

Exercise and Type 1 Diabetes (T1DM)

Pietro Galassetti^{*1} and Michael C. Riddell²

ABSTRACT

Physical exercise is firmly incorporated in the management of type 1 diabetes (T1DM), due to multiple recognized beneficial health effects (cardiovascular disease prevention being preeminent). When glycemic values are not excessively low or high at the time of exercise, few absolute contraindications exist; practical guidelines regarding amount, type, and duration of age-appropriate exercise are regularly updated by entities such as the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes. Practical implementation of exercise regimens, however, may at times be problematic. In the poorly controlled patient, specific structural changes may occur within skeletal muscle fiber, which is considered by some to be a disease-specific myopathy. Further, even in well-controlled patients, several homeostatic mechanisms regulating carbohydrate metabolism often become impaired, causing hypo- or hyperglycemia during and/or after exercise. Some altered responses may be related to inappropriate exogenous insulin administration, but are often also partly caused by the “metabolic memory” of prior glycemic events. In this context, prior hyperglycemia correlates with increased inflammatory and oxidative stress responses, possibly modulating key exercise-associated cardio-protective pathways. Similarly, prior hypoglycemia correlates with impaired glucose counterregulation, resulting in greater likelihood of further hypoglycemia to develop. Additional exercise responses that may be altered in T1DM include growth factor release, which may be especially important in children and adolescents. These multiple alterations in the exercise response should not discourage physical activity in patients with T1DM, but rather should stimulate the quest for the identification of the exercise formats that maximize beneficial health effects. © 2013 American Physiological Society. *Compr Physiol* 3:1309-1336, 2013.

Introduction

Physical activity (i.e., any type of daily activity requiring bodily movement), including what is commonly referred to as “exercise” (i.e., a subset of physical activity that is characterized by a planned and purposeful training) (47), is increasingly considered a critical component of a healthy, balanced lifestyle, helping prevent, delay, or limit a number of common chronic pathologies (315). The relationship that many patients with type 1 diabetes (T1DM) have with exercise/physical activity can often be defined as one of love-hate. On one hand, regular physical activity can enhance a number of aspects of diabetes management: improve insulin sensitivity (thereby reducing exogenous insulin requirement); control body weight and lipid profiles; boost self-confidence; improve psychological issues associated with the disease; reduce systemic inflammation; and most importantly, optimize long-term protection against cardiovascular disease. The necessity for appropriate regimens to be in place for diabetic patients is therefore now clearly stressed by most health care professionals (144, 250, 326). Dealing with exercise on a daily basis, on the other hand, implies for the T1DM patient a number of practical issues (adjustment of insulin administration; timing, type, and quantity of food ingestion before and after exercise; unexpected hypo- and/or hyperglycemia during and after exercise, etc.) whose impact may become at times very frustrating and in many cases discourage subjects from being physically

active (41, 259). For the remainder of this article, the terms “physical activity” and “exercise” are used interchangeably.

Diabetes mellitus refers to a group of metabolic diseases characterized by hyperglycemia due to deficient insulin secretion, impaired insulin action, or a combination of both (1). T1DM is associated with deficient insulin secretion due to the autoimmune destruction of pancreatic β cells and the need for exogenous insulin for survival. Although several aspects of macronutrient metabolism are affected by T1DM, the alterations in carbohydrate metabolism (i.e., hyperglycemia) are the main characteristics of the disease. Indeed, chronic hyperglycemia is largely thought to be the mechanism by which vascular damage leading to diabetes-related complications, such as coronary artery disease (CAD), stroke, nephropathy, retinopathy, and neuropathy, occur over decades after disease onset (40). The rate of β -cell destruction has been shown to be quite variable between individuals (1). In instances where

*Correspondence to pgalasse@uci.edu

¹ Departments of Pediatrics and Pharmacology, and Institute for Clinical Translational Science, University of California Irvine, Irvine, California

² School of Kinesiology and Health Science, Muscle Health Research Centre, Physical Activity and Chronic Disease Unit, Faculty of Health, York University, Toronto, Ontario, Canada

Published online, July 2013 (comprehensivephysiology.com)

DOI: 10.1002/cphy.c110040

Copyright © American Physiological Society

β -cell destruction is rapid (predominantly occurring in children and adolescents), the first manifestation of T1DM may be ketoacidosis (1). Other individuals might develop modest hyperglycemia initially, which later progresses to severe hyperglycemia and/or ketoacidosis if left untreated (or undiagnosed). Symptoms of diabetes may include polyuria, polydipsia, lethargy, and weight loss, sometimes with polyphagia and blurred vision (1, 82).

Carbohydrate metabolism is a crucial component of the exercise response. In T1DM, unfortunately, the organism's ability to effectively adapt to the increased energy substrate requirements of the exercising muscle is often severely impaired. The extent and characteristics of this impairment, therefore, stands at the very heart of the complex interaction between T1DM patients and physical activity. Phenotypically, the result is a series of unique features associated with most aspects of exercise in these patients. Some alterations are permanent, such as the reduced or loss of epinephrine response associated with the development of diabetic autonomic neuropathy (37). Others are transient, such as the widespread blunting of counterregulatory response to exercise following prior activation of the hypothalamus-pituitary-adrenal axis, as is the case with antecedent hypoglycemia (106, 107, 109). Furthermore, some of these features are not an intrinsic part of diabetes *per se*, but rather the effect of the aggressive, albeit still somewhat inadequate, iatrogenic attempt to treat the disease. Insulin replacement, although enormously important and certainly able to prevent most diabetic microvascular complications, is still an imperfect art. It is often associated with undesired glycemic fluctuations, both in the hyper- and hypoglycemic direction, which impact most aspects of diabetic's everyday life, including performance of therapeutic and recreational competitive exercise.

These considerations very succinctly outline the importance that exercise should have in T1DM management, and some of the problems associated with its practical implementation. This article will explore in greater depths the most important aspects of this complex interaction.

Overview of Glucose Homeostasis During "Moderate" and "Vigorous" Exercise in Type 1 Diabetes

In the healthy human, plasma glucose concentrations are judiciously maintained within a narrow range through the interactions of multiple simultaneous mechanisms. Glucose concentration is constantly "sensed" at a number of sites, both centrally (hypothalamus) and peripherally (pancreatic islets), and corrective actions are undertaken if glucose concentration is too high (with insulin release) or too low (with release of the counterregulatory hormones cortisol, glucagon, epinephrine, and norepinephrine) (65, 67, 68, 257). During any type of physical activity, these homeostatic mechanisms undergo variable degrees of stress. Simultaneous changes

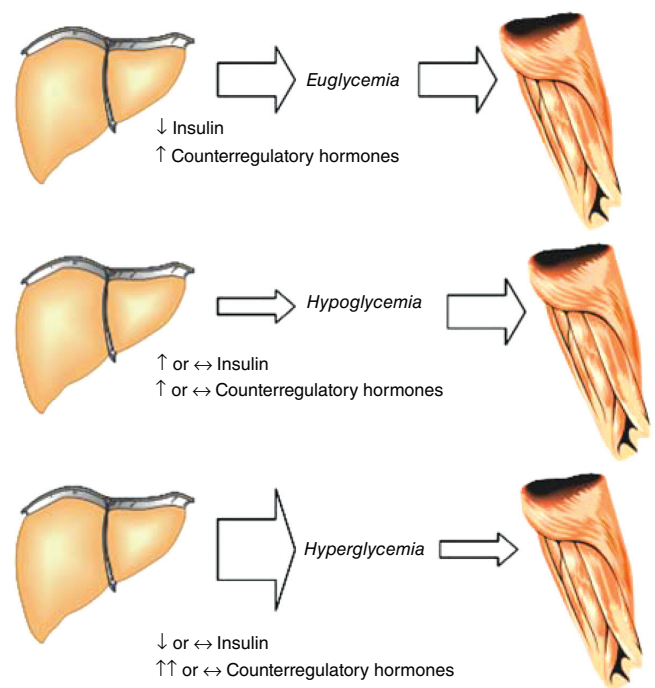


Figure 1 Various blood glucose responses to exercise. Euglycemia occurs when there is a decrease in the insulin/counterregulatory hormone ratio (glucagon, catecholamines, etc.) that permits increased glucose production that matches the increase in glucose disposal into working muscle (top panel). Hypoglycemia occurs if insulin levels are not lowered at the onset of exercise in patients with T1DM (middle panel). Hyperglycemia occurs when the exercise intensity is very vigorous ($>80\%$ $\text{VO}_{2\text{max}}$), if insulin administration is withheld, or if competition stress exists (bottom panel).

occur in insulin sensitivity, in energy substrate requirements, and in the ratio of carbohydrate/lipid oxidation by which these requirements are met. Not surprisingly, therefore, major disruptions of this complex equilibrium may occur in T1DM (169, 243, 252). While a whole range of events are possible, these may be ascribed to the combination of two main categories of alterations: (i) the inability to maintain euglycemia, resulting in hypoglycemic episodes during or after exercise, more commonly occurring with prolonged exertions of submaximal intensity (50, 70); and (ii) acute hyperglycemia, more commonly occurring with shorter, very intense exertions (Fig. 1) (51, 151).

In resting conditions and in the postabsorptive state (i.e., after all nutrients from the last meal have been absorbed from the GI tract), a healthy person of average weight has a rate of disposal (R_d) of glucose of ~ 2 mg/min per kg of body weight (Fig. 2). This is all the glucose collectively taken up by all body cells, with a baseline systemic insulin concentration that is normally between 5 and 10 $\mu\text{U/mL}$. Plasma glycemia would, therefore, gradually drop over time, if endogenous sources (mostly the liver but also to some extent the kidney and some sections of the gut) did not simultaneously provide an exactly identical glucose output, through breakdown of existing glycogen stores (glycogenolysis) and *de novo* synthesis of

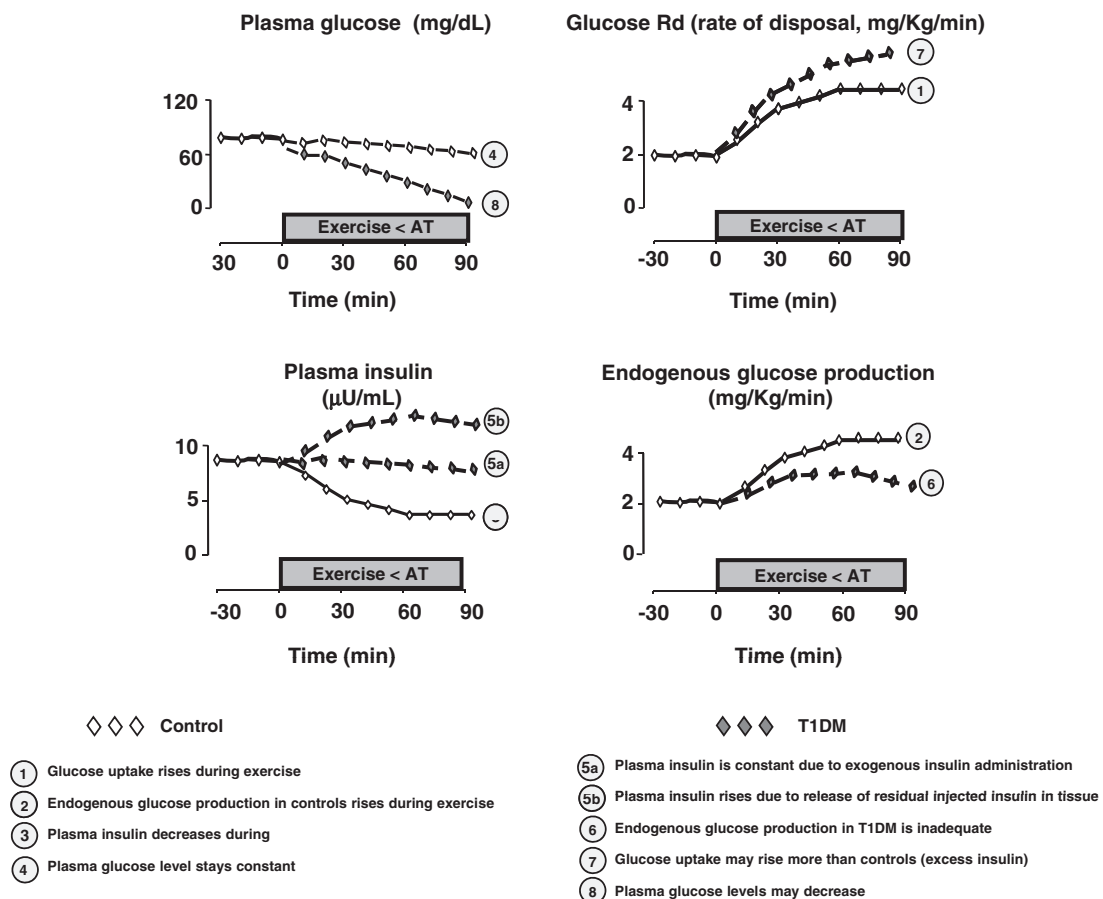


Figure 2 Schematic of sequence of homeostatic events affecting carbohydrate metabolism during moderate, constant-load exercise in healthy and T1DM subjects, showing the possible causes of exercise-associated hypoglycemia in T1DM.

glucose molecules (gluconeogenesis) (249). During a physical exertion of prolonged, submaximal intensity (i.e., below the subjects anaerobic threshold, which commonly occurs at 50%-60% of individual maximal aerobic capacity), the glucose Rd can increase twofold to threefold, mostly because of increased skeletal muscle uptake (324). While glycemia normally drops by a few mg/dL by 30 to 45 min into exercise, it is maintained within the physiological range by two mechanisms: a rapid increase in endogenous glucose production (94, 249), and a drop in systemic insulin levels. The drop in insulin, mediated by increased alpha-adrenergic efferent impulses to the pancreas, is necessary because during exercise insulin sensitivity is acutely increased and insulin-independent glucose transport mechanisms become activated in skeletal muscle cells (146, 147). If baseline insulin concentrations were not reduced, excessive glucose would be transported into muscle cells, causing a drop in glycemia. In T1DM subjects, as insulin is no longer endogenously regulated, prevention of exercise-associated hypoglycemia depends on how accurately the normal insulin profile can be reproduced. Subjects using an insulin-infusion pump often decrease, or may completely suspend, their insulin infusion during exercise (330). Subjects on a multiple insulin injection regimen, on the other hand, cannot easily lower their basal insulin levels; in some

instances in fact, quite the opposite occurs as subcutaneously injected insulin may have accelerated absorption rates during exercise (27, 330). Occasionally, after an insulin injection, especially if performed on the side of the thigh, part of the injected fluid may be trapped in a subcutaneous pocket, and be acutely mobilized into the bloodstream when exercise is started, practically resulting in a small additional insulin boost (101). The excess insulin will then have the dual effect of causing exaggerated glucose uptake in the skeletal muscle, and to suppress endogenous glucose production. The cumulative result of these alterations is the possibility of a hypoglycemic episode (106, 143).

Substantially different, is the series of responses that may occur when the physical exertion is very intense, that is, above the anaerobic threshold and close to the subject's maximal aerobic capacity (Fig. 3) (51, 151). In this setting, that can only be sustained for a relatively short time (normally no more than 20-30 min). The body undergoes a massive adrenergic activation, whose magnitude is driven by the cardiovascular response to intense exercise. This level of adrenergic activation also increases endogenous glucose production to an extent that exceeds peripheral tissue metabolic needs (282); this induces a state of moderate, transient hyperglycemia (normally no more than 140 mg/dL), that is promptly corrected

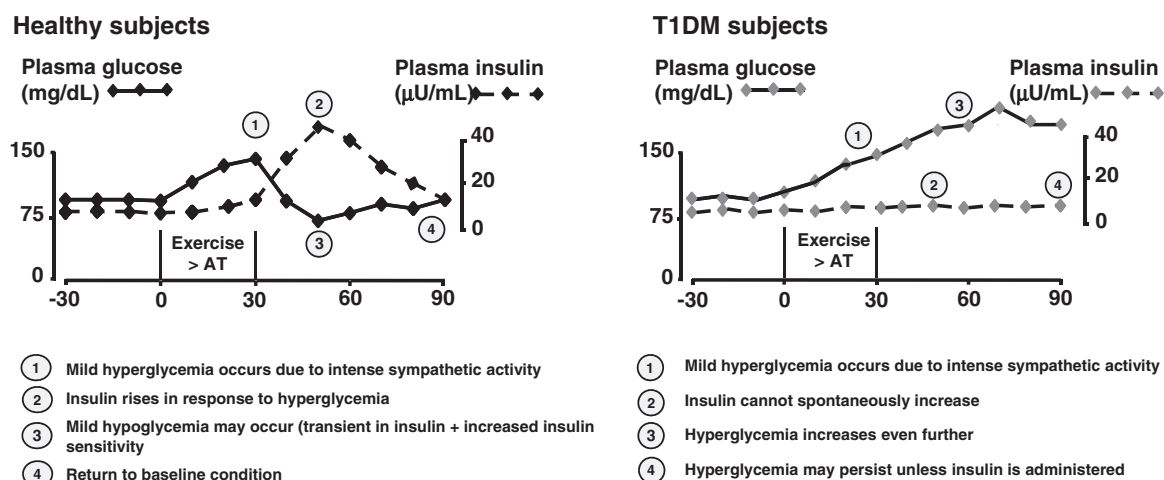


Figure 3 Schematic of sequence of homeostatic events affecting carbohydrate metabolism during and immediately after intense exercise (above the anaerobic threshold, AT) in healthy and T1DM subjects, showing the possible causes of postexercise hyperglycemia in T1DM.

upon exercise cessation in the nondiabetic individual. In the individual with T1DM, in whom insulin cannot be secreted in response to this hyperglycemic response, the magnitude of hyperglycemia often continues increasing after exercise, sometimes to alarming levels (>400 mg/dL) (196).

