reduced by 40-60%. Interestingly, while healthy subjects, unlike T1DM, \don't ever experience hypoglycemia of this depth in normal life, when exposed to the same experimental protocol they displayed an identical pattern of blunted exercise responses (Davis *et al.* 2000b). An important notion to keep in mind is also that this blunting effect is not an all-or-nothing phenomenon, but occurs in a dose-dependent fashion with respect to the depth of the antecedent hypoglycemic episode. This was well exemplified in a separate set of experiments, similar to those described above, in which again a group of patients with T1DM performed a standard 90 min cycling exercise after having been exposed to hypoglycemia for four hours on the previous day. This time, however, each subjects performed the study several times, with several weeks between study visits, and each time was exposed to hypoglycemia of different depth (50 mg/dl, 60 mg/dl, 7- mg/dl or no hypoglycemia). Not surprisingly, the deeper the antecedent hypoglycemia, the more blunted were the responses to subsequent exercise. Considering the glucagon response, for instance, the milder prior hypoglycemia (70 mg/dl) induced a suppression of ~ 35%, prior hypoglycemia of 60 mg/dl a suppression of ~ 60%, and prior hypoglycemia of 50 mg/dL an almost complete suppression of > 95% (Galassetti *et al.* 2001a). A progressively smaller blunting effect on subsequent exercise responses, in addition to a smaller prior stimulus, can be observed as time passes after t he blunting has occurred. In the studies, reported above, prior hypoglycemia occurred ~18-20 before the exercise challenge during which blunted responses were measured. To date no definitive data have been published reporting the exact duration of this blunting effects; however, general consensus exists that within a few days to a week following the antecedent stimulus, provided that no additional blunting stimuli occur, the full ability to mount physiological counterregulatory responses is re-gained. Preventing these recurrent blunting stimuli, however, is no minor challenge in every-day diabetes management. Recurrent, often profound episodes of hypoglycemia are unfortunately very common, and this paradoxically seems to occur even more often in subjects who are very aggressive in their attempts to obtain close to perfect glycemic control (Anonymous 1993a). A final piece of the puzzled is generated by the fact that exercise itself may act as an antecedent blunting stimulus. Going back to our initial paradigm, we can then derive two more combinations:



Both these possibilities have been documented to actually occur. An exercise bout performed in the morning, for instance, was shown to reduces a wide range of adaptive response to a second bout of exercise performed in the afternoon of the same day (while counterregulatory responses were attenuated, in this study hypoglycemia was not actually allowed to occur, to prevent its confounding effect on data interpretation) (Galassetti *et al.* 2001a). Further, in at least one study prior exercise of different intensity was shown to reduce next-day responses to hypoglycemia, again in a dose dependent manner (Sandoval *et al.* 2004). While a somewhat similar protocol form a different laboratory failed to reproduced the same effect (McGregor *et al.* 2001), possibly due to differences in the intensity of the exercise format used during experiments, an increased incidence of hypoglycemia in the hours following exercise is commonly reported by T1DM patients. This is especially true if exercise was of long duration and/or high intensity, after which insulin sensitivity is markedly increased and redistribution of circulating carbohydrate is shifted toward preferential replenishment muscle glycogen stores, that become depleted during the exercise activity (Borghouts & Keizer 2000).

Further, counterregulatory responses to hypoglycemia, even in standard physiological conditions, become attenuated during sleep (Jones *et al.* 1998); therefore, not surprisingly, a second peak of incidence of hypoglycemia has been described occurs during the nights that follow intense physical activity (Anonymous 2007; Kaufman *et al.* 2002; Tsalikian *et al.* 2005a), with the highest incidence occurring between midnight and 4 am. (McMahon *et al.* 2007).