As bouts of structured exercise, or other forms of physical activity in real life are most often a combination of moderate and more intense bouts of varying duration and with variable temporal distribution, the actual glycemic response to any individual type of physical activity can be anywhere across the range. So much so, in fact, that the correct balance of prolonged, moderate exercise, and brief, intense exercise could induce opposing hypo- and hyperglycemic stimuli that would largely cancel each other out, and result in optimal glycemic control. This is in fact the conceptual basis of a series of interesting studies performed by an Australian group of researchers, in which a short, very intense sprint performed before a standard sports practice was able to eliminate most of the occurrence of post exercise hypoglycemia in a group of diabetic youth (42).

Physical Activity Guidelines in Type 1 Diabetes Mellitus

Exercise recommendations

As highlighted in the in the US Department of Health and Human Services Physical Activity Guidelines Advisory Committee Report (5) and in the Canadian Diabetes Association Clinical Practice Guidelines (281), regular exercise improves insulin action, increases cardiorespiratory fitness, improves psychosocial status, and reduces the risk of diabetes-related complications in persons with T1DM. Both aerobic and resistance training have been shown to be beneficial, likely acting through differing mechanisms, to improve diabetes metabolism and function (5, 100).

Currently, there are no specific guidelines on the amount or intensity of physical activity needed to optimize health in persons with T1DM. Similar to nondiabetic individuals, however, youth with diabetes should be encouraged to be physically active at a moderate to vigorous intensity for at least 60 min a day, according to the US Department of Health and Human Services (<http://www.cdc.gov/HealthyYouth/physicalactivity/guidelines.htm>). The Public Health Agency of Canada recommends 60 min of moderate activity plus an additional 30 min of vigorous activity each day for those ages 10 to 14 years, while the recommendation for adults is at least 60 min a day (<http://www.phac-aspc.gc.ca>). These recommendations are likely reasonable for adolescents and adults with T1DM, who tend to perform less physical activity than their nondiabetic peers, according to some limited research findings using standardized physical activity questionnaires (306). It should be noted that the amount of performed physical activity is typically quantified via self-reported questionnaires, of which a variety is available to investigators, such as the Previous Day Physical Activity recall, the Three Day Physical activity recall, the Physical Activity Interview, the Computerized Activity recall, the Activitygram, and the Multimedia Activity recall for Children and Adolescents (98). While each of these presents with advantages and limitations, these seem to apply similarly to healthy and diabetic children.

Whether or not regular physical activity helps to optimize glycemic control in young people with T1DM is controversial. Limited longitudinal data suggest that glycemic control can be improved with aerobic training (190, 335), although improvements in HbA1c are not always observed (258, 319). Cross-sectional data suggest that children and adolescents with T1DM who are very inactive, exercising less than 60 min per week, have a higher mean HbA1c level ($8.9 \pm 0.5\%$) than those who exercise 120 to 360 min/week ($8.3 \pm 0.4\%$; $p = 0.002$) or 360 to 480 min/week ($8.0 \pm$

0.6 %; $p < 0.01$) (29). In contrast, the relationship between aerobic fitness and HbA1c in adults with T1DM has also been reported to be modest and, in fact, positive ($r = 0.17$) (320). Importantly, the Finn Diane study of 1030 subjects with T1DM found that self-reported physical activity correlates negatively with HbA1c in women ($r = -0.12$), but not in men (318). It should be noted, however, that the accuracy of physical activity self-report tools may be limited by a number of factors, including gender; in most reports, in fact, an overestimation of energy expenditure has been observed in women (286).

In addition, Herbst and colleagues (144) studied more than 23,000 subjects with T1DM and found a small, but highly significant improvement in HbA1c (by 0.3%) in the two active groups (exercising one to two times a week and three or more times a week) compared to the sedentary group. Thus, the general consensus is that regular exercise should not be expected to dramatically impact a patient's HbA1c, likely because other variables such as increased food intake or reduced insulin dosages compensate for any increases in glucose disposal. Nonetheless, epidemiological evidence is emerging that being physically active, rather than sedentary, can lower mortality and morbidity for any given level of HbA1c (247).

Although increased physical activity may not necessarily be expected to dramatically improve glycemic control, it has been demonstrated to improve insulin sensitivity and thus lower the amount of insulin required to maintain a given HbA1c (319), as well as reduce the risk of both microvascular and macrovascular complications from the disease (259). There is also good evidence to suggest that being more physically active with T1DM is associated with lower lipoprotein levels and diastolic blood pressure (144) and lowers overall mortality rates (209). A large cohort study of patients with T1DM reported that 7-year mortality was 50% lower in those reporting ≥ 2000 kcal of weekly exercise (equivalent to ≥ 7 h/week of brisk walking) compared to those reporting < 1000 kcal of PA participation per week (209). As such, physical activity should remain the cornerstone of care for persons with T1DM, although managing blood glucose (BG)

levels can be quite challenging in those who are very physically active (193, 250).

Relative and absolute contraindications to exercise

The risk for cardiovascular disease and other diabetes-related complications including neuropathy, retinopathy, and nephropathy in persons with long-standing disease is high and care should be taken to properly screen individuals before recommending a new exercise program. Nonetheless, the incidence of an adverse event associated with exercise is rare in patients with T1DM, at least according to what has been published on the topic. However, caution is warranted for those with advanced disease complications and medical screening, possibly with a graded exercise stress test, should be considered before initiating any new vigorous exercise program (153).

In persons with T1DM, as with any individual, symptoms of chest pain or pressure are considered absolute contraindications to vigorous exercise. Persons with diabetes may have other atypical symptoms of myocardial insufficiency (see table 1), including dyspnea on exertion or unexplained gastrointestinal complaints that would also constitute contraindications to exercise at least until further medical screening is conducted (153). In addition, if individuals report having had a previous MI or if they have been told they have myocardial ischemia (e.g., resting ST segment abnormalities), then an exercise stress test is recommended prior to initiating an exercise program (3).

The most feared risk of initiating a physical activity regimen is sudden death secondary to an arrhythmia or an ischemic event. Sudden death may be more likely to occur when underlying coronary disease is undiagnosed, and undiagnosed CAD is particularly common in persons with T1DM who have been living with the condition for more than 15 years (i.e., 10-fold higher risk than non diabetics in 30-50 year olds) (224). The relative risk of an adverse cardiac event following vigorous exercise is 3.5-fold higher in persons with diabetes who have just performed vigorous exertion

Table 1 Typical and Atypical or Variant Symptoms of CVD in Persons with Diabetes Mellitus

- 1 Pain or discomfort in the chest, neck, jaw, arms, or other areas that may be due to myocardial ischemia (lack of adequate circulation)
- 2 Difficulty completing usual tasks
- 3 Dizziness with activity
- 4 Dyspnoea with minimal exertion
- 5 Orthopnea (breathing discomfort when not in an upright position) or paroxysmal nocturnal dyspnea (interrupted breathing at night)
- 6 Ankle edema (swelling)
- 7 Palpitations (abnormal rapid beating of the heart) or tachycardia (rapid heartbeat)
- 8 Intermittent claudication (cramping pain and weakness in legs, especially calves, during walking due to inadequate blood supply to muscles)
- 9 Easy fatigability
- 10 Lack of energy
- 11 Neck or jaw discomfort
- 12 Shoulder pain with a history similar to bursitis and related to activity

Modified from (ACSM guidelines for exercise testing and prescription; Hughes & White, 2005).

(>6 Metabolic Equivalents (METs)) compared to when they have been sedentary or have been performing light activity (204). However, the overall absolute risk is estimated to be rather low (risk of a myocardial infarction during 60 min of physical activity is estimated to be 1 in 10,000) (204). Since those with T1DM who are regularly more physically active, though, have much less overall risk for a cardiovascular event than those with disease who are sedentary, the general consensus is that the risks of exercise are outweighed by the numerous benefits, as long as appropriate screening is performed (70). A pertinent evidence-based review on screening procedures was published recently (254).

A few other relative contraindications to exercise exist in those with T1DM. In particular, those with advanced autonomic dysfunction or polyneuropathy should be evaluated medically and cleared before participation in any activity more vigorous than walking (41). Those with severe nonproliferative or proliferative retinopathy should also have clinical evaluation, which may include a graded exercise test with ECG and blood pressure monitoring, before starting a program of exercise more vigorous than brisk walking. After appropriate screening, persons with severe diabetic nonproliferative retinopathy or proliferative diabetic retinopathy should avoid strenuous exercise (aerobic or resistance) that raises blood pressure > 170 mmHg systolic, particularly when vitreous hemorrhage and/or fibrous retinal traction is present (41). The suspension of exercise should occur pending further screening by an ophthalmologist if there is a sign of worsening preproliferative or proliferative retinopathy because of the elevated risk for traction retinal detachment or vitreous hemorrhage. Individuals with end-stage renal failure should undergo medical screening prior to initiating an exercise program and following clinical evaluation and vigorous exercise should be avoided. In those with advanced nephropathy, undergoing dialysis, exercise testing should be performed before the initiation of an exercise program more vigorous than walking, but both mild aerobic and low-intensity exercise is still not contraindicated when under appropriate supervision (41).

At the current time, some debate exists as to whether exercise can be performed if individuals are hyperglycemic (i.e., BG > 180 mg/dL) at the time of initiating the activity, since exercise itself may worsen the metabolic state (281, 325). Indeed, vigorous exercise can increase BG levels into the hyperglycemic range in many individuals who are otherwise well controlled (196, 251). However, since hyperglycemia is transient in these situations and can easily be managed with additional insulin treatment (196, 284), hyperglycemia alone should not be considered an absolute contraindication to exercise. If, however, there are elevations in ketone levels in the blood or urine at the start of exercise, then vigorous physical activity can worsen hyperglycemia and cause ketoacidosis (26). As such, physical activity should be postponed if there are elevations in urine (> 30 mg/dL). The clinical management of hypo and hyperglycemia in the patient with T1DM is discussed elsewhere in this article.

Motor Unit Contractile Characteristics in Type 1 Diabetes

General considerations

In addition to a reduction in muscle fiber size that occurs with poorly controlled diabetes, there may also be changes to the distribution of muscle fiber types. One investigation of muscle biopsy samples from adults with T1DM reported an increase in the percentage of glycolytic/fast-twitch muscle fibers and an impairment in oxidative capacities (102). The increased percentage of type II fibers in this study should be interpreted with caution; however, as the reduced fiber area of the type II fibers usually increases the number of fibers counted in a given cross-sectional area. In rodent models of disease, slow-twitch, or type I fibers appear to exhibit minimal loss in cross sectional area and may even gain fiber area in response to overload stimuli (21). In contrast, in rodents with T1DM, fast-twitch glycolytic (type IIB) fibers exhibit severe relative atrophy (20, 54, 176, 183). As pointed out by Krause et al., given that the glycolytic fibers produce the most force by way of high myosin ATPase activity and shortening velocity, it follows that atrophy of those fibers should lead to a loss of maximal force production capacities at the level of the whole muscle (184).

Muscle atrophy and weakness

Scientists and clinicians realized that T1DM causes relative muscle atrophy, impaired muscle mass development, and reductions in muscular strength well before the discovery of insulin. If exercise can help restore this potential deficiency in muscle mass has also been a recurrent question. Even the Roman physician and philosopher Celsus (30 BC to 50 AD) noted that his patients with polyuria were often extremely weak and had a much smaller muscle mass than nonpolyuric individuals. Regular activity was prescribed to these patients as it was observed that exercise increased strength, stamina and survival in these early years (256). The Greek physician Aretaeus of Cappadokia noted, in the second century AD, that regular exercise improved the disease condition that he wrote as “an awkward affection melting down the flesh and limbs into urine” and at the time of the discovery of insulin in Toronto, the clinical observations of some of the first patients to be given exogenous insulin confirmed that the hormone had transformative effects on body growth and development (32). Thus, it had long been speculated that insulin played a key role in skeletal muscle protein synthesis and growth.

Soon after the discovery of insulin, considerable research was initiated to determine the mechanistic role that insulin had on muscular growth and development. In the late 1960s, A. L. Goldberg had shown that the growth of skeletal muscle in young diabetic rats required an adequate supply of both insulin and contractile activity (117–119). Moreover, untreated T1DM patients, who had very low levels of circulating insulin, and who would be expected to be less physically

active because of their sheer exhaustion from the disease, were shown to be suffering from mass muscle wasting, likely as a function of low rates of protein synthesis (43).

Several investigators have questioned the physiological role that insulin (or lack of insulin) has on protein turnover, speculating that insulin only lowers protein degradation rather than stimulating protein synthesis. One human study of five T1DM subjects in poor glycemic control showed, using stable isotope methodology, that a lack of insulin actually increases rates of whole body protein synthesis (213), although this effect may not necessarily be attributable to muscle protein turnover (211). This human study conflicts with what has repeatedly been observed in rodent models (125, 198, 225, 226), however, in which insulin deficiency has been shown to lower rates of skeletal muscle protein synthesis. Moreover, in cell culture studies (132, 279, 289, 290), insulin clearly facilitates skeletal muscle protein synthesis via upregulation of the AKT/mammalian target of rapamycin (mTOR) signaling pathway. The role of insulin in the regulation of protein synthesis remains controversial, however, with the finding that insulin does not stimulate muscle protein synthesis in the postabsorptive state in healthy humans, but rather achieves protein anabolism by inhibition of muscle protein breakdown (49). Indeed, it may be that rodent models of disease do not recapitulate what appears to be occurring in humans in response to disuse, hypoinsulinemia, and exercise (125). As a consequence of this lack of consensus, evidence-based nutritional strategies specifically targeting the interaction between insulin action and protein metabolism in T1DM are not currently available.

In addition to potential for a low rate of protein synthesis in poorly controlled T1DM, an accelerated rate of protein degradation occurs in humans with the disease (142). Indeed, in adults with T1DM, who are in a state of insulin deprivation, whole body rates of protein degradation are elevated (194, 212, 305) and it may be that this higher rate of muscle protein degradation explains the lower muscle mass in poorly controlled patients with T1DM, rather than any deficiency in protein synthesis, *per se*.

Glucagon is the hormone determined to be largely responsible for the increased energy expenditure during insulin deprivation in T1DM. Increased glucagon levels increase leucine and phenylalanine oxidation and facilitate an increase in protein breakdown in T1DM (1), thereby providing additional mechanisms, in addition to a lack of physiologic insulin replacement, by which protein loss from skeletal muscle occurs in T1DM (212, 214). Indeed, following an amino acid load in fasted individuals, hyperglucagonemia reduces glucogenic plasma amino acids by more than 50%, thereby reducing the available substrate for protein synthesis (1).

Diabetic “myopathy”

Adult patients with long-standing T1DM have been reported to have dramatic losses in skeletal muscle mass, perhaps as a result of diabetic neuropathy rather than any deficiency in

insulin action (12–14, 17, 19, 278). It is clear, however, that disruption to muscle turnover and function can occur well before any development of neuropathy. For example, in a group of recently diagnosed young patients (age range 16–43 years, with disease duration from 1 to 28 weeks), muscle biopsies demonstrate marked fiber atrophy, disruption of Z-lines, and morphological abnormalities in the mitochondria without any morphological indicators of neuropathy (248). Reduced muscle fiber size, a correlate of muscle mass, has also been observed in newly diagnosed young males with T1DM (160). In a recent review, Krause and colleagues have proposed that the muscles of newly diagnosed or poorly controlled youth with T1DM can be considered “myopathic” with respect to their capacity for growth and development for a number of possible hormonal and nonhormonal reasons (184).

Several strategies to facilitate increases in skeletal muscle mass in T1DM have been proposed including exercise (87, 88, 173), intensive insulin therapy (173), and exogenous leptin administration (321, 332). Indeed, insulin administration appears to normalize protein balance, at least in part, in humans with T1DM (211, 214), and insulin treatment plus resistance exercise in diabetic rats has been shown to dramatically improve the decrement in muscle mass (87–89). Importantly, insulin therapy has been shown to increase mitochondrial, but not myosin heavy chain fractional synthesis rates in the muscles of nondiabetic swine (34, 56). In untreated diabetic rats, rates of protein synthesis are reduced in the gastrocnemius muscle via reduced mTOR signaling and lowered activity of eukaryotic initiation factor 2B (eIF2B) (56). Interestingly, chronic resistance exercise does not increase rates of protein synthesis in situations of severe diabetes in rats (92), perhaps because some permissive amount of insulin is needed to activate the pathways of protein synthesis. Recently, aerobic-type exercise has been shown to help normalize rates of muscle protein synthesis and growth in partially pancreatectomized diabetic rats, independent of insulin signaling (277). Taken together, these animal and human studies suggest that a combination of aggressive insulin therapy and regular exercise (resistance and aerobic) may be needed to normalize muscle mass in diabetic individuals.

Exercise Performance in Type 1 Diabetes

Level of performance

Normally, insulin therapy is rapidly initiated at the time of diagnosis in patients with T1DM and dramatic metabolic improvements are achievable within a fairly short timeframe (days to weeks after the initiation of treatment) (48). However, clinical diagnosis may be delayed and the overall management in youth with the disease is usually suboptimal for a variety of physiological and psychosocial reasons (135). It should also be noted that normal restoration in glucose homeostasis is nearly impossible in T1DM since the sophisticated

control system is no longer in place that maintains a critical, but small amount, of BG constant (323). As such, a number of physiological challenges exist in substrate metabolism that places the individual at risk for suboptimal exercise performance. For example, in a large study of healthy and diabetic adolescents/young adults, matched similarly in age, weight, height, and body composition, and aerobic capacity was shown to be about 20% lower in those with T1DM (179). Several cardiovascular, muscular, and metabolic impairments in T1DM might help to explain their potential decrement in aerobic performance. A number of studies report reduced physical work capacity or maximal aerobic power (VO_2max , i.e., the workload at which the maximal individual rate of whole-body oxygen uptake is achieved) in young patients with T1DM, despite insulin therapy, when compared to their nondiabetic peers (25, 130, 155, 179, 186, 187, 235). Moreover, both end diastolic volume and left ventricular ejection fraction fail to increase normally during exercise in young adults with T1DM compared with controls (185). In contrast, however, Nugent and colleagues (223) report no difference in VO_2 peak (i.e., the highest measure of oxygen uptake during an exercise test in which VO_2max cannot be reliably determined, but often used interchangeably with VO_2max) during a progressive incremental exercise test in adult subjects with long-standing diabetes, while Veves et al. (311) found that only adults with demonstrated neuropathic complications or sedentary lifestyles demonstrated reduced VO_2max . This later study is particularly relevant as it suggests that if one is physically active with T1DM, then aerobic capacity can be normal, at least if neuropathy has not developed. In support of this finding, a study of athletes and nonathletes with T1DM, and nondiabetic controls, found that VO_2 peak is similar between athletes with and without T1DM, although the anaerobic threshold was lower in subjects with T1DM than in control subjects (178).

Impairments in the ability to perform exercise in those with T1DM may be related to the level of glycemic control (Fig. 4). For example, Poortmans et al. (235) and Hutunen et al. (155) both report that physical capacities are

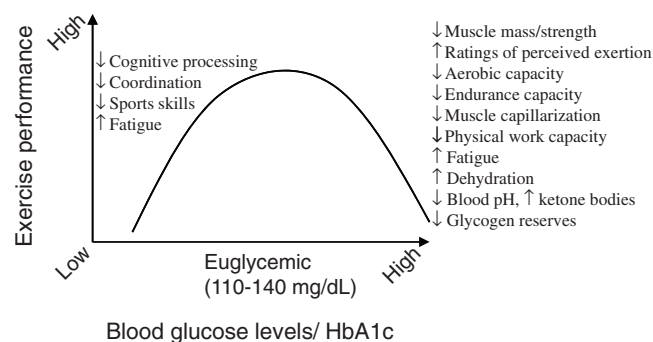


Figure 4 Theoretical effects of blood glucose control on exercise performance in T1DM. A number of possible mechanisms exist that may explain deteriorated exercise performance during both hypoglycemia and hyperglycemia in individuals with T1DM.

inversely related to the level of metabolic control, as measured by HbA1c. In contrast, however, a more recent cross-sectional study has reported that patients with T1DM who have good aerobic capacity have poorer glycemic control (77) and athletes with T1DM tend to have higher levels of HbA1c compared to sedentary patients (73). It is unclear, however, if a reduced work capacity in youth with T1DM compared with healthy youth is a result of poorer oxygenation of muscle (73), a lower amount of muscle capillarization (175), or if poorer metabolic control is a function of lower amounts of habitual physical activity (259). In an experimentally induced murine model of diabetes, there is altered expression of several genes involved in angiogenesis and reduced muscle capillarization, which could not be normalized by high volume endurance exercise training (175). For example, levels of proangiogenic VEGF-A, VEGF-B, neuropilin-1, VEGFR-1, and VEGFR-2 were reduced and the levels of antiangiogenic thrombospondin-1 and retinoblastoma like-2 were increased in diabetic rodents compared to controls. Although exercise training alleviated some of these molecular changes, it could not fully restore muscle capillarization (175).

Studies investigating muscular strength and endurance in individuals with T1DM have shown mixed results with some researchers reporting decrements in strength (11, 12, 15, 16, 18), while others have shown no obvious strength deficit (10). Although fatigue is a common complaint of patients with diabetes (293, 307), the effect of T1DM on exercise endurance (i.e., the ability to sustain a given workload over time) is not well documented. Compared to controls, patients with T1DM have been reported to have both impaired (10) and enhanced (11) endurance capacity during relatively brief bouts of intense exercise. Ratings of perceived exertion during prolonged exercise have been reported to be higher in boys with T1DM compared to age, weight and aerobic fitness matched controls (253). Also, during prolonged exercise those with T1DM who are under reasonable glycemic control have a higher glycolytic flux (55) and tend to rely considerably more on muscle glycogen utilization (260), which might reduce endurance capacity, although this hypothesis has yet to be tested. Moreover, exercising while hyperglycemic has been shown to increase reliance on muscle glycogen compared to exercising while euglycemic (161) and the individual who is exercising while hypoinsulinemic/hyperglycemic would be expected to be prone to early dehydration and acidosis (195), all factors that might promote early fatigue. Surprisingly, a diet rich in carbohydrate (~60% of total energy) for 3 weeks has been shown to increase glycemia and insulin requirements, reduce muscle glycogen levels, and lower exercise capacity compared to a normal diet (50% energy from carbohydrate) in diabetic athletes (200).

The presence of hyperglycemia may also affect strength in the setting of at least certain types of resistance exercise, causing early fatigue. Increasing BG levels to 16 mmol/L, in fact, has been shown to reduce isometric muscle strength, but not

maximal isokinetic muscle strength, compared with strength measured at glycemia clamped at 5 mmol/L in patients with T1DM (15).

Acute changes in glycemia can also influence exercise performance (see Section “Blood glucose levels and performance”). A summary schema of the possible relationship between glucose control and exercise performance is shown in Figure 1.

If individuals with T1DM are actively engaged in regular exercise, they can achieve a near normal performance (see below section on the “elite athlete”). In one German study of 10 middle aged long-distance triathletes with T1DM studied over 3 years, overall endurance performance was said to be “normal,” despite documented hyperglycemia during the early part of a race, then hypoglycemia during the marathon leg (33). Thus, overall, evidence suggests that optimal glycemic control and regular exercise may be needed to maximize muscle strength and endurance performance.

Acute blood glucose fluctuations and performance

The degree to which acute changes in BG levels influence sports performance is unclear. Circumstantial evidence suggests that an increase in plasma glucose availability might improve aerobic exercise capacity, perhaps because more fuel is readily available for muscle contraction. However, this hypothesis has not been supported by one study that “clamped” nondiabetic cyclists at hyperglycemia and euglycemia and found no difference in endurance performance (36). Unfortunately, very few studies have been conducted in which aerobic exercise performance is examined during differing levels of BG concentrations in those with T1DM (145, 171, 252, 291). In one study of prepubertal boys with T1DM ($n = 16$), lowering the insulin dose prior to exercise to reduce the likelihood of hypoglycemia did not influence aerobic capacity during cycling compared to their usual insulin dose (145). In eight endurance-trained adults with T1DM, elevating BG levels from 5.3 ± 0.6 to 12.4 ± 2.1 mmol/L, via hyperinsulinemic glucose clamp technique, failed to change peak power output or other physiological endpoints such as lactate, heart rate or respiratory exchange ratio during aerobic exercise (291). In another study, compared with hyperglycemia or euglycemia, exercise capacity was reduced and ratings of perceived exertion increased with hypoglycemia in a group of youth with T1DM (252), although the exercise was always stopped by the research investigators, rather than the subjects, for safety reasons.

Profound or sustained hyperglycemia, associated with sustained insufficient insulin delivery, may impair endurance performance in those with T1DM, although the evidence for this statement is limited. Prolonged hypoinsulinemia/hyperglycemia would be expected to lower muscle glycogen levels (as the exercising muscle can rely less on circulating glucose), reduce muscle strength (due to the effect of hyperglycemia described in Section “Diabetic myopathy”)

and predispose the individual to dehydration and electrolyte imbalance because of polyuria (163). As mentioned above, exercising while hyperglycemic has been shown to increase the reliance on muscle glycogen as a fuel source and limits the capacity to switch from carbohydrate to lipid as an energy source (161). Importantly, substrate oxidation during prolonged endurance exercise can be similar to what is observed in nondiabetics if diabetic subjects are clamped euglycemic (161).

Although aerobic exercise capacity *per se* may not be impacted significantly by short-term alterations in glycemia, sports performance may be impacted by impairments in cognitive processing when glucose levels drop below a certain threshold. In a recent sports camp field study of 28 youth with T1DM, Kelly et al., (171) showed that the ability to carry out fundamental sports skills markedly reduced by mild hypoglycemia (whole BG levels <3.6 mmol/L) compared to when whole BG was in an acceptable glucose range (3.6–13.9 mmol/L). Short-term hyperglycemia (BG >13.9) was shown not to significantly impact sport performance in that study. Importantly, this finding of significantly impaired sports performance with mild hypoglycemia appeared universally across nearly all subjects and is similar to the well-documented detrimental effects of hypoglycemia on cognitive processing (123, 171). It is, therefore, likely that there is an inverted-U shape relationship between glycemia and exercise/sport performance, with the best performance in the euglycemic range (Fig. 1).

The impact of glycemia on resistance exercise has yet to be firmly established, although a higher muscle lactate accumulation in T1DM, compared to controls, may limit maximal anaerobic capacity (137). Importantly, high-intensity interval training in young patients with T1DM is well tolerated and improves muscle oxidative capacity to that of nondiabetic trained individuals (137). In addition, both adolescents (60) and adults (76, 241) with T1DM appear to respond with the expected strength gains with resistance training.

The diabetic athlete

Although impairments in physiological functioning will occur in poorly managed individuals with T1DM, a number of exceptional sporting accomplishments have been documented for persons who have excelled in spite of their disease (see www.diabetes-exercise.org/). A vast number of elite athletes have competed and excelled with T1DM. A partial list of highly accomplished athletes include British Olympic rower Sir Steven Redgrave; US Olympic multigold medal swimmer Gary Hall Jr.; NBA basketball player Adam Morrison; Major League baseball player Jason Johnson; NFL players Jay Cutler, Mike Echolas, and Jay Leewenburg; Ironman triathlete Bill Carlson; and female golf pro Mimmi Hjorth. Elite road cycling team, “Team Type 1,” have won numerous races including the 2009 and 2010 8-person Race Across America. Even at extreme altitude, a number of papers have cited the

accomplishments and physiological performances of T1DM athletes (207, 227, 228).

The care of athletes with T1DM is particularly challenging for health care professionals (193). For top performance, glycemic control needs to be optimized and there are a number of considerations related to the management of injury and therapeutic modalities on BG control. Consensus recommendations exist to optimize the care of athletes with T1DM and considerable preparedness is required to maintain glucose control and maximize performance (163).

For most elite athletes with T1DM, intensive insulin therapy, usually in the form of continuous insulin infusion therapy, is required to maintain glycemia as normal as possible. Intensive insulin therapy uses basal and bolus insulin doses to regulate BG levels during fasting, feeding, and hyperglycemic periods. Basal insulin is used to maintain glycemic stability during fasting periods and delivers a steady, low dose of insulin 24 h a day. Bolus insulin is used to control elevations in BG levels that occur after eating or to lower BG levels during hyperglycemia. Bolus insulin doses are determined by several factors, including the prevailing BG level, carbohydrate content of a meal, and anticipated exercise. Even with intensive therapy, glycemic control has been shown to be suboptimal in athletes with T1DM (77, 157), although the recent advent of continuous glucose monitoring may help improve glycemic control in athletes with T1DM (251). Interestingly, one cross-sectional study has reported positive associations between aerobic capacity and handgrip strength versus HbA1c level, thus suggesting that those in the best physical condition may have compromised metabolic control (320). The inability to maintain glucose homeostasis in the athlete with T1DM (158) is likely related to the sheer complexity of glucose control during exercise (323) and the fear of exercise associated hypoglycemia (39).

Effects Of T1DM on Glycemic Fluctuations During Exercise

Hyperglycemia during exercise: Causes and prevention

As stated above, moderate exercise typically causes a decrease in BG levels in individuals with T1DM, while a rise in glucose concentration may occur with very intense exercise, and, in some individuals, in particular circumstances (196). For example, in individuals in poor metabolic control, exercise can cause an additional increase in BG concentration and ketoacidosis (26). The rise in BG is caused by exaggerated hepatic glucose production, facilitated primarily via increased catecholamines and impairment in exercise-induced glucose utilization (283, 284) (Fig. B). Hyperglycemia and excessive ketosis during exercise are particularly undesirable as they can cause dehydration and may decrease blood pH, both of which impair exercise performance. Intense exercise

(i.e., >60-70% VO_2max or >75-85% of maximal heart rate) may particularly aggravate this condition, since increases in catecholamines and glucocorticoids will further exaggerate the elevations in BG concentrations and ketone production. High-intensity exercise may be defined as activities above the "lactate threshold," which is approximately > 60% to 70% VO_2max or 85% to 90% maximal heart rate. This threshold coincides with dramatic elevations in catecholamines, free fatty acids, and ketone bodies, all of which impair muscle glucose utilization (31). Even those individuals on intensive insulin therapy may have increases in BG levels during and after high-intensity exercise (203), likely due to a failure in insulin release to offset the increases in counterregulatory hormones (196). This rise in glycemia is usually transient and tends to last only as long as there are elevations in counterregulatory hormones (i.e., 30-60 min). Although some individuals can easily correct the elevations with an insulin bolus at the end of vigorous exercise, particularly if they take rapid-acting insulin analogues, others may be resistant to taking additional insulin following exercise, since there will be greater risk of late-onset postexercise hypoglycemia in the next several hours (particularly if the prior exercise bout was >30 min) (156).

The psychological stress of competition via adrenergic stimulation and increased catecholamines may also cause an increase in BG concentration during sport. Those pursuing vigorous aerobic exercise may find that on regular training or practice days they become hypoglycemic, but on the day of competition they develop hyperglycemia. Although empirical data do not exist for patients with T1DM, excessive increases in counterregulatory hormones likely occur just prior to exercise, when anticipatory stress is high. As mentioned above, the elevated levels of stress hormones (catecholamines and cortisol) are known to increase hepatic glucose production and decrease peripheral glucose uptake (196). In people with diabetes, the body's failure to compensate for the "stress" associated with exercise by increasing insulin secretion make them particularly susceptible to elevations in glycemia during anaerobic activities (42, 129). Some patients may find this hyperglycemic response to stressful competition frustrating, particularly when they are participating in team sports that necessitate breaks in play (e.g., baseball, basketball, and hockey). In these instances, periods of physical inactivity coupled with elevations in stress hormones may cause very large increases in BG levels, particularly if the individual has reduced their insulin dosage in anticipation of exercise. In these individuals, the use of real time continuous glucose monitors may be helpful (251). In these situations, small boluses of rapid-acting insulin may be required to recover from hyperglycemia. Individuals may find that training or competing in warm and humid environments also elevates BG levels, likely because of excessive increases in circulating plasma catecholamines, glucagon, cortisol, and growth hormone (GH) (136) (while this is indeed a fairly common situation, surprisingly very little has been published in this area in diabetic subjects).