A separate of issues to be taken into consideration is that male and female patients may responds differently to the same blunting stimulus. Gender differences, often very pronounced, are very common in many aspects of human physiology, and the coordinated adaptive response to stress is no exception(Diamond *et al.* 1993). In particular, the hormonal response to stresses activating the hypothalamo-pituitary-adrenal axis are in general much more pronounced in males than in females. This is true for hypoglycemia as well as exercise which, as we stated in detail above, share many of their adaptive responses. This concept was recently confirmed in group of young healthy adults of both genders, who performed 90 minutes of submaximal cycling exercise. In this group, all hormonal and metabolic responses to the exercise challenge were significantly lower, after normalization for individual exercise intensity, in women as compared to men (Davis *et al.* 2000a). When a blunting stimulus occurs prior to exercise or hypoglycemia, the extent of the blunting on counterregulatory responses is much greater in men (who had a greater response to begin with, and in whom some of the counterregulatory hormones can be suppressed by 80-95%), while in women a much milder, 20-40% blunting occurs (Galassetti *et al.* 2001b). Therefore, in a blunted state responses in males and females become much more similar. In T1DM, the same pattern is preserved, with men displaying greater responses to exercise than women in conditions of standard glycemic control, and again greater blunting of responses after appropriate stimulus in male patients(Galassetti *et al.* 2004).