Prior hyperglycemia: Increase inflammatory status during subsequent exercise

A situation of special relevance for T1DM is the prolonged effect of hyperglycemia on inflammatory status. It is now well established, in fact, that hyperglycemia, whether acute or chronic, in both healthy and diabetic individuals, is associated with increased inflammation, as reflected by activation of immune cells and increased systemic concentrations of proinflammatory cytokines/chemokines (124, 215, 220). Importantly, this increase in inflammatory status appears not to be confined to the duration of the hyperglycemic episodes, but also to extend into the first several hours or days after hyperglycemia has been resolved (78, 262). Therefore, if physical exercise, which already physiologically induces some degree of proinflammatory activation, were to occur during this phase of posthyperglycemic proinflammatory state, an exaggerated inflammatory response to exercise may occur, potentially reducing the beneficial effects of that exercise session. While this concept seems reasonable, it is difficult to exactly quantify the extent of this exaggerated inflammatory effect with respect to the magnitude and duration of the prior hyperglycemic episode(s). In a group of 28 T1DM children, early morning hyperglycemia of up to 425 mg/dL has been reported to cause roughly a doubling of the interleukin-6 (IL-6) response to a standard exercise challenge performed later on the same morning and at least 2 h after euglycemia had been restored (111). Further, the IL-6 response to exercise was also observed to become progressively greater (again during euglycemic exercise performed at least 2 h after glucose normalization) in a larger groups of T1DM youths, proportionally to their average glycemia during the previous 3 days, as measured through a continuous glucose monitor (261) (Fig. 5). Interestingly, in the latter study, it was also observed that a “hierarchical” effect of prior hyperglycemia may be in place: while a higher mean glycemia over the prior few days predicted a greater inflammatory response during subsequent euglycemic exercise among subjects with similar 3-day glycemia, a greater inflammatory response to exercise occurred in those with greater hyperglycemia just a few hours before exercise. These findings may have practical implication for everyday management of diabetes. Preventing hyperglycemia of any magnitude and duration remains the main target of T1DM treatment, and may eliminate the excess inflammation during exercise as well. Once the prior episode(s) of hyperglycemia have occurred, however, (and this is unfortunately a daily occurrence even in well-controlled patients), the subjects is left with three options: (i) postpone or cancel the planned exercise activity until the proinflammatory effects have faded; (ii) perform exercise in a proinflammatory status; (iii) reduce exercise-associated inflammation via pharmacological means. As prior hyperglycemia is not currently included in the contraindications to exercise, the second option is the norm. The additional possibility to administer anti-inflammatory medication before exercise, when severely increased inflammation can

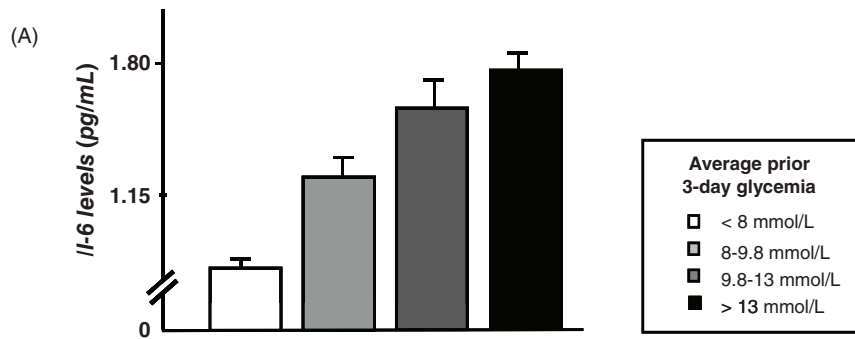
be expected, is not really part of current diabetes management. In fact, anti-inflammatory therapy in diabetes in general, (especially including the use of novel salicylate preparations) (121), and not only in association with exercise, is the object of both considerable interest and controversy, and varying degrees of consensus exists on its efficacy and indications (97, 122).

Hypoglycemia before, during, and after exercise: Causes, prevention, and impaired counterregulatory responses

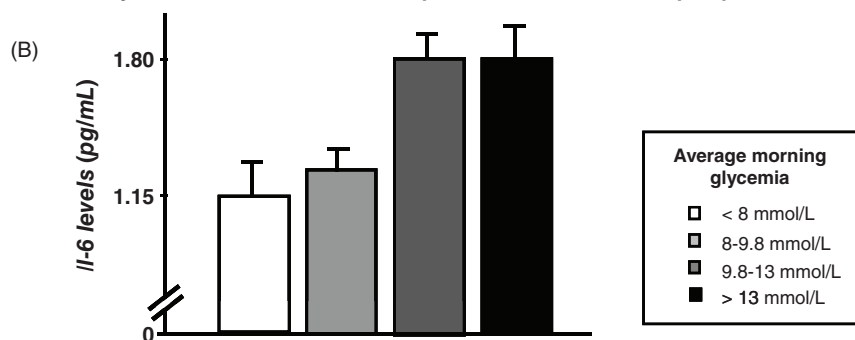
Hypoglycemia, defined here as a drop of plasma glucose concentration below the physiological range, can occur for several reasons, including the presence of a relative excess of insulin, or an abrupt increase in peripheral uptake, such as may occur when energy production suddenly increases in the skeletal muscle performing intense exercise. In these circumstances, compensatory (counterregulatory) mechanisms are triggered, so that frank hypoglycemia (under 60 mg/dL) is prevented or reversed (57, 59). During physical exercise, obtaining a given net amount of glucose transport across the cell membrane of myocytes requires 30% to 50% less insulin than in resting conditions, because a considerable fraction of exercise-stimulated transmembrane glucose transport occurs via noninsulin-dependent mechanisms (141). Pancreatic insulin secretion is, therefore, physiologically reduced during exercise by a proportional amount, preventing glucose lowering in the bloodstream below preexercise values (44). The reduction in pancreatic insulin output is mediated via activation of α -adrenergic autonomic afferent pancreatic fibers (196). Exercise also simultaneously triggers the release of the major counterregulatory hormones glucagon, epinephrine, norepinephrine, GH, and cortisol. Through various parallel biochemical pathways (increased hepatic glycogenolysis and gluconeogenesis, lipolysis from adipose tissue) these molecules accelerate the mobilization of energy substrates (66–68). Recently, in addition to the “classic” counterregulatory hormones cited above, evidence has also been accumulating toward the potential counterregulatory effect of additional molecules, among which is notable IL-6, a cytokine abundantly released by the exercising skeletal muscle in a dose-dependent relation with the intensity of exercise (111, 280). Initially, this cytokine’s functions were mainly considered a proinflammatory mediator, but they are now believed to include more complex immunomodulatory, even anti-inflammatory, effects (231).

Alterations in both insulin regulation and counterregulatory responses during exercise may be present in patients with T1DM. Reproducing the physiological drop in insulin levels, for instance, may be problematic. Patients who inject insulin via an insulin infusion pump can reduce the infusion rate before or during exercise; this is not easy to do correctly, as seemingly identical exercise conditions in different days may result in different metabolic responses. If the insulin reduction is excessive, hyper-, rather than hypoglycemia, may in

IL-6 levels at end exercise in 47 T1DM, subdivided in quartiles based on average glycemia during prior 3 days; higher prior glycemia resulted in progressively greater IL-6 levels.



If the same subjects are subdivided based only on glycemic levels in the morning immediately before exercise, the IL-6 response in bottom 2 and top 2 quartiles is similar.



If subjects from the top 2 quartiles in panel B, are now repooled together, and then subdivided in 2 new groups based on mean prior 3-day glycemia, again those with worse prior glucose control display a greater IL-6 response to exercise.

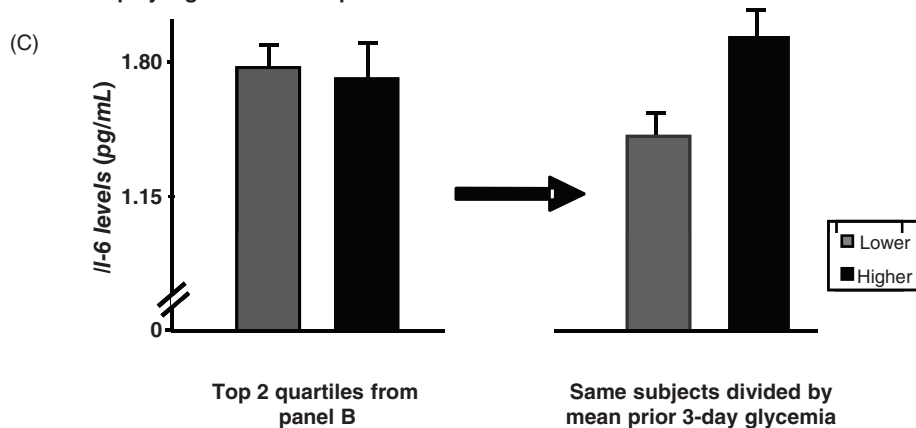


Figure 5 Increased inflammatory response to exercise in subjects with T1DM with worse glycemic control over the previous 3 days (261). In 47 young adults with T1DM, the exercise-induced increase in interleukin-6 (IL-6), a proinflammatory cytokine was progressively greater in subjects who had experienced higher mean average glycemic values over the prior 3 days (A). When the same IL-6 responses were analyzed based only on morning hyperglycemia on the day of the exercise challenge, the half of the subject with higher morning hyperglycemia had a greater IL-6 response than the lower half (B), but within each half a close dose response was not observed. When the half with the highest morning hyperglycemia, however, was resubdivided in two quarters based on prior 3-day glycemia, again a dose response with magnitude of prior hyperglycemia became evident (C). Our data indicate that a hierarchical proinflammatory effect is induced by prior hyperglycemia occurred at different times in the past: recent hyperglycemia seems to have the strongest effect, but among subject with similar recent hyperglycemia, hyperglycemia occurred at an earlier time seems to exert an additional proinflammatory reinforcement.

fact occur, but many subjects prefer this risk (hyperglycemia being asymptomatic unless really extreme) and actually completely shut off their pump. Patients on multiple insulin injections, including a long-acting component, on the other hand cannot reduce their baseline insulin concentrations, and are, therefore, likely to find themselves exposed to relative hyperinsulinemia. Excessive glucose uptake from insulin-sensitive tissues would then ensue, lowering glycemia too rapidly; simultaneous, desuppression of endogenous glucose production and free fatty acid mobilization, which are also effects of lower insulin levels, would not occur, further facilitating onset of hypoglycemia (44, 232). Occasionally, the situation can be exacerbated by the fact that when insulin is injected in areas close to the exercising muscle, it is more rapidly absorbed (28). The result is a *de facto* small insulin bolus, transiently increasing insulin levels at exercise onset; hypoglycemia, sometimes severe, may then occur.

Simultaneously with increased insulin absorption during exercise (rather than the expected decrease), the activation of counterregulatory hormones may also be impaired in T1DM (37). In general, the release of major counterregulatory hormones in response to exercise appears reduced in T1DM, although the magnitude of attenuation and class of hormones involved vary across studies (110, 296, 322). This phenomenon is completely parallel to the reduced counterregulatory response to hypoglycemia that occurs in T1DM, now very well characterized (hypoglycemia-associate autonomic failure, or HAAF) (58). HAAF also causes blunting of a number of symptom of neurogenic origin (anxiety, sensation of hunger, sweating, palpitations, etc.), mediated by the sympathoadrenal effects of epinephrine (148). Exercise and hypoglycemia, therefore, share a number of adaptive hormonal and autonomic pathways that can become similarly altered in T1DM, with important related implications in every-day management.

In this context, glucagon behaves differently than other counterregulatory hormones. The ability to increase secretion of this hormone in response to hypoglycemia is in fact permanently and completely abolished in T1DM 2 to 4 years after disease onset (114, 266). In the nondiabetic, glucagon secretion during hypoglycemia can only be triggered if the low BG level is accompanied by concomitant low insulin (23) (when glucose drop, insulin secretion is reduced to prevent further progression of hypoglycemia). In T1DM, however, hypoglycemia is caused by excessive exogenous insulin administration, meaning that the pancreatic α -cell is presented with low glycemia but high insulinemia, which blocks glucagon release. In animal models of T1DM, in fact, the loss of glucagon response to hypoglycemia is restored with hypoglycemia induced with AICAR and phlorizin, instead of exogenous insulin (24, 199). Unlike islet β -cells, however, which in T1DM are irreversibly lost, pancreatic α -cells are preserved, and in fact maintain the ability to secrete glucagon, and even to increase the rate of glucagon secretion in response to stimuli other than hypoglycemia. Importantly, the ability

to increase glucagon secretion is maintained in response to physical exercise (30).

At this point, it may be helpful to clarify that alterations in counterregulatory responses to exercise in T1DM are fundamentally of two types: transient (reversible) and permanent (irreversible). The two “first-line” hormones, accounting for most of counterregulatory effects during the first 60 to 90 min after hypoglycemia or exercise have started, are epinephrine and glucagon. A common complication of long-standing, poorly controlled diabetes is autonomic neuropathy, which is often associated with a progressive attenuation, or even a complete suppression, of the catecholamine response to stress (59). While this, like other diabetic complications, can be avoided with consistently optimal glycemic control (299), once established it is irreversible, practically eliminating early counterregulation to hypoglycemia, and leaving the burden of early counterregulation to exercise onto glucagon alone.

Independent of the presence of autonomic dysfunction, counterregulatory responses can become transiently attenuated, or even abolished, following certain blunting stimuli. A study on young T1DM subjects of both genders, (106), for instance, reported that after several days of very tight glycemic control, prolonged, submaximal exercise resulted in glucagon, epinephrine, and other counterregulatory responses indistinguishable from those at of age-matched, healthy subjects. If the very same subjects, however, performed an identical exercise challenge after having been exposed to 4 h of hypoglycemia of ~ 50 mg/dL, their glucagon response to exercise was completely suppressed, while the epinephrine response was cut in half. Exercise-induced changes of other counterregulatory hormones, as well as tracer-determined endogenous glucose production and lipolysis, were also significantly blunted. Prior hypoglycemia has also been demonstrated to exert a similar blunting effect even in non-diabetic subjects (61). Further, the magnitude of the blunting follows a clear dose-dependent pattern with the depth of antecedent hypoglycemia. A separate study, again in T1DM patients, reported how antecedent prolonged hypoglycemia of 70, 60, or 50 mg/dL, suppressed the glucagon response to subsequent exercise by 40%, 60%, and 95%, respectively (109) (Fig. 6). It should be noted that in these experiments the blunting stimulus (prior hypoglycemia) occurred between 10 am and 4 pm of 1 day, while the actual blunting of exercise responses occurred in the morning of the following day, that is, ~ 16 h after prior hypoglycemia had been resolved. While complete data about the duration of this effect are not available, it is believed that the counterregulatory responses would become progressively less blunted, and eventually fully recovered, within a few days, if no additional blunting event occurs. Unfortunately, the reality of T1DM glycemic management is that recurrent, often profound episodes of hypoglycemia are common, and paradoxically even more so among those patients who maintain close-to normal values of HbA1c (an index of long-term glucose control) through aggressive insulin regimens (299). To add another layer of

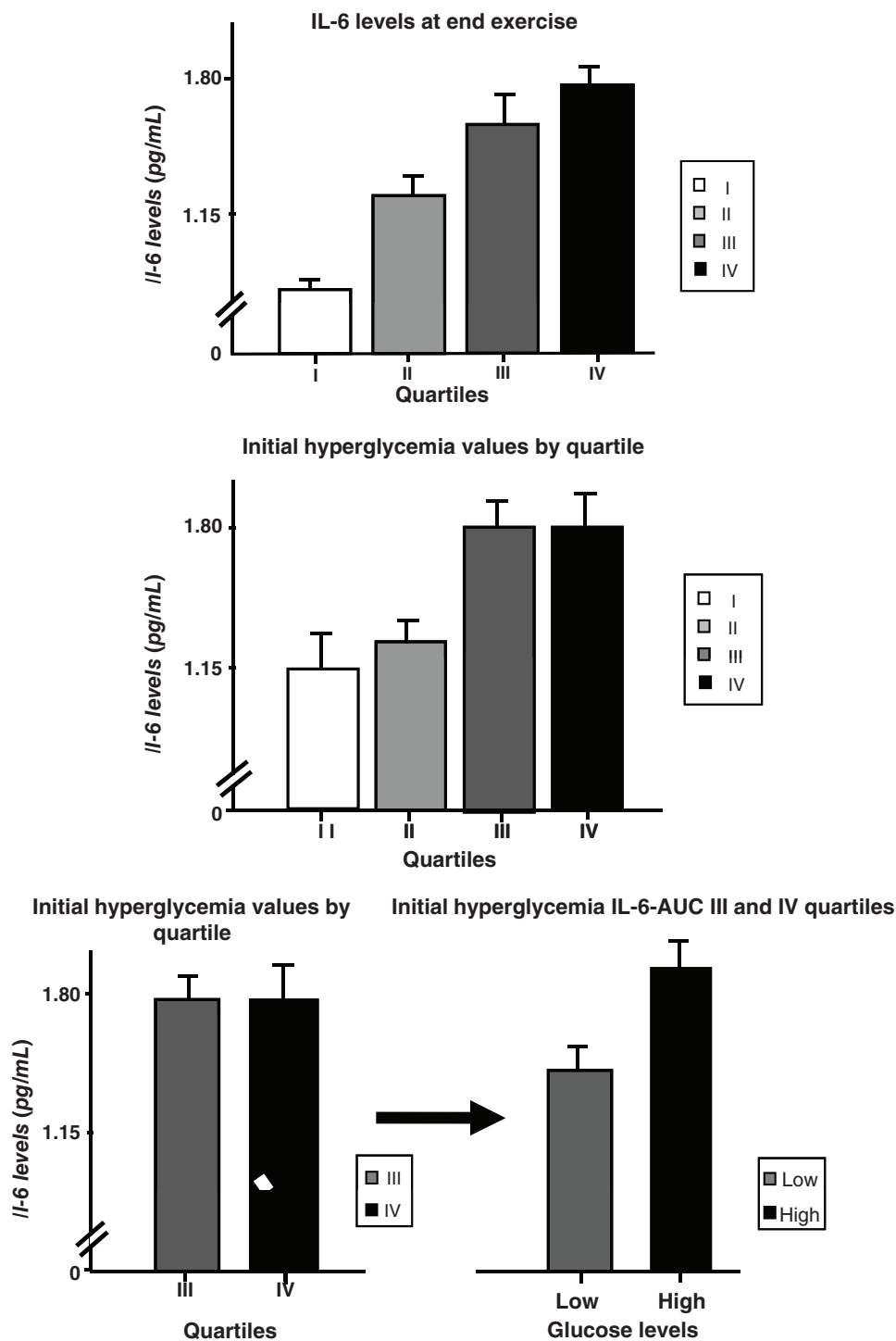
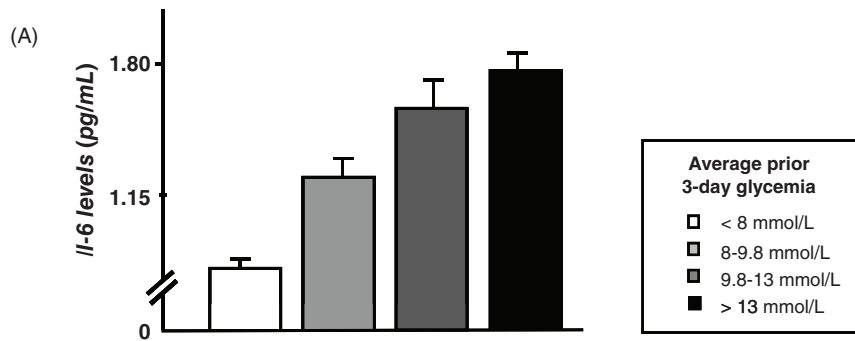
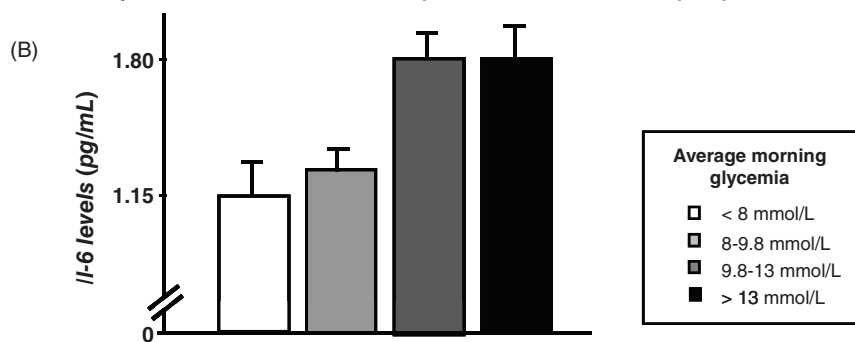


Figure 6 Blunted counterregulatory responses to exercise in a group of 16 patients with T1DM during a 2-day controlled study (109). On day 1, subjects were exposed to 4 h (two 2-h blocks) of hypoglycemia of varying depth, and on day 2 they exercise in euglycemic conditions. While in all experiments, when exercise started, prior hypoglycemia had been corrected for at least 16 h, a dose-response blunting of major counterregulatory response to exercise occurred, proportional to the depth of hypoglycemia experienced the day before.

IL-6 levels at end exercise in 47 T1DM, subdivided in quartiles based on average glycemia during prior 3 days; higher prior glycemia resulted in progressively greater IL-6 levels.



If the same subjects are subdivided based only on glycemic levels in the morning immediately before exercise, the IL-6 response in bottom 2 and top 2 quartiles is similar.



If subjects from the top 2 quartiles in panel B, are now repooled together, and then subdivided in 2 new groups based on mean prior 3-day glycemia, again those with worse prior glucose control display a greater IL-6 response to exercise.

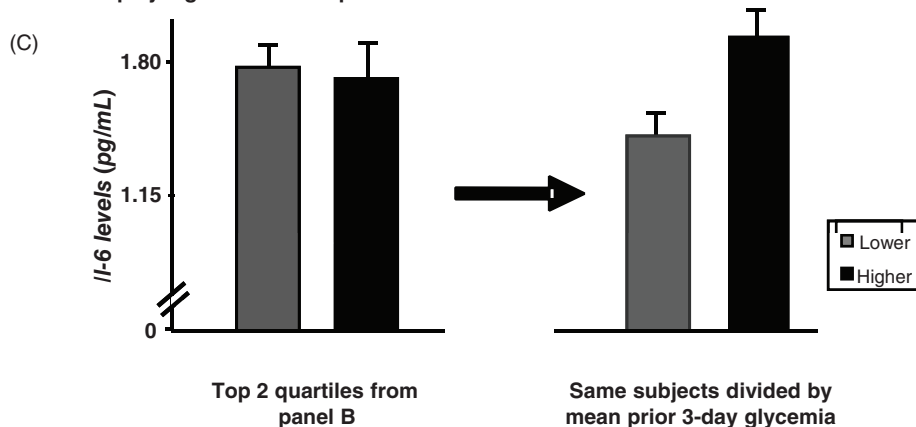


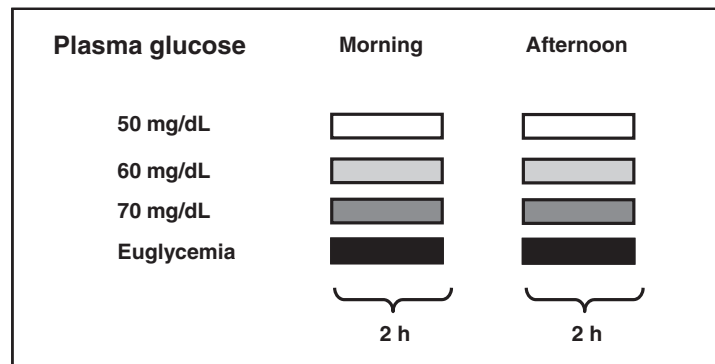
Figure 6 (Continued)

complexity, exercise itself may act as an antecedent blunting stimulus. Studies measuring counterregulatory response to repeated exercise challenges have reported that during later exercise bouts, counterregulation was impaired, even if hypoglycemia was not allowed to occur by supplementing glucose (105). In real-life terms, this means that any hypoglycemic episode in T1DM generates a time window of susceptibility during which more hypoglycemia may occur more easily, either through a slight excess in insulin or with exercise,

practically establishing a vicious cycle leading to more and more hypoglycemia (303).

So far, we have only addressed prior hyperglycemia and hypoglycemia occurring during exercise; the increased susceptibility to hypoglycemia, however, extends well after exercise cessation. In fact, exercise has been clearly shown to blunt counterregulatory responses to hypoglycemia induced via insulin infusion the next day (270), in a reversal of the sequence of events described above. In the hours

Day 1:
Hypoglycemia



Day 2:
Exercise challenge

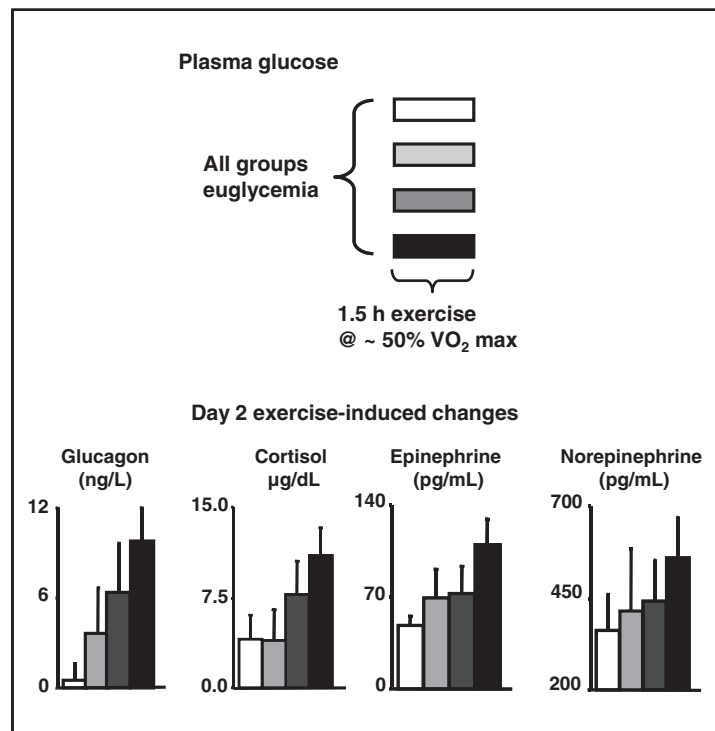


Figure 6 (Continued)

following exercise, especially if it was prolonged and intense, insulin sensitivity is increased and the need to replenish exhausted muscle glycogen reserves shift the greater part of whole body glucose uptake toward the skeletal muscle (35), increasing the likelihood of an hypoglycemic episode. Importantly, counterregulatory responses are also physiologically attenuated during sleep (53); therefore, a “second peak” of incidence of hypoglycemia has been regularly observed during the night following exercise activities (2, 170, 303), particularly between midnight and 4 am (201).

Due to the variety and instability of factors influencing the characteristics of exercise-associated hypoglycemia, its clinical management is often difficult (128). The main approaches include empirical adjustment of insulin administration (103, 271, 304), and supplementations of carbohydrate-rich drinks and snacks at critical times before, during, and after exercise (252, 255, 271). Recently, a novel concept has also been proposed to offset the prohypoglycemic effects of some exercise formats (prolonged, moderate intensity exercise) by incorporating some brief, very intense bouts which, if isolated, would have a prohyperglycemic effect. By adding

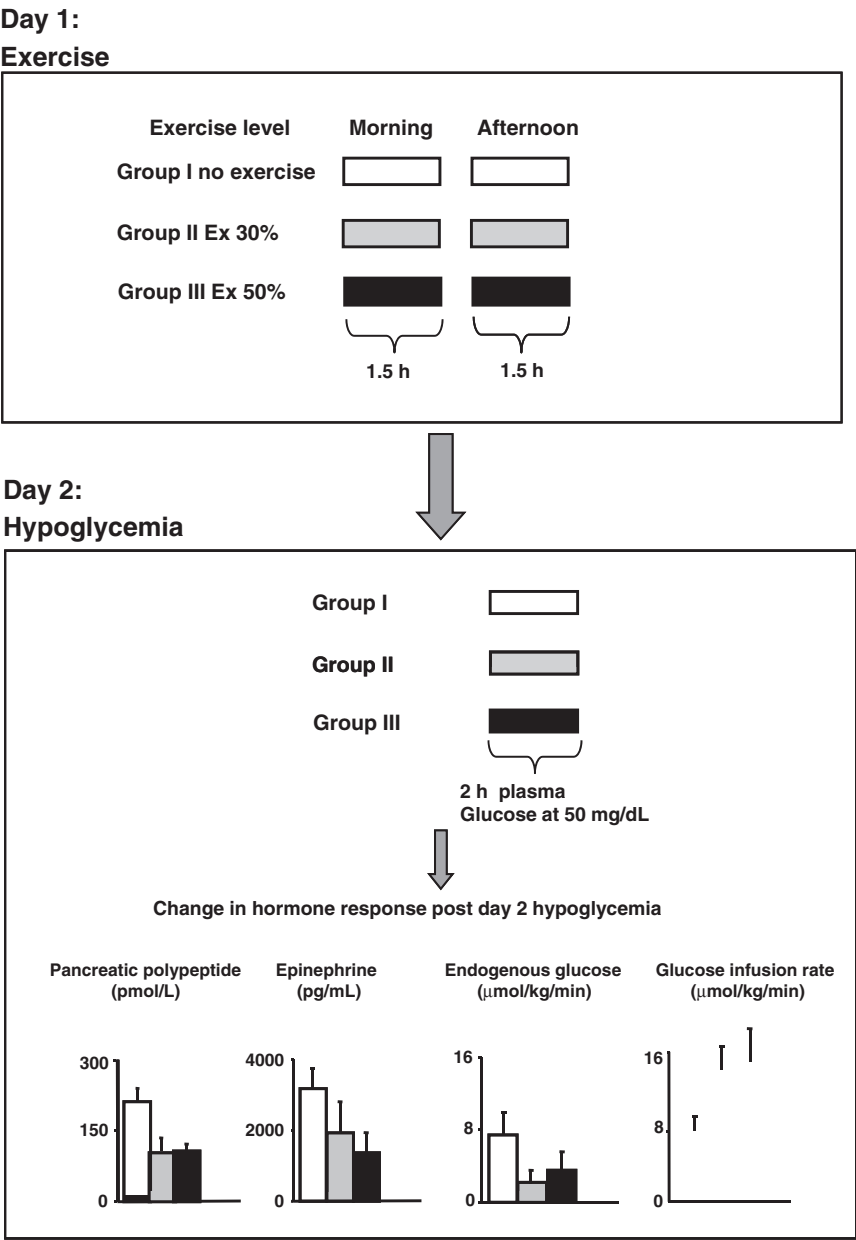


Figure 6 (Continued)

intense exercise bouts as short as 10 s to a standard sport training session, in fact, an Australian group has recently demonstrated that postexercise hypoglycemic hypoglycemia could be dramatically reduced (42, 129, 129). Taken together, these several lines of evidence underscore the complexity of the decision process relative to the prevention of exercise-associated hypoglycemia, which should take into account, in addition to subject's metabolic conditions at the time of exercise, also careful consideration of stressful events during the preceding 24 to 48 h, as these may significantly affect the characteristics and efficacy of the response to subsequent exercise challenges. Greater details on specific management issues relating to exercise-associated hypoglycemia are available in specialty publications, such as the Clinical

Practice Consensus Guidelines of the International Society for Pediatric and Adolescents Diabetes (259).

Specific Issues Associated with Exercise and Diabetes

Growth factor responses to exercise in the type 1 diabetic child

Among the multiple synchronous hormonal responses to exercise is an acute increase in growth factors, especially GH. The notion that physical exercise is a potent stimulus for the secretion of GH has been established since the 1963 classic paper by Roth et al. (267), and later characterized in detail by a

considerable number of experiments. It is now clear that GH levels begin increasing as early as 10 min after exercise onset, and keep increasing until or shortly after exercise is terminated (188, 246, 316). While virtually all types of exercise result in some degree of activation of GH secretion, the actual magnitude of this response has been shown to be directly proportional to the intensity and duration of exercise (90, 95, 139, 192, 216, 217, 236, 288, 294, 328), as well as being influenced by the type of physical activity (126, 133, 134, 167, 180–182, 245, 308). Further, the magnitude of the GH response appears enhanced by greater fitness (131, 150, 192, 295), and reduced by age (131, 150, 333), greater BMI (165, 309, 310) and colder temperature (115), while exercising at different times during the day seems to exert little or no effect (166).

The metabolic implications of the growth factor response to exercise are substantially different between adults, in whom this is mostly considered one of several responses regulating carbohydrate availability, and in children, in whom it also plays an essential role in the modulation of physiological growth and development.

In fact, in children, physical activity occurs spontaneously, continuously and repeatedly, and is often of relatively high intensity, the constant exercise-induced stimulation of the GH->IGF-1 axis during childhood is increasingly seen as a necessary component of balanced and effective growth processes (52). In animal models, early-life rate of growth is significantly enhanced by physical activity, in parallel with greater GH pulse frequency and amplitude (164). In humans, lack of physical activity early in life has been associated with inadequate bone mineralization (208) and sarcopenia later in life (268). Insufficient activation of the GH->IGF-1 axis during critical periods of growth and development, on the other hand, has been associated with impaired bone elongation and muscle growth (64, 219). Additional evidence tying the effects of exercise and the GH->IGF-1 axis on the modulation of growth and development is provided by the close correlation existing between levels of these hormones, muscle mass and fitness in children, adolescents, and adults (79, 234, 302).

In children with T1DM, the GH responses to exercise are particularly important, as in this group of patients not only widespread alterations in exercise responses are systematically present, but also, independent of exercise, the action of the GH->IGF-1 axis is altered as an intrinsic feature of the disease (149, 191, 297).

In T1DM, when hypoglycemia occurs in the hours preceding exercise (even if it is corrected by the time exercise starts), a number of responses are markedly blunted, decreasing the body's ability to match the increased need for energy substrates (glucose, free fatty acids) (58, 274). This effect has been demonstrated to be clearly dose dependent, and therefore, more pronounced when the depth of hypoglycemia reaches 40 to 50 mg/dL (108). The GH response to exercise is one of the most clearly blunted by prior hypoglycemia. Four hours of prior hypoglycemia of ~ 50 mg/dL, for instance (divided in two 2-h blocks separated by 2 h of rest) have been shown to markedly suppress the GH response to subsequent,

submaximal exercise (90 min of constant load cycling at about 60% of maximal aerobic capacity) in healthy young adults of average fitness (61). It should be noted that in these healthy subjects, hypoglycemia of this depth (which during the experiments was induced via supraphysiological infusion of exogenous insulin) is unlikely to ever occur in real-life situations. This level of hypoglycemia, however, (and unfortunately often even deeper), is a frequent, unwelcome accompanying event of insulin therapy in diabetic patients (especially T1DM), and when studies similar to the one reported above were performed in populations of type 1 diabetic patients, a widespread blunting of adaptive responses to exercise, including the GH response, was confirmed following prior hypoglycemia (106), again in a dose dependent fashion (108). Considering that hypoglycemia in many diabetic patients occurs almost daily, and that they still engage in repeated, often competitive physical and sports activities, these data indicate that the exercise-induced GH peaks are most likely systematically reduced in T1DM children.