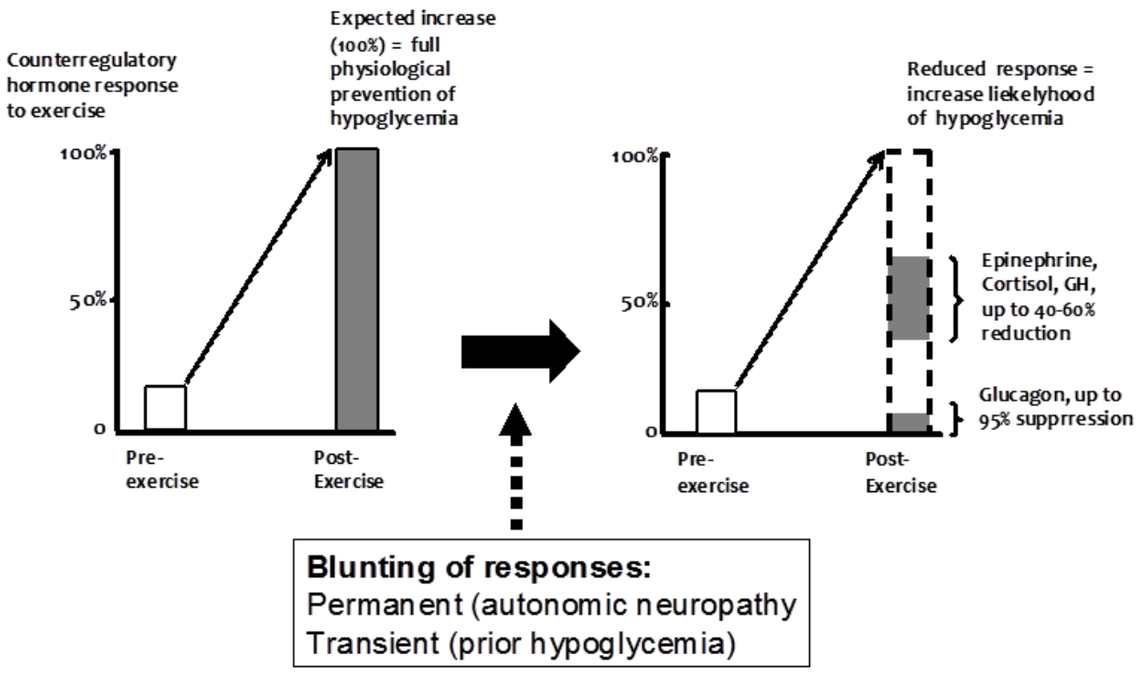


Fig. 1. Schematic representation of counterregulatory events occurring during exercise in healthy subjects and in patients with type 1 diabetes. Counterregulatory responses, including increased secretion of glucagon, epinephrine, norepinephrine, cortisol and growth hormone, display a typical amplitude, exemplified on the left hand-side panel by a 100% response (this general concept can in fact be extrapolated to a number of additional responses not directly related to glucose homeostasis, such as production of the appropriate balance of pro- and anti-inflammatory mediators, or of growth factors; the physiological, full manifestation f the possible, expected health of exercise only occurs when these responses are 100% activated). In the right hand-side panel, conversely, is exemplified the presence of multiple, simultaneous failures of sever involved counterregulatory hormones. Depending of the degree of suppression of these responses, a variable impairment will also occur in endogenous glucose production, which these hormones regulate, and therefore glucose availability will become acutely inadequate to match the increase metabolic needs of the exercising muscle, resulting in the likely onset of a hypoglycemic episode.

Translated in practical terms, this complex interaction between exercise and hypoglycemia means that the more frequent the hypoglycemia, the more likely that subsequent slight hyperinsulinemia (or bouts of exercise) will result in additional hypoglycemia, and so on (Tsalikian *et al.* 2005b). Due to the variety and instability of these several factors, exercise-associated hypoglycemia is often difficult to manage clinically. One of the most basic approaches is trying to optimize circulating insulin. Patients on an insulin pump can reduce the basal infusion rate, in the attempt to reproduce the physiological 40-50% insulin drop occurring in non-diabetic subjects (many T1DM subjects in fact are even more aggressive than that, and completely stop insulin infusion. Absolute recommendation as to the magnitude and duration of insulin reduction/suspension are impossible to generate, as every subjects will react differently, and within the same subject, different strategies will have to be implemented for exercise of different duration and intensity. Further, none of the currently available sets of practical guidelines incorporates the effects of prior stimuli

described above. Therefore, often, even in the same subjects exercising in seemingly identical conditions in two different days, in one occasion glycemic control may be perfect, and in the next hypoglycemia may occur. A combination of insulin reduction and ingestion of carbohydrate snacks may be the best overall approach, but again the exact type and amount of ingested carbohydrate, as well as the fractioning and timing of the ingestion, is the objects of considerable controversy, and personal, careful experience seems to still yield the best results. Carbohydrate ingestion is the only tool available for patients utilizing multiple insulin injection, who derive their basal insulin rate from long-acting insulin preparation, and for whom therefore rapid reduction in insulin concentrations during exercise is not possible. Finally, as briefly mentioned above, a new approach has been proposed recently by members of the research group lead by Dr TW Jones, who have attempted to use the intrinsic characteristics of exercise itself to counterbalance its hypoglycemic effects. The principle is simple: to utilize the hyperglycemic effect of brief, intense exercise, to offset the opposite effect of prolonged, moderate exercise. In two studies performed in well controlled T1DM subjects, these authors have introduced a very brief (only 10 seconds) all-out sprint either before or at the end of a prolonged, moderate exercise session. When the sprint was performed before the training session, it decrease the magnitude of glycemic decline only for the first 45 min after exercise; when it was performed at the end, it reduced glycemic decline for several hours after exercise (Bussau *et al.* 2007b; Guelfi *et al.* 2007). The beauty of this approach, if its broader applicability to diabetes management will be confirmed by larger follow-up studies, is that it utilizes only physiological tools, it takes very little time and is easily implemetable any time exercise is performed. More in-depth description of hypoglycemic prevention techniques, in relation to physical exercise, can be found in several excellent recent publications, such as the Clinical Practice Consensus Guidelines of the International Society for Pediatric and Adolescent Diabetes (Robertson K *et al.* 2009).