An additional level of complication is induced by the fact that subjects with T1DM, in the attempt to avoid carbohydrates in their meals, often end up significantly increasing consumption of fat-rich nutrients. This, however, may in fact exert the effect of transiently worsening glycemic control, as hyperlipidemia, even brief, acutely induces insulin resistance, allowing even small amounts of ingested carbohydrates to cause hyperglycemia. Further, if the fat-rich meal is ingested before exercising, it may independently suppress the GH response to exercise. This was first demonstrated in a paper published in 1994 (45), showing that the GH response to exercise in a group of healthy male subjects is influenced by dietary composition of a meal. In that study, the format of exercise was 10 min of strenuous exertion on a cycle ergometer, and the meal was ingested 45 min before exercise. Following both a noncaloric placebo meal and a carbohydrate rich meal, a similar, robust GH response was observed; following exercise, GH concentrations remained elevated well above baseline for at least 1 h. After ingestion of the high-fat meal, however, the GH response to exercise was reduced by over 50%. The physiological implications of this finding, in adults, may be restricted to the modulation of the glucoregulatory function of GH in response to exercise and other stresses. In children, however, its implications may be considerably more complex, extending to the regulation of growth and development. The above phenomenon, therefore, may have particular relevance for pediatric subjects. It was not until 2006, however, that this observation was confirmed in children (104). In this report, 12 children (6 males/6 females) performed 30 min of intermittent, intense cycling exercise (10 repeats of 2-min cycling bouts at 80% of their predetermined maximal aerobic capacity, separated by 1 min intervals), 45 min after ingestion of either a noncaloric placebo or a semiliquid meal containing 0.8 g of fat per kg of body weight. Similar to the observations in adults, after lipid ingestion the GH response to exercise was blunted by ~ 40%. We believe the real-life implications of these findings to be self-evident. The design

of the latter study, in fact, was created to simulate ingestion of a “fast food” meal on the way to a sports practice—an all-too-common scenario in western societies—and the results underscore the profound impact that acquired habits (i.e., excessive fat consumption) may have on otherwise healthy activities (as physical exercise is expected to induce, proportional to its intensity, up to a ~20-fold increase in resting GH concentrations) (236). In a separate set of experiments, based on the rationale that despite lower IGF-1 concentrations GH levels have been reported to be elevated in T1DM (149, 191, 297), the GH response to a similar exercise challenge in a group of 12 children with this condition was studied. Indeed, while in our experimental conditions pre- and end-exercise GH concentrations were similar in healthy and T1DM children, in the postexercise state GH concentrations in diabetic children remained significantly elevated above baseline for at least 30 min ($+9 \pm 2 \mu\text{g/L}$) while returning to close to baseline levels in controls ($+3 \pm 1 \mu\text{g/L}$) (110). Importantly, it should be noted that inflammatory and oxidative mediator response (which may be exaggerated in T1DM) are closely networked to growth factor responses. Several cytokines, for instance, can inhibit the anabolic activities of the GH→IGF-I axis by decreasing hepatic GH sensitivity (7, 86), possibly reducing hepatic IGF-I production and altering its downstream effects on physiological growth (63). Despite these numerous observations, the collective effect of altered growth factor signaling during exercise in T1DM is still incompletely defined, further underscoring the importance to fully understand all exercise-associated molecular and biochemical adaptive mechanism.

Exercise-Associated Mechanisms Regulating the Pathogenesis of Cardiovascular Disease

Inflammation and oxidative stress in type 1 diabetics

Numerous studies in T1DM patients report elevated circulating inflammatory and oxidative stress markers (69, 82, 110, 116, 206, 220, 298). While part of this proinflammatory status is considered by some an intrinsic component of diabetes, that is, regardless of glycemic control at any given time, broad consensus now exists on the concept that hyperglycemia has a major role in perpetuating and exacerbating inflammatory and oxidative processes.

Oxidative stress is defined as an imbalance between production of reactive oxygen species (ROS) and antioxidant defenses. During mitochondrial respiration, 0.4 to 4% of consumed O_2 is converted to the free radical superoxide ($\bullet\text{O}_2^-$) (38) which generates ROS and reactive nitrogen species (RNS). With inadequate antioxidant defenses, an excess of highly reactive hydroxyls, peroxy, and hydroperoxy is generated, that can damage functional molecules, cells, and tissues. Oxidative stress damage is mediated via several mechanisms, the most important of which is probably the activation of stress-sensitive signaling pathways such as

the NF- κ B, regulating expression of genes encoding vascular growth factors (VEGFs), inflammatory cytokines, adhesion molecules and receptor for advanced glycation end-products (84). In this respect, oxidative stress may be seen as one of the mechanisms activating systemic inflammation, paralleling other inflammatory stimuli in the common downstream effects of micro- and macrovascular damage.

Even in nondiabetic subjects, transient hyperglycemia can acutely increase systemic biomarkers of oxidative stress (F2-isoprostanes) (269) and inflammation (83). Four distinct biochemical pathways have been identified linking hyperglycemia in the diabetic to the development of micro- and macrovascular complications, through the activation of inflammatory and oxidative mediators (40): increased polyol pathway flux (4, 81, 113, 127, 189), increased intracellular formation of advanced glycation end-products (6, 74, 174, 272, 287, 317), activation of protein kinases (233, 329, 331), and increased flux through the hexosamine pathway (140, 177, 197).

A unifying underlying cause for alteration of all four of the above pathways is now believed to be hyperglycemia-induced overproduction of superoxide by the mitochondrial electron transport chain (75, 222). Several downstream effects ensue, including: different degrees of further ROS and RNS production, with potential direct tissue damage and indirect inflammatory activation; vasomotor activity, vascular permeability and contractility, extracellular matrix composition, cell growth, angiogenesis, cytokine action, and leukocyte adhesion, all of which are altered in diabetes (172, 244). In particular, several components of atherogenesis are enhanced in diabetic patients, including activation of transcription factors stimulating expression of proinflammatory cytokines (9, 242, 265); activation of vascular endothelium with expression of adhesion molecules (VCAM-1, ICAM-1, selectins), leukocyte recruitment and activation (292); secretion of chemoattractant molecules (IL-8, MCP-1) (30); penetration across the vascular wall of monocytes and their transformation to macrophages; overexpression of proatherogenic receptors and ligands (CD40, CD44); overexpression of heat shock proteins which, via binding to the TLR4/CD14 complex, further activate NF- κ B-mediated proinflammatory cytokine secretion (71). This overview of the complex pattern of molecular interactions that lead to micro- and macrovascular damage in diabetes, although somewhat simplified for the purposes of this review, underscores the concept that a varying degree of activation of inflammatory and oxidative mechanisms is almost invariably present in the diabetic patient, and that a very close relationship exists between the biochemical alterations listed above and magnitude, duration, and frequency of hyperglycemia.

Inflammation, oxidative stress, and exercise in type 1 diabetics

Physical exercise has been long identified as a critical modulator of coordinated inflammatory and oxidative processes. A

prolonged regimen of exercise appears to reduce, at least in healthy individuals, basal oxidative and inflammatory status, by reducing circulating inflammatory cytokines and increasing antioxidant enzymes (85, 99, 152, 205, 276). This process, modulated by exercise intensity and individual fitness level (80, 85, 152, 154, 202, 205, 276, 300), is now believed to be the main determinant of exercise's long-term protection against cardiovascular disease. Prolonged exercise regimens, however, are composed of individual exercise sessions each inducing, paradoxically, a proinflammatory, oxidative stimulus.

A key concept that has emerged in recent years is in fact that acute exercise, even in healthy people, leads to a robust inflammatory response characterized by mobilization of leukocytes (even for bouts as short as 6 min) (273) and increases in circulating potent inflammatory mediators like TNF- α , IL-1 β , IL-6, IL-8, IL-10, IL-1Ra, GCSF, TNF-R1 (218, 229, 334). This response is reproducible, dose dependent, and occurs in all age groups (230). After exercise is stopped, peripheral blood mononuclear cells (PBMCs) decrease immediately, while neutrophils (PMNs) remain elevated for up to several hours (221). This may be important, as while for many years PBMCs had been considered the only blood cells responsible for *de novo* synthesis of polypeptide mediators, in PMNs an inducible increase in the secretion of proinflammatory cytokines (TNF- α , IL-1 β), CC, and CXC chemokines (IL-8, IL-10, MIP-1 α) and angiogenic factors such as VEGF (168) have been demonstrated in response to a variety of stimuli, with regulatory input by circulating IFN- γ , IL-4, IL-10, and IL-13. Further, we now also know that the exercise-induced leukocytosis is accompanied by changes in gene expression (93, 138). A 30-min bout of heavy exercise significantly altered the expression of hundreds of genes both in PBMCs (8) and PMNs (239) in young adults and children (240), including proinflammatory and anti-inflammatory genes, growth factors (EREG, ERG-1, and ECGF1), cytokine binding molecules and receptors, the HSP family, as well as genes regulating apoptosis. These critical circulating immune cells and inflammatory mediators undergo some degree of activation even with physical exertions of short duration and low intensity, leading to the belief that this activation is physiologically expected to happen repeatedly and frequently in everyday life (53). As exercise increases O₂ flow through the mitochondria, ROS production is increased and acute oxidative stress is induced (22, 120, 276, 301), proportionally to the intensity of exercise, (72, 112, 276, 313, 314). In the physiological state, however, the inflammatory and oxidative pathways triggered by exercise are balanced by adequate antioxidant mechanisms limiting their potential damage (159, 237, 275), and allowing the long-term beneficial effects of exercise to manifest.

This apparently paradoxical dichotomy between acute proinflammatory/oxidative and long-term protective effects of exercise may be a crucial issue in T1DM, in whom, as described above, inflammatory and oxidative status may already be persistently altered (210, 238), as well as undergo

periodic exacerbation related to recurrent hyperglycemia (96, 262, 312). As a logical consequence, inappropriate inflammatory/oxidative responses to exercise may result. We have already discussed how prior hyperglycemic fluctuations may affect the inflammatory IL-6 response to subsequent exercise (111, 261). Further characterization of inflammatory/oxidative response to exercise in T1DM, however, has been attempted in surprisingly few studies. IL-6 is higher in T1DM children than in healthy controls before, during, and 30 min after exercise (12), and studies in a rodent model of T1DM, as well as in adult human patients, revealed exaggerated oxidative marker responses to various formats of exercise (62, 285). Along with the majority of exercise studies in general, these reports were limited to pre- and postexercise measurements of pertinent variables, while very little information exists on serial measurements of inflammatory mediators during exercise. In fact, to date, only one report has appeared displaying the kinetic profiles (measurements taken at 6 min intervals) of a panel of pro- and anti-inflammatory cytokines in T1DM children, during 30 min of intermittent exercise. Compared to healthy children (263), exercise-induced changes of several key cytokines were greater and occurred earlier in T1DM (264). Finally, a single study has been published (162) comparing cytokine responses during euglycemic versus hyperglycemic otherwise identical exercise in T1DM; in this study, the IL-6 response was actually lower with hyperglycemia, confirming similar prior data in healthy controls (91).

We would like to make it absolutely clear, however, that physical activity remains a major mechanism in T1DM to increase overall well being and reduce the likelihood of developing long-term vascular complications (46, 114, 327). The exaggerated proinflammatory effects reviewed above, therefore, do not render exercise harmful in T1DM, but somewhat reduce the overall beneficial health effect. Rather than avoiding exercise, particular attention should be placed in understanding what exercise types and durations are likely to preserve the greatest degree of cardiovascular protection despite the apparent increase in proinflammatory mechanisms. To this end, more extensive studies clarifying the physiological and molecular basis of exercise adaptive responses, and their possible alterations in diabetes, are imperative.

Summary and Conclusions

Physical exercise is highly recommended in subjects with T1DM for its numerous beneficial health effects, among which the prevention of long-term cardiovascular complications is paramount. Numerous issues, however, render the systematic implementations of effective exercise strategies complicated in these patients; in fact, in subjects with chronically poorly controlled disease, characteristic muscle tissue changes occur, identified by some as specific form of myopathy. Even in relatively well-controlled subjects the marked alterations in carbohydrate metabolism associated

with diabetes may cause the frequent occurrence of both hypo- or hyperglycemic episodes during and after exercise. These episodes are often caused by inappropriate dosage of insulin that patients inject multiple times per day. Further, the “metabolic memory” of prior episodes of hypo- or hyperglycemia can affect exercise response during exercise occurring hours or days after the episode was resolved. In addition to glycemic regulation, other adaptive response to exercise that may be altered are the secretion of inflammatory/oxidative factors, now considered a key component of exercise-associated cardio-protection, and the secretion of growth factors, especially important in still-growing T1DM youths. Many of these alterations can now be effectively prevented or managed by a combination of optimal glycemic control, empirical adjustments of insulin administration at the time of exercise, and ingestion of carbohydrate supplements tailored to the type, intensity, and duration of the exercise activity. It is important to stress that collectively, the many possible alterations in exercise responses that may occur in T1DM do not render this activity harmful, but at worst reduce its full beneficial health effects.