4. Conclusion

Recent research advances, summarizing the efforts of a large number of laboratories across the globe, demonstrate the high (sometimes incomprehensibly so) complexity of the many interwoven molecular mechanisms that translate exercise into a long-term positive health status. Most likely, our still incomplete understanding of these many mechanisms derives from the fact that they are often activated simultaneously, can partially replace each other in function, and can markedly influence the reciprocal effects. Complex as they may be, some of them have been relatively well elucidated in physiological conditions. Specific alterations in some of these mechanisms, however, appear to be present in subjects with T1DM, potentially reducing the overall benefits of exercise. Among these, alterations in the mechanisms regulating the glycemic homeostasis are especially important, as this alteration may result in exercise-associated hypoglycemia, one of the acute complications of diabetes that patients fear the most. Exercise-associated hypoglycemia may be caused by permanent counterregulatory impairment, as can be seen for instance in the failure to secrete catecholamines when diabetic autonomic neuropathy has become established. More commonly, however, it is observed as the result of acute and reversible blunting of adaptive responses, caused by the occurrence of some prior events, such as prior hypoglycemia, intense exercise or even intense emotional stress. The latter category of events is therefore preventable with the avoidance of these prior stimuli, rendering the control of hypoglycemia, or the identification of the most appropriate exercise formats, a priority in

every-day diabetes management. The issue of optimization of exercise regimens is indeed not a simple one, as many different formats (with varying type of activity, duration, intensity and repetition patterns) may not be similarly applicable to all subjects. Finally, it is absolutely necessary to gain a definitive, thorough understanding of all molecular complexities underlying exercise adaptations; in no other way will we be able to conclusively provide the conceptual foundation on which evidence-based exercise guidelines can be systemically developed. As a very final thought, I would like to address here a question that is very often asked after I give a talk on some of the topics discussed above. Considering that the multiple possible alterations in the exercise response that are observed in patients with T1DM, and their implications regarding the overall health effects of exercise in general and on increased incidence of hypoglycemia in particular, I am in fact often asked something along the lines of: "Should then T1DM patients avoid exercise?". I would like to make absolutely clear that the answer is no, they should not avoid exercise. In fact, with all the limitations related to their altered metabolism, they should still try to exercise as much as possible. The possibility that in several situations the potential health effects of exercise may be somewhat reduced, does not take away from the fact that some beneficial effects are still there, and these normally by far outweigh the decision of not exercising. It is up to us, who work in this field, to keep elucidating all possible ways in which the discrepancy between possible and actually achieved beneficial effects of exercise in these patients can be gradually narrowed and hopefully, in the not too distant future, completely eliminated.

5. Acknowledgements

Several of the studies included in this review were performed by the author at the UCI Institute for Clinical and Translational Science, whose nursing, technical, and administrative staff members are thankfully acknowledged for their outstanding research support. This is truly a wonderful research environment that fosters not only the performance of outstanding science, but also the training a new generations of clinical scientists.
The author would also like to acknowledge the outstanding editorial support of Ms Rebecca Flore and Ms Diana Vigil, who have helped to remarkably improve the overall appearance of this manuscript.
Financial support for some of the above experiments was provided through JDRF grant # 11-2003-332, and NIH grants K23 RR-018661, PO1 HD-048721, MO1 RR00827, K24 DK085223, and UL 1RR031985.

6. References

Anonymous (1993b) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N.Engl.J Med*, 329, 977-986.

Anonymous (2002) Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*, 287, 2563-2569.

Anonymous (1993a) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N.Engl.J Med*, 329, 977-986.

Anonymous (2007) Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes*, 8, 199-205.

Amiel, S. A., Tamborlane, W. V., Simonson, D. C. & Sherwin, R. S. (1987) Defective glucose counterregulation after strict control of insulin-dependent diabetes mellitus. *N.Engl.J.Med.*, 316, 1376-1383.

Banarer, S., McGregor, V. P. & Cryer, P. E. (2002) Intraislet hyperinsulinemia prevents the glucagon response to hypoglycemia despite an intact autonomic response. *Diabetes*, 51, 958-965.

Berenson, G. S., Srinivasan, S. R., Bao, W., Newman, W. P., III, Tracy, R. E. & Wattigney, W. A. (1998) Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N.Engl.J Med*, 338, 1650-1656.

Biggers, D. W., Myers, S. R., Neal, D. W., Stinson, R., Cooper, N. B., Jaspan, J. B., Williams, P. E., Cherrington, A. D. & Frizzell, R. T. Role of brain in counterregulation of insulin-induced hypoglycemia in dogs. Diabetes 38[1], 7-16. 1989. Ref Type: Journal (Full)

Bjorgaas, M., Vik, T., Sand, T., Birkeland, K., Sager, G., Vea, H. & Jorde, R. (1997) Counterregulatory hormone and symptom responses to hypoglycemia in diabetic children. *Diabet.Med.*, 14, 433-441.

Borghouts, L. B. & Keizer, H. A. (2000) Exercise and insulin sensitivity: a review. *Int.J.Sports Med.*, 20, 1-12.

Bussau, V. A., Ferreira, L. D., Jones, T. W. & Fournier, P. A. (2007a) A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. *Diabetologia*, 50, 1815-1818.

Bussau, V. A., Ferreira, L. D., Jones, T. W. & Fournier, P. A. (2007b) A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. *Diabetologia*, 50, 1815-1818.

Cherrington, A. D. The acute regulation of hepatic glucose production. Pagliassotti, M. J., Davis, S. N., and Cherrington, A. D. [Chapter 2], 19-43. 1994. R.G.Landes Company. The role of the liver in maintaining glucose homeostasis. Ref Type: Serial (Book,Monograph)

Cooper, D. M., Nemet, D. & Galassetti, P. (2004) Exercise, stress, and inflammation in the growing child: from the bench to the playground. *Curr.Opin.Pediatr.*, 16, 286-292.

Cooper, D. M., Radom-Aizik, S., Schwindt, C. & Zaldivar, F., Jr. (2007) Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. *J Appl Physiol*, 103, 700-709.

Cryer, P. E. (1993) Glucose counterregulation: prevention and correction of hypoglycemia in humans. *Am J Physiol*, 264, E149-E155.

Cryer, P. E., Davis, S. N. & Shamoon, H. (2003) Hypoglycemia in diabetes. *Diabetes Care*, 26, 1902-1912.

Davis, S. N., Galassetti, P., Wasserman, D. H. & Tate, D. (2000a) Effect of gender on neuroendocrine and metabolic counterregulatory responses to exercise in normal man. *J.Clin.Endocrinol.Metab.*, 85, 224-230.

Davis, S. N., Galassetti, P., Wasserman, D. H. & Tate, D. (2000b) Effects of antecedent hypoglycemia on subsequent counterregulatory responses to exercise. *Diabetes*, 49, 73-81.

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N.Engl.J Med*, 353, 2643-2653.

Diamond, M. P., Jones, T., Caprio, S., Hallarman, L., Diamond, M. C., Addabbo, M., Tamborlane, W. V. & Sherwin, R. S. (1993) Gender influences conterregulatory hormone responses to hypoglycemia. *Metabolism*, 42, 1568-1572.

Donovan, C. M., Hamilton-Wessler, M., Halter, J. B. & Bergman, R. N. (1994) Primacy of liver glucosensors in the sympathetic response to progressive hypoglycemia. *Proc.Natl.Acad.Sci.USA*, 91, 2863-2867.

Galassetti, P., Mann, S., Tate, D., Neill, R. A., Wasserman, D. H. & Davis, S. N. (2001a) Effect of morning exercise on counterregulatory responses to subsequent, afternoon exercise. *J.Appl.Physiol.*, 91, 91-99.

Galassetti, P., Tate, D., Neill, R. A., Morrey, S., Wasserman, D. H. & Davis, S. N. (2003) Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in Type 1 Diabetes. *Diabetes*, 52, 1761-1769.

Galassetti, P., Neill, R. A., Tate, D., Ertl, A. C., Wasserman, D. H. & Davis, S. N. (2001b) Sexual dimorphism in counterregulatory responses to hypoglycemia after antecedent exercise. *J.Clin.Endocrinol.Metab.*, 86, 3516-3524.