References

- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 30(Suppl 1): S42-S47, 2007.
- Diabetes Research in Children Network (DirecNet) Study Group. Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes* 8: 199-205, 2007.
- American College of Sports Medicine. *ACSM Guidelines for Exercise Testing and Prescription*. Lippincott, Williams & Wilkins, 2005.
- Mohammed Q, Gillies MC, Wong TY. A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy. Sorbinil Retinopathy Trial Research Group. *Arch Ophthalmol* 108: 1234-1244, 1990.
- U.S. Department of Health and Human Services. Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A: Executive summary. *Nutr Rev* 67: 114-120, 2009.
- Abordo EA, Westwood ME, Thornalley PJ. Synthesis and secretion of macrophage colony stimulating factor by mature human monocytes and human monocytic THP-1 cells induced by human serum albumin derivatives modified with methylglyoxal and glucose-derived advanced glycation endproducts. *Immunol Lett* 53: 7-13, 1996.
- Ahmad I, Zaldivar F, Iwanaga K, Koepfel R, Grochow D, Nemet D, Waffarn F, Eliakim A, Leu SY, Cooper DM. Inflammatory and growth mediators in growing preterm infants. *J Pediatr Endocrinol Metab* 20: 387-396, 2007.
- Akerstrom T, Steensberg A, Keller P, Keller C, Penkowa M, Pedersen BK. Exercise induces interleukin-8 expression in human skeletal muscle. *J Physiol* 563: 507-516, 2005.
- Alikhani Z, Alikhani M, Boyd CM, Nagao K, Trackman PC, Graves DT. Advanced glycation end products enhance expression of proapoptotic genes and stimulate fibroblast apoptosis through cytoplasmic and mitochondrial pathways. *J Biol Chem* 280: 12087-12095, 2005.
- Almeida S, Riddell MC, Cafarelli E. Slower conduction velocity and motor unit discharge frequency are associated with muscle fatigue during isometric exercise in type 1 diabetes mellitus. *Muscle Nerve* 37: 231-240, 2008.
- Andersen H. Muscular endurance in long-term IDDM patients. *Diabetes Care* 21: 604-609, 1998.
- Andersen H, Gadeberg PC, Brock B, Jakobsen J. Muscular atrophy in diabetic neuropathy: A stereological magnetic resonance imaging study. *Diabetologia* 40: 1062-1069, 1997.
- Andersen H, Gjerstad MD, Jakobsen J. Atrophy of foot muscles: A measure of diabetic neuropathy. *Diabetes Care* 27: 2382-2385, 2004.
- Andersen H, Poulsen PL, Mogensen CE, Jakobsen J. Isokinetic muscle strength in long-term IDDM patients in relation to diabetic complications. *Diabetes* 45: 440-445, 1996.
- Andersen H, Schmitz O, Nielsen S. Decreased isometric muscle strength after acute hyperglycaemia in Type 1 diabetic patients. *Diabet Med* 22: 1401-1407, 2005.
- Andersen H, Stalberg E, Gjerstad MD, Jakobsen J. Association of muscle strength and electrophysiological measures of reinnervation in diabetic neuropathy. *Muscle Nerve* 21: 1647-1654, 1998.
- Andreassen CS, Jakobsen J, Andersen H. Muscle weakness: A progressive late complication in diabetic distal symmetric polyneuropathy. *Diabetes* 55: 806-812, 2006.
- Andreassen CS, Jakobsen J, Flyvbjerg A, Andersen H. Expression of neurotrophic factors in diabetic muscle—relation to neuropathy and muscle strength. *Brain* 132: 2724-2733, 2009.
- Andreassen CS, Jakobsen J, Ringgaard S, Ejksjaer N, Andersen H. Accelerated atrophy of lower leg and foot muscles—a follow-up study of long-term diabetic polyneuropathy using magnetic resonance imaging (MRI). *Diabetologia* 52: 1182-1191, 2009.
- Armstrong RB, Gollnick PD, Ianuzzo CD. Histochemical properties of skeletal muscle fibers in streptozotocin-diabetic rats. *Cell Tissue Res* 162: 387-394, 1975.
- Armstrong RB, Ianuzzo CD. Compensatory hypertrophy of skeletal muscle fibers in streptozotocin-diabetic rats. *Cell Tissue Res* 181: 255-266, 1977.
- Atalay M, Laaksonen DE, Khanna S, Kaliste-Korhonen E, Hanninen O, Sen CK. Vitamin E regulates changes in tissue antioxidants induced by fish oil and acute exercise. *Med Sci Sports Exerc* 32: 601-607, 2000.
- Banarer S, McGregor VP, Cryer PE. A decrease in β -cell insulin secretion is a signal to increased α -cell glucagon secretion. *Diabetes* 50(Suppl 2): A140, 2001.
- Banarer S, McGregor VP, Cryer PE. Intra-islet hyperinsulinemia prevents the glucagon response to hypoglycemia despite an intact autonomic response. *Diabetes* 51: 958-965, 2002.
- Baraldi E, Monciotti C, Filippone M, Santuz P, Magagnoli G, Zanconato S, Zaccello F. Gas exchange during exercise in diabetic children. *Pediatr Pulmonol* 13: 155-160, 1992.
- Berger M, Berchtold P, Cuppers HJ, Drost H, Kley HK, Muller WA, Wiegmann W, Zimmermann-Telchow H, Gries FA, Kruskemper HL, Zimmermann H. Metabolic and hormonal effects of muscular exercise in juvenile type 1 diabetes. *Diabetologia* 13: 355-365, 1977.
- Berger M, Halban PA, Assal JP, Offord RE, Vranic M, Renold AE. Pharmacokinetics of subcutaneously injected tritiated insulin: Effects of exercise. *Diabetes* 28(Suppl 1): 53-57, 1979.
- Berger M, Halban PA, Muller WA, Offord RE, Renold AE, Vranic M. Mobilization of subcutaneously injected tritiated insulin in rats: Effects of muscular exercise. *Diabetologia* 15: 133-140, 1978.
- Bernardini AL, Vanelli M, Chiari G, Iovane B, Gelmetti C, Vitale R, Errico MK. Adherence to physical activity in young people with type 1 diabetes. *Acta Biomed* 75: 153-157, 2004.
- Binder CJ, Chang MK, Shaw PX, Miller YI, Hartvigsen K, Dewan A, Witztum JL. Innate and acquired immunity in atherosclerosis. *Nat Med* 8: 1218-1226, 2002.
- Bjorkman O, Miles P, Wasserman D, Lickley L, Vranic M. Regulation of glucose turnover during exercise in pancreatectomized, totally insulin-deficient dogs. Effects of beta-adrenergic blockade. *J Clin Invest* 81: 1759-1767, 1988.
- Bliss M. Resurrections in Toronto: The emergence of insulin. *Horm Res* 64(Suppl 2): 98-102, 2005.
- Boehncke S, Poettgen K, Maser-Gluth C, Reusch J, Boehncke WH, Badenhop K. Endurance capabilities of triathlon competitors with type 1 diabetes mellitus. *Dtsch Med Wochenschr* 134: 677-682, 2009.
- Boirie Y, Short KR, Ahlman B, Charlton M, Nair KS. Tissue-specific regulation of mitochondrial and cytoplasmic protein synthesis rates by insulin. *Diabetes* 50: 2652-2658, 2001.
- Borghouts LB, Keizer HA. Exercise and insulin sensitivity: A review. *Int J Sports Med* 20: 1-12, 2000.
- Bosch AN, Kirkman MC. Maintenance of hyperglycaemia does not improve performance in a 100 km cycling time trial. *South African Journal of Sports Medicine* 19: 94-98, 2007.
- Bottini P, Boschetti E, Pampanelli S, Ciofetta M, Del Sindaco P, Scionti L, Brunetti P, Bolli GB. Contribution of autonomic neuropathy to reduce plasma adrenaline responses to hypoglycemia in IDDM. *Diabetes* 46: 814-823, 1997.
- Boveris A. Determination of the production of superoxide radicals and hydrogen peroxide in mitochondria. *Methods Enzymol* 105: 429-435, 1984.
- Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care* 31: 2108-2109, 2008.
- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 414: 813-820, 2001.
- Burr JF, Rowan CP, Jamnik VK, Riddell MC. The role of physical activity in type 2 diabetes prevention: Physiological and practical perspectives. *Physician Sports Med* 38: 72-82, 2010.

42. Bussau VA, Ferreira LD, Jones TW, Fournier PA. 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, 2007.
43. Cahill GF Jr, Aoki TT, Marliss EB. Insulin and muscle protein. In: Steiner DF, Freinkel N, editors. *Handbook of Physiology. Section 7: Endocrinology*. Baltimore, Maryland: Williams and Wilkins. 1972, pp. 563-577.
44. Camacho RC, Galassetti P, Davis SN, Wasserman DH. Glucoregulation during and after exercise in health and insulin-dependent diabetes. *Exerc Sport Sci Rev* 33: 17-23, 2005.
45. Cappon JP, Ipp E, Brasel JA, Cooper DM. Acute effects of high fat and high glucose meals on the growth hormone response to exercise. *J Clin Endocrinol Metab* 76: 1428-1422, 1993.
46. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR, Jr, Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA* 290: 3092-3100, 2003.
47. Caspersen CJ. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep* 100: 126-131, 1985.
48. Chase HP, Lockspeiser T, Peery B, Shepherd M, Mackenzie T, Anderson J, Garg SK. The impact of the diabetes control and complications trial and humalog insulin on glycohemoglobin levels and severe hypoglycemia in type 1 diabetes. *Diabetes Care* 24: 430-434, 2001.
49. Chow LS, Albright RC, Bigelow ML, Toffolo G, Cobelli C, Nair KS. Mechanism of insulin's anabolic effect on muscle: Measurements of muscle protein synthesis and breakdown using aminoacyl-tRNA and other surrogate measures. *Am J Physiol Endocrinol Metab* 291: E729-E736, 2006.
50. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. The relationship between nonroutine use of insulin, food, and exercise and the occurrence of hypoglycemia in adults with IDDM and varying degrees of hypoglycemia awareness and metabolic control. *Diabetes Educ* 23: 55-58, 1997.
51. Coggan A, Raguso CA, Gastaldelli A, Williams BD, Wolfe RR. Regulation of glucose production during exercise at 80% VO_2 peak in untrained humans. *Am J Physiol* 273: E348-E354, 1997.
52. Cooper DM, Nemet D, Galassetti P. Exercise, stress, and inflammation in the growing child: From the bench to the playground. *Curr Opin Pediatr* 16: 286-292, 2004.
53. Cooper DM, Radom-Aizik S, Schwindt C, Zaldivar F. A minireview: Dangerous exercise-lessons learned from dysregulated inflammatory responses to physical activity. *J Appl Physiol* Aug;103(2): 700-709, 2007.
54. Cotter M, Cameron NE, Lean DR, Robertson S. Effects of long-term streptozotocin diabetes on the contractile and histochemical properties of rat muscles. *Q J Exp Physiol* 74: 65-74, 1989.
55. Crowther GJ, Milstein JM, Jubrias AS, Kushmerick MJ, Gronka RK, Conley KE. Altered energetic properties in skeletal muscle of men with well-controlled insulin-dependent (type 1) diabetes. *Am J Physiol Endocrinol Metab* 284: E655-E662, 2003.
56. Crozier SJ, Anthony JC, Schworer CM, Reiter AK, Anthony TG, Kimball SR, Jefferson LS. Tissue-specific regulation of protein synthesis by insulin and free fatty acids. *Am J Physiol Endocrinol Metab* 285: E754-E762, 2003.
57. Cryer PE. Glucose counterregulation in man. *Diabetes* 30: 261-264, 1981.
58. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. *Am J Physiol Endocrinol Metab* 281: E1115-E1121, 2001.
59. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 26: 1902-1912, 2003.
60. D'hooge R, Hellinckx T, Van LC, Stegen S, De SJ, Van AS, Dewolf D, Calders P. Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: A randomized controlled trial. *Clin Rehabil* 25: 349-359, 2011.
61. Davis SN, Galassetti P, Wasserman DH, Tate D. Effects of antecedent hypoglycemia on subsequent counterregulatory responses to exercise. *Diabetes* 49: 73-81, 2000.
62. Davison GW, George L, Jackson SK, Young IS, Davies B, Bailey DM, Peters JR, Ashton T. Exercise, free radicals, and lipid peroxidation in type 1 diabetes mellitus. *Free Radic Biol Med* 33: 1543-1551, 2002.
63. De BF, Alonzi T, Moretta A, Lazzaro D, Costa P, Poli V, Martini A, Ciliberto G, Fattori E. Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. *J Clin Invest* 99: 643-650, 1997.
64. Decsi T, Molnar D. Insulin resistance syndrome in children: Pathophysiology and potential management strategies. *Paediatr Drugs* 5: 291-299, 2003.
65. DeFeo P, Perriello G, De Cosmo S, Ventura MM, Campbell PJ, Brunetti P, Gerich JE, Bolli GB. Comparison of glucose counterregulation during short-term and prolonged hypoglycemia in normal humans. *Diabetes* 35: 563-569, 1986.
66. DeFeo P, Perriello G, Torlone E, Fanelli C, Ventura MM, Santeusano F, Brunetti P, Gerich JE, Bolli GB. Contribution of adrenergic mechanisms to glucose counterregulation in humans. *Am J Physiol* 261: E725-E736, 1991.
67. DeFeo P, Perriello G, Torlone E, Ventura M, Santeusano F. Demonstration of a role for growth hormone in glucose counterregulation. *Am J Physiol* 256: E835-E843, 1989.
68. DeFeo P, Perriello G, Torlone E, Ventura MM, Fanelli C, Santeusano F, Brunetti P, Gerich JE, Bolli GB. Contribution of cortisol to glucose counterregulation in humans. *Am J Physiol* 257: E35-E42, 1989.
69. Devaraj S, Glaser N, Griffen S, Wang-Polagruto J, Miguelino E, Jialal I. Increased monocytic activity and biomarkers of inflammation in patients with type 1 diabetes. *Diabetes* 55: 774-779, 2006.
70. Devlin J, Ruderman NB. *Handbook of Exercise and Diabetes*. Alexandria, VA: American Diabetes Association. 2002.
71. Di Marzio D, Mohn A, Mokini ZH, Giannini C, Chiarelli F. Macroangiopathy in adults and children with diabetes: From molecular mechanisms to vascular damage (part 1). *Horm Metab Res* 38: 691-705, 2006.
72. Dillard CJ, Litov RE, Savin WM, Dumelin EE, Tappel AL. Effects of exercise, vitamin E, and ozone on pulmonary function and lipid peroxidation. *J Appl Physiol* 45: 927-932, 1978.
73. Ditzel J, Standl E. The problem of tissue oxygenation in diabetes mellitus. *Acta Med Scand Suppl* 578: 59-68, 1975.
74. Doi T, Vlassara H, Kirstein M, Yamada Y, Striker GE, Striker LJ. Receptor-specific increase in extracellular matrix production in mouse mesangial cells by advanced glycosylation end products is mediated via platelet-derived growth factor. *Proc Natl Acad Sci U S A* 89: 2873-2877, 1992.
75. Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci U S A* 97: 12222-12226, 2000.
76. Durak EP, Jovanovic-Peterson L, Peterson CM. Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type I diabetic men. *Diabetes Care* 13: 1039-1043, 1990.
77. Ebeling P, Tuominen JA, Bourey R, Koranyi L, Koivisto VA. Athletes with IDDM exhibit impaired metabolic control and increased lipid utilization with no increase in insulin sensitivity. *Diabetes* 44: 471-477, 1995.
78. El-Osta A, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, Cooper ME, Brownlee M. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *J Exp Med* 205: 2409-2417, 2008.
79. Eliakim A, Scheett TP, Newcomb R, Mohan S, Cooper DM. Fitness, training, and the growth hormone-->insulin-like growth factor I axis in prepubertal girls. *J Clin Endocrinol Metab* 86: 2797-2802, 2001.
80. Elosua R, Moliona L, Fito M, Arquer A, Sanchez-Quesada JL, Covas M-I, Ordonez-Llanos J, Marrugat J. Response of oxidative stress biomarkers to a 16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. *Atherosclerosis* 167: 334, 2003.
81. Engerman RL, Kern TS, Larson ME. Nerve conduction and aldose reductase inhibition during 5 years of diabetes or galactosaemia in dogs. *Diabetologia* 37: 141-144, 1994.
82. Erbagci AB, Tarakcioglu M, Coskun Y, Sivasli E, Sibel NE. Mediators of inflammation in children with type I diabetes mellitus: Cytokines in type I diabetic children. *Clin Biochem* 34: 645-650, 2001.
83. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: Role of oxidative stress. *Circulation* 106: 2067-2072, 2002.
84. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of Type 2 Diabetes. *Endocr Rev* 23: 599-622, 2002.
85. Evelo CT, Palmén NG, Artur Y, Janssen GM. Changes in blood glutathione concentrations, and in erythrocyte glutathione reductase and glutathione S-transferase activity after running training and after participation in contests. *Eur J Appl Physiol* 64: 354-358, 1992.
86. Fan J, Wojnar MM, Theodorakis M, Lang CH. Regulation of insulin-like growth factor (IGF)-I mRNA and peptide and IGF-binding proteins by interleukin-1. *Am J Physiol* 270: R621-R629, 1996.
87. Farrell PA, Fedele MJ, Hernandez J, Fluckey JD, Miller JL, III, Lang CH, Vary TC, Kimball SR, Jefferson LS. Hypertrophy of skeletal muscle in diabetic rats in response to chronic resistance exercise. *J Appl Physiol* 87: 1075-1082, 1999.
88. Farrell PA, Fedele MJ, Vary TC, Kimball SR, Jefferson LS. Effects of intensity of acute-resistance exercise on rates of protein synthesis in moderately diabetic rats. *J Appl Physiol* 85: 2291-2297, 1998.