Galassetti, P., Tate, D., Neill, R. A., Morrey, S., Wasserman, D. H. & Davis, S. N. (2004) Effect of sex on counterregulatory responses to exercise after antecedent hypoglycemia in type 1 diabetes. *Am.J.Physiol Endocrinol.Metab*, 287, E16-E24.

Galassetti, P. R., Iwanaga, K., Crisostomo, M., Zaldivar, F. P., Larson, J. & Pescatello, A. (2006a) Inflammatory cytokine, growth factor and counterregulatory responses to exercise in children with type 1 diabetes and healthy controls. *Pediatr Diabetes*, 7, 16-24.

Galassetti, P. R., Iwanaga, K., Crisostomo, M., Zaldivar, F. P., Larson, J. & Pescatello, A. (2006b) Inflammatory cytokine, growth factor and counterregulatory responses to exercise in children with type 1 diabetes and healthy controls. *Pediatr Diabetes*, 7, 16-24.

Gerich, J. E., Langlois, M., Noacco, C., Karam, J. & Forsham, P. H. (1973) Lack of a glucagon response to hypoglycemia in diabetes: evidence for an intrinsic pancreatic alpha-cell defect. *Science*, 182, 171-173.

Guelfi, K. J., Ratnam, N., Smythe, G. A., Jones, T. W. & Fournier, P. A. (2007) Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. *Am J Physiol Endocrinol Metab*, 292, E865-E870.

Hambrecht, R., Wolf, A., Gielen, S., Linke, A., Hofer, J., Erbs, S., Schoene, N. & Schuler, G. (2000) Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*, 342, 454-460.

Hamilton-Wessler, M., Bergman, R. N., Halter, J. B., Watanabe, M. & Donovan, C. M. (1994) The role of liver glucosensors in the integrated sympathetic response induced by deep hypoglycemia in dogs. *Diabetes*, 43, 1052-1060.

Hannon, T. S., Rao, G. & Arslanian, S. A. (2005) Childhood obesity and type 2 diabetes mellitus. *Pediatrics*, 116, 473-480.

Hoffman, R. P., Singer-Granick, C., Drash, A. L. & Becker, D. J. (1991) Plasma catecholamine responses to hypoglycemia in children and adolescents with IDDM. *Diabetes Care*, 14, 81-88.

Jones, T. W., Porter, P., Sherwin, R. S., Davis, E. A., O'Leary, P., Frazer, F., Byrne, G., Stick, S. & Tamborlane, W. V. (1998) Decreased epinephrine response to hypoglycemia during sleep. *N.Engl.J.Med.*, 338, 1657-1662.

Karavanaki, K. & Baum, J. D. (2003) Coexistence of impaired indices of autonomic neuropathy and diabetic nephropathy in a cohort of children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*, 16, 79-90.

Kaufman, F. R., Austin, J., Neinstein, A., Jeng, L., Halvorson, M., Devoe, D. J. & Pitukcheewanont, P. (2002) Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. *J Pediatr*, 141, 625-630.

Laaksonen, D. E., Atalay, M., Niskanen, L. K., Mustonen, J., Sen, C. K., Lakka, T. A. & Uusitupa, M. I. (2000) Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial. *Med Sci Sports Exerc.*, 32, 1541-1548.

Lakka, T. A., Venalainen, J. M., Rauramaa, R., Salonen, R., Tuomilehto, J. & Salonen, J. T. (1994) Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N.Engl.J Med*, 330, 1549-1554.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P. & Kukull, W. (2006) Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann.Intern.Med*, 144, 73-81.

Marliss, E. B. & Vranic, M. (2002) Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. *Diabetes*, 51 Suppl 1, S271-S283.

McCrimmon, R. J., Evans, M. L., Jacob, R. J., Fan, X., Zhu, Y., Shulman, G. I. & Sherwin, R. S. (2002) AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. *Am J Physiol Endocrinol Metab*, 283, E1076-E1083.

McGregor, V. P., Greiwe, J. S., Banarer, S. & Cryer, P. (2001) Limited impact of vigorous exercise on defenses against hypoglycemia: relavence to hypoglycemia-associated autonomic failure. *Diabetes*, 40, A138.

McMahon, S. K., Ferreira, L. D., Ratnam, N., Davey, R. J., Youngs, L. M., Davis, E. A., Fournier, P. A. & Jones, T. W. (2007) Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. *J Clin Endocrinol Metab*, 92, 963-968.

Nemet, D., Connolly, P. H., Pontello-Pescatello, A. M., Rose-Gottron, C., Larson, J. K., Galassetti, P. & Cooper, D. M. (2004) Negative energy balance plays a major role in the IGF-I response to exercise training. *J.Appl.Physiol*, 96, 276-282.

Nemet, D., Oh, Y., Kim, H.-S., Hill, M. A. & Cooper, D. M. (2002) The effect of intense exercise on inflammatory cytokines and growth mediators in adolescent boys. *Pediatrics*, 110, 681-689.

Nieman, D. C., Davis, J. M., Henson, D. A., Gross, S. J., Dumke, C. L., Utter, A. C., Vinci, D. M., Carson, J. A., Brown, A., McAnulty, S. R., McAnulty, L. S. & Triplett, N. T. (2005a) Muscle cytokine mRNA changes after 2.5 h of cycling: influence of carbohydrate. *Med Sci Sports Exerc*, 37, 1283-1290.

Nieman, D. C., Davis, J. M., Henson, D. A., Gross, S. J., Dumke, C. L., Utter, A. C., Vinci, D. M., Carson, J. A., Brown, A., McAnulty, S. R., McAnulty, L. S. & Triplett, N. T. (2005b) Muscle cytokine mRNA changes after 2.5 h of cycling: influence of carbohydrate. *Med Sci Sports Exerc*, 37, 1283-1290.

Nikolaidis, M. G., Kyparos, A., Hadziioannou, M., Panou, N., Samaras, L., Jamurtas, A. Z. & Kouretas, D. (2007) Acute exercise markedly increases blood oxidative stress in boys and girls. *Appl Physiol Nutr Metab*, 32, 197-205.

Pagliassotti, M. J., Myers, S. R., Moore, M. C., Neal, D. W. & Cherrington, A. D. (1991) Magnitude of negative arterial-portal glucose gradient alters net hepatic glucose balance in conscious dogs. *Diabetes*, 40, 1659-1668.

Pedersen, O., Beck-Nielsen, H. & Heding, L. (1980) Increased insulin receptors after exercise in patients with insulin-dependent diabetes mellitus. *N Engl J Med*, 302, 886-892.

Robertson K, Adolfsson P, Scheiner G, Hanas R & Riddell MC (2009) Exercise in children and adolescents with diabetes. *Pediatr Diabetes*, 10, 154-168.

Ross, L. A., Warren, R. E., Kelnar, C. J. & Frier, B. M. (2005) Pubertal stage and hypoglycaemia counterregulation in type 1 diabetes. *Arch Dis Child*, 90, 190-194.

Sandoval, D. A., Guy, D. L., Richardson, M. A., Ertl, A. C. & Davis, S. N. (2004) Effects of low and moderate antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes. *Diabetes*, 53, 1798-1806.

Simonson, D. C., Tamborlane, W. V., DeFronzo, R. A. & Sherwin, R. S. (1985) Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with Type I diabetes. *Ann.Intern.Med.*, 103, 184-190.

Smith, A. G. & Muscat, G. E. (2005) Skeletal muscle and nuclear hormone receptors: implications for cardiovascular and metabolic disease. *Int J Biochem.Cell Biol*, 37, 2047-2063.

Strong, W. B., Malina, R. M., Blimkie, C. J., Daniels, S. R., Dishman, R. K., Gutin, B., Hergenroeder, A. C., Must, A., Nixon, P. A., Pivarnik, J. M., Rowland, T., Trost, S. & Trudeau, F. (2005) Evidence based physical activity for school-age youth. *J.Pediatr.*, 146, 732-737.

Tansey, M. J., Tsalikian, E., Beck, R. W., Mauras, N., Buckingham, B. A., Weinzimer, S. A., Janz, K. F., Kollman, C., Xing, D., Ruedy, K. J., Steffes, M. W., Borland, T. M., Singh, R. J. & Tamborlane, W. V. (2006a) The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care*, 29, 20-25.

Tansey, M. J., Tsalikian, E., Beck, R. W., Mauras, N., Buckingham, B. A., Weinzimer, S. A., Janz, K. F., Kollman, C., Xing, D., Ruedy, K. J., Steffes, M. W., Borland, T. M., Singh, R. J. & Tamborlane, W. V. (2006b) The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care*, 29, 20-25.

Teran-Garcia, M., Rankinen, T., Koza, R. A., Rao, D. C. & Bouchard, C. (2005) Endurance training-induced changes in insulin sensitivity and gene expression. *Am J Physiol Endocrinol Metab*, 288, E1168-E1178.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group (2000) Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N.Engl.J Med*, 342, 381-389.

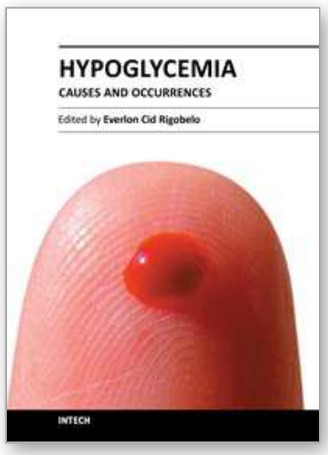
Tsalikian, E., Mauras, N., Beck, R. W., Tamborlane, W. V., Janz, K. F., Chase, H. P., Wysocki, T., Weinzimer, S. A., Buckingham, B. A., Kollman, C., Xing, D. & Ruedy, K. J. (2005a) Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. *J Pediatr*, 147, 528-534.

Tsalikian, E., Mauras, N., Beck, R. W., Tamborlane, W. V., Janz, K. F., Chase, H. P., Wysocki, T., Weinzimer, S. A., Buckingham, B. A., Kollman, C., Xing, D. & Ruedy, K. J. (2005b) Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. *J Pediatr*, 147, 528-534.

Urso, M. L. & Clarkson, P. M. (2003) Oxidative stress, exercise, and antioxidant supplementation. *Toxicology*, 189, 41-54.

Wanke, T., Auinger, M., Formanek, D., Merkle, M., Lahrmann, H., Ogris, E., Zwick, H. & Irsigler, K. (1996) Defective endogenous opioid response to exercise in type I diabetic patients. *Metabolism*, 45, 137-142.

White, N. H., Cleary, P. A., Dahms, W., Goldstein, D., Malone, J., Tamborlane, W. V. & Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. (2001) Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J.Pediatr.*, 139, 804-812.



Hypoglycemia - Causes and Occurrences
Edited by Prof. Everlon Rigobelo

ISBN 978-953-307-657-7
Hard cover, 238 pages
Publisher InTech
Published online 10, October, 2011
Published in print edition October, 2011

Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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In order to correctly reference this scholarly work, feel free to copy and paste the following:

Pietro Galassetti (2011). Pathogenetic Mechanisms of Exercise-Associated Hypoglycemia: Permanent and Reversible Counterregulatory Failure, Hypoglycemia - Causes and Occurrences, Prof. Everlon Rigobelo (Ed.), ISBN: 978-953-307-657-7, InTech, Available from: http://www.intechopen.com/books/hypoglycemia-causes-and-occurrences/pathogenetic-mechanisms-of-exercise-associated-hypoglycemia-permanent-and-reversible-counterregulato

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