89. Farrell PA, Fedele MJ, Vary TC, Kimball SR, Lang CH, Jefferson LS. Regulation of protein synthesis after acute resistance exercise in diabetic rats. *Am J Physiol* 276: E721-E727, 1999.
90. Farrell PA, Garthwaite TL, Gustafson AB. Plasma adrenocorticotropin and cortisol responses to submaximal and exhaustive exercise. *J Appl Physiol* 55: 1441-1444, 1983.
91. Febbraio MA, Steensberg A, Keller C, Starkie RL, Nielsen HB, Krstrup P, Ott P, Secher NH, Pedersen BK. Glucose ingestion attenuates interleukin-6 release from contracting skeletal muscle in humans. *J Physiol* 549: 607-612, 2003.
92. Fedele MJ, Hernandez JM, Lang CH, Vary TC, Kimball SR, Jefferson LS, Farrell PA. Severe diabetes prohibits elevations in muscle protein synthesis after acute resistance exercise in rats. *J Appl Physiol* 88: 102-108, 2000.
93. Fehrenbach E. Multifarious microarray-based gene expression patterns in response to exercise. *J Appl Physiol* 102: 7-8, 2007.
94. Felig P, Cherif A, Minagerf A, Wahren J. Hypoglycemia during prolonged exercise in man. *N Engl J Med* 306: 895-900, 1982.
95. Felsing NE, Brasel JA, Cooper DM. Effect of low and high intensity exercise on circulating growth hormone in men. *J Clin Endocrinol Metab* 75: 157-162, 1992.
96. Fenster CP, Weinsier RL, Darley-Usmar VM, Patel RP. Obesity, aerobic exercise, and vascular disease: The role of oxidant stress. *Obes Res* 10: 964-968, 2002.
97. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. *Diabetes Care* 31: 289-294, 2008.
98. Foley L, Maddison R, Olds T, Ridley K. Self-report use-of-time tools for the assessment of physical activity and sedentary behaviour in young people: Systematic review. *Obes Rev* 13: 711-722, 2012.
99. Ford ES, Mokdad AH, Giles WH, Brown DW. The metabolic syndrome and antioxidant concentrations: Findings from the third national health and nutrition examination survey. *Diabetes* 52: 2346-2352, 2003.
100. Fredrickson DS, Ono K. CO₂ trapping: A new cunning trick. *J Lab Clin Med* 41: 147-151, 1958.
101. Frid A, Ostman J, Linde B. Hypoglycemia risk during exercise after intramuscular injection of insulin in thigh in IDDM. *Diabetes Care* 13: 473-477, 1990.
102. Fritzsche K, Bluher M, Schering S, Buchwalow IB, Kern M, Linke A, Oberbach A, Adams V, Punkt K. Metabolic profile and nitric oxide synthase expression of skeletal muscle fibers are altered in patients with type 1 diabetes. *Exp Clin Endocrinol Diabetes* 116: 606-613, 2008.
103. Frohnauer M, Lui K, Devlin J. Adjustment of basal Lispro insulin in CSII to minimize glycemic fluctuations caused by exercise. *Diabetes Res Clin Pract* 50(suppl 1): S80, 2000.
104. Galassetti P, Larson J, Iwanaga K, Salsberg SL, Eliakim A, Pontello A. Effect of a high-fat meal on the growth hormone response to exercise in children. *J Pediatr Endocrinol Metab* 19: 777-786, 2006.
105. Galassetti P, Mann S, Tate D, Neill RA, Wasserman DH, Davis SN. Effect of morning exercise on counterregulatory responses to subsequent, afternoon exercise. *J Appl Physiol* 91: 91-99, 2001.
106. Galassetti P, Tate D, Neill RA, Morrey S, Wasserman DH, Davis SN. Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in Type 1 Diabetes. *Diabetes* 52: 1761-1769, 2003.
107. Galassetti P, Tate D, Neill RA, Morrey S, Wasserman DH, Davis SN. Effect of sex on counterregulatory responses to exercise after antecedent hypoglycemia in type 1 diabetes. *Am J Physiol Endocrinol Metab* 287: E16-E24, 2004.
108. Galassetti P, Tate D, Neill RA, Richardson MA, Davis SN. Effect of differing antecedent hypoglycemia on counterregulatory responses to subsequent exercise in Type 1 diabetes. *Diabetes* 52: A349, 2003.
109. Galassetti P, Tate D, Neill RA, Richardson A, Leu SY, Davis SN. Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. *Am J Physiol Endocrinol Metab* 290: E1109-E1117, 2006.
110. Galassetti PR, Iwanaga K, Crisostomo M, Zaldivar FP, Larson J, Pescatello A. Inflammatory cytokine, growth factor and counterregulatory responses to exercise in children with type 1 diabetes and healthy controls. *Pediatr Diabetes* 7: 16-24, 2006.
111. Galassetti PR, Iwanaga K, Pontello AM, Zaldivar FP, Flores RL, Larson JK. Effect of prior hyperglycemia on IL-6 responses to exercise in children with type 1 diabetes. *Am J Physiol Endocrinol Metab* 290: E833-E839, 2006.
112. Galbo H. The hormonal response to exercise. *Diabetes Metab Rev* 1: 385-408, 1986.
113. Garcia SF, Virag L, Jagtap P, Szabo E, Mabley JG, Liaudet L, Marton A, Hoyt DG, Murthy KG, Salzman AL, Southan GJ, Szabo C. Diabetic endothelial dysfunction: The role of poly(ADP-ribose) polymerase activation. *Nat Med* 7: 108-113, 2001.
114. Gerich JE, Langlois M, Noacco C, Karam J, Forsham PH. Lack of a glucagon response to hypoglycemia in diabetes: Evidence for an intrinsic pancreatic alpha-cell defect. *Science* 182: 171-173, 1973.
115. Gibney J, Healy ML, Sonksen PH. The growth hormone/insulin-like growth factor-I axis in exercise and sport. *Endocr Rev* 28: 603-624, 2007.
116. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care* 19: 257-267, 1996.
117. Goldberg AL. Protein synthesis in tonic and phasic skeletal muscles. *Nature* 216: 1219-1220, 1967.
118. Goldberg AL. Protein synthesis during work-induced growth of skeletal muscle. *J Cell Biol* 36: 653-658, 1968.
119. Goldberg AL. Role of insulin in work-induced growth of skeletal muscle. *Endocrinology* 83: 1071-1073, 1968.
120. Goldfarb AH, McIntosh MK, Boyer BT. Vitamin E attenuates myocardial oxidative stress induced by DHEA in rested and exercised rats. *J Appl Physiol* 80: 486-490, 1996.
121. Goldfine AB, Fonseca V, Shoelson SE. Therapeutic approaches to target inflammation in type 2 diabetes. *Clin Chem* 57: 162-167, 2011.
122. Goldfine AB, Silver R, Aldhahi W, Cai D, Tatro E, Lee J, Shoelson SE. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clin Transl Sci* 1: 36-43, 2008.
123. Gonder-Frederick LA, Zrebiec JF, Bauchowitz AU, Ritterband LM, Magee JC, Cox DJ, Clarke WL. Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes: A field study. *Diabetes Care* 32: 1001-1006, 2009.
124. Gordin D, Forsblom C, Rönnback M, Parkkonen M, Wadén J, Hietala K, Groop PH. Acute hyperglycaemia induces an inflammatory response in young patients with type 1 diabetes. *Ann Med* 40: 627-633, 2008.
125. Gordon CS, Serino AS, Krause MP, Campbell JE, Cafarelli E, Adegoke OA, Hawke TJ, Riddell MC. Impaired growth and force production in skeletal muscles of young partially pancreatectomized rats: A model of adolescent type 1 diabetic myopathy? *PLoS One* 5: e14032, 2010.
126. Gray AB, Telford RD, Weidemann MJ. Endocrine response to intense interval exercise. *Eur J Appl Physiol Occup Physiol* 66: 366-371, 1993.
127. Greene DA, Arezzo JC, Brown MB. Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy. Zenarestat Study Group. *Neurology* 53: 580-591, 1999.
128. Grimm JJ, Ybarra J, Berne C, Muchnick S, Golay A. A new table for prevention of hypoglycaemia during physical activity in type 1 diabetic patients. *Diabetes Metab* 30: 465-470, 2004.
129. Guelfi KJ, Ratnam N, Smythe GA, Jones TW, Fournier PA. 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, 2007.
130. Gusso S, Hofman P, Lalande S, Cutfield W, Robinson E, Baldi JC. Impaired stroke volume and aerobic capacity in female adolescents with type 1 and type 2 diabetes mellitus. *Diabetologia* 51: 1317-1320, 2008.
131. Hagberg JM, Seals DR, Yerg JE, Gavin J, Gingerich R, Premachandra B, Holloszy JO. Metabolic responses to exercise in young and older athletes and sedentary men. *J Appl Physiol* 65: 900-908, 1988.
132. Hajdich E, Alessi DR, Hemmings BA, Hundal HS. Constitutive activation of protein kinase B alpha by membrane targeting promotes glucose and system A amino acid transport, protein synthesis, and inactivation of glycogen synthase kinase 3 in L6 muscle cells. *Diabetes* 47: 1006-1013, 1998.
133. Hakkinen K, Pakarinen A. Acute hormonal responses to two different fatiguing heavy-resistance protocols in male athletes. *J Appl Physiol* 74: 882-887, 1993.
134. Hakkinen K, Pakarinen A, Alen M, Kauhanen H, Komi PV. Neuromuscular and hormonal responses in elite athletes to two successive strength training sessions in one day. *Eur J Appl Physiol Occup Physiol* 57: 133-139, 1988.
135. Hamilton J, Daneman D. Deteriorating diabetes control during adolescence: Physiological or psychosocial? *J Pediatr Endocrinol Metab* 15: 115-126, 2002.
136. Hargreaves M, Angus D, Howlett K, Conus NM, Febbraio M. Effect of heat stress on glucose kinetics during exercise. *J Appl Physiol* 81: 1594-1597, 1996.
137. Harmer AR, Chisholm DJ, McKenna MJ, Hunter SK, Ruell PA, Naylor JM, Maxwell LJ, Flack JR. Sprint training increases muscle oxidative metabolism during high-intensity exercise in patients with type 1 diabetes. *Diabetes Care* 31: 2097-2102, 2008.
138. Harrell JS, McMurray RG, Baggett CD, Pennell ML, Pearce PF, Bangdiwala SI. Energy costs of physical activities in children and adolescents. *Med Sci Sports Exerc* 37: 329-336, 2005.
139. Hartley LH, Mason JW, Hogan RP, Jones LG, Kotchen TA, Mougey EH, Wherry FE, Pennington LL, Ricketts PT. Multiple hormonal responses to prolonged exercise in relation to physical training. *J Appl Physiol* 33: 607-610, 1972.
140. Hawkins M, Barzilai N, Liu R, Hu M, Chen W, Rossetti L. Role of the glucosamine pathway in fat-induced insulin resistance. *J Clin Invest* 99: 2173-2182, 1997.

141. Hayashi T, Wojtaszewski JF, Goodyear LJ. Exercise regulation of glucose transport in skeletal muscle. *Am J Physiol* 273: E1039-E1051, 1997.
142. Hebert SL, Nair KS. Protein and energy metabolism in type 1 diabetes. *Clin Nutr* 29: 13-17, 2010.
143. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after one episode of hypoglycemia in nondiabetic humans. *Diabetes* 40: 223-226, 1991.
144. Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: A multicenter study of 23,251 patients. *Diabetes Care* 30: 2098-2100, 2007.
145. Heyman E, Briard D, Dekerdanet M, Gratas-Delamarche A, Delamarche P. Accuracy of physical working capacity 170 to estimate aerobic fitness in prepubertal diabetic boys and in 2 insulin dose conditions. *J Sports Med Phys Fitness* 46: 315-321, 2006.
146. Hirsh IB, Marker JC, Smith LJ, Spina RJ, Parvin CA, Holloszy J, Cryer PE. Insulin and glucagon in prevention of hypoglycemia during exercise in humans. *Am J Physiol* 260: E695-E704, 2001.
147. Hoelzer DR, Dalsky GP, Clutter WE, Shah SD, Holloszy JO, Cryer PE. Glucoregulation during exercise: Hypoglycemia is prevented by redundant glucoregulatory systems, sympathochromaffin activation, and changes in islet hormone secretion. *J Clin Invest* 77: 212-221, 1986.
148. Hoffman RP, Singer-Granick C, Drash AL, Becker DJ. Plasma catecholamine responses to hypoglycemia in children and adolescents with IDDM. *Diabetes Care* 14: 81-88, 1991.
149. Holt RI, Simpson HL, Sonksen PH. The role of the growth hormone-insulin-like growth factor axis in glucose homeostasis. *Diabet Med* 20: 3-15, 2003.
150. Holt RI, Webb E, Pentecost C, Sonksen PH. Aging and physical fitness are more important than obesity in determining exercise-induced generation of GH. *J Clin Endocrinol Metab* 86: 5715-5720, 2001.
151. Howlett K, Febbraio M, Hargreaves M. Glucose production during strenuous exercise in man: Role of epinephrine. *Am J Physiol* 276: E1130-E1135, 1999.
152. Hubner-Wozniak E, Panczenko-Kresowka B, Lerczak K, Posnik J. Effects of graded treadmill exercise on the activity of blood antioxidant enzymes, lipid peroxides and nonenzymatic anti-oxidants in long-distance skiers. *Biol Sport* 11: 217-226, 1994.
153. Hughes BC, White RD. *Exercise Testing for Primary Care and Sports Medicine*. New York: Springer-Verlag, 2005, pp. 55-77.
154. Husain K, Somani SM, Boley TM, Hazelrigg SR. Interaction of physical training and chronic nitroglycerin treatment on blood pressure and plasma oxidant/antioxidant systems in rats. *Mol Cell Biochem* 247: 37-44, 2003.
155. Huttunen NP, Kaar ML, Knip M, Mustonen A, Puukka R, Akerblom HK. Physical fitness of children and adolescents with insulin-dependent diabetes mellitus. *Ann Clin Res* 16: 1-5, 1984.
156. Iscoe KE, Campbell JE, Jamnik V, Perkins BA, Riddell MC. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: Spinning with a continuous glucose monitoring system. *Diabetes Technol Ther* 8: 627-635, 2006.
157. Iscoe KE, Corcoran M, Riddell MC. High rates of nocturnal hypoglycemia in a unique sports camp for athletes with type 1 diabetes: Lessons learned from continuous glucose monitoring. *Can J Diabet* 32: 182-189, 2008.
158. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: Effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabet Med* 28: 824-832, 2011.
159. Jackson MJ. Muscle damage during exercise: Possible role of free radicals and protective effect of vitamin E. *Proc Nutr Soc* 46: 77-80, 1987.
160. Jakobsen J, Reske-Nielsen E. Diffuse muscle fiber atrophy in newly diagnosed diabetes. *Clin Neuropathol* 5: 73-77, 1986.
161. Jenni S, Oetliker C, Allemann S, Ith M, Tappy L, Wuertli S, Egger A, Boesch C, Schneiter P, Diem P, Christ E, Stettler C. Fuel metabolism during exercise in euglycaemia and hyperglycaemia in patients with type 1 diabetes mellitus—a prospective single-blinded randomised crossover trial. *Diabetologia* 51: 1457-1465, 2008.
162. Jenni S, Wuest S, Konrad D, Stettler C. Response of interleukin-6 during euglycaemic and hyperglycaemic exercise in patients with type 1 diabetes mellitus. *Diabetes Res Clin Pract* 89: e27-e29, 2010.
163. Jimenez CC, Corcoran MH, Crawley JT, Guyton HW, Peer KS, Philbin RD, Riddell MC. National athletic trainers' association position statement: Management of the athlete with type 1 diabetes mellitus. *J Athl Train* 42: 536-545, 2007.
164. Kaji H, Asanuma Y, Ide H, Saito N, Hisamura M, Murao M, Yoshida T, Takahashi K. The auto-brewery syndrome—the repeated attacks of alcoholic intoxication due to the overgrowth of *Candida* (albicans) in the gastrointestinal tract. *Mater Med Pol* 8: 429-435, 1976.
165. Kanaley JA, Weatherup-Dentes MM, Jaynes EB, Hartman ML. Obesity attenuates the growth hormone response to exercise. *J Clin Endocrinol Metab* 84: 3156-3161, 1999.
166. Kanaley JA, Weltman JY, Pieper KS, Weltman A, Hartman ML. Cortisol and growth hormone responses to exercise at different times of day. *J Clin Endocrinol Metab* 86: 2881-2889, 2001.
167. Karagiorgos A, Garcia JF, Brooks GA. Growth hormone response to continuous and intermittent exercise. *Med Sci Sports* 11: 302-307, 1979.
168. Kasama T, Miwa Y, Izozaki T, Odai T, Adachi M, Kunkel SL. Neutrophil-derived cytokines: Potential therapeutic targets in inflammation. *Curr Drug Targets Inflamm Allergy* 4: 273-279, 2005.
169. Kaufman FR. The role of the continuous glucose monitoring system in pediatric patients. *Diabetes Technol Ther* 2: S49-S52, 2000.
170. Kaufman FR, Austin J, Neinstein A, Jeng L, Halvorson M, Devoe DJ, Pitukcheewanont P. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. *J Pediatr* 141: 625-630, 2002.
171. Kelly D, Hamilton JK, Riddell MC. Blood glucose levels and performance in a sports camp for adolescents with type 1 diabetes mellitus: A field study. *Int J Pediatr* 1-8, 2010.
172. Kim JK, Fillmore JJ, Sunshine MJ, Albrecht B, Higashimori T, Kim DW, Liu ZX, Soos TJ, Cline GW, O'Brien WR, Littman DR, Shulman GI. PKC- θ knockout mice are protected from fat-induced insulin resistance. *J Clin Invest* 114: 823-827, 2004.
173. Kimball SR, Farrell PA, Jefferson LS. Invited Review: Role of insulin in translational control of protein synthesis in skeletal muscle by amino acids or exercise. *J Appl Physiol* 93: 1168-1180, 2002.
174. Kirstein M, Aston C, Hintz R, Vlassara H. Receptor-specific induction of insulin-like growth factor I in human monocytes by advanced glycosylation end product-modified proteins. *J Clin Invest* 90: 439-446, 1992.
175. Kivela R, Silvennoinen M, Touva AM, Lehti TM, Kainulainen H, Vihko V. Effects of experimental type 1 diabetes and exercise training on angiogenic gene expression and capillarization in skeletal muscle. *FASEB J* 20: 1570-1572, 2006.
176. Klueber KM, Feczko JD. Ultrastructural, histochemical, and morphometric analysis of skeletal muscle in a murine model of type 1 diabetes. *Anat Rec* 239: 18-34, 1994.
177. Kolm-Litty V, Sauer U, Nerlich A, Lehmann R, Schleicher ED. High glucose-induced transforming growth factor beta1 production is mediated by the hexosamine pathway in porcine glomerular mesangial cells. *J Clin Invest* 101: 160-169, 1998.
178. Komatsu WR, Barros Neto TL, Chacra AR, Dib SA. Aerobic exercise capacity and pulmonary function in athletes with and without type 1 diabetes. *Diabetes Care* 33: 2555-2557, 2010.
179. Komatsu WR, Gabbay MA, Castro ML, Saraiva GL, Chacra AR, de Barros Neto TL, Dib SA. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. *Pediatr Diabetes* 6: 145-149, 2005.
180. Kraemer WJ, Fleck SJ, Dziados JE, Harman EA, Marchitelli LJ, Gordon SE, Mello R, Frykman PN, Koziris LP, Triplett NT. Changes in hormonal concentrations after different heavy-resistance exercise protocols in women. *J Appl Physiol* 75: 594-604, 1993.
181. Kraemer WJ, Gordon SE, Fleck SJ, Marchitelli LJ, Mello R, Dziados JE, Friedl K, Harman E, Maresh C, Fry AC. Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. *Int J Sports Med* 12: 228-235, 1991.
182. Kraemer WJ, Marchitelli L, Gordon SE, Harman E, Dziados JE, Mello R, Frykman P, McCurry D, Fleck SJ. Hormonal and growth factor responses to heavy resistance exercise protocols. *J Appl Physiol* 69: 1442-1450, 1990.
183. Krause MP, Riddell MC, Gordon CS, Imam SA, Cafarelli E, Hawke TJ. Diabetic myopathy differs between Ins2Akita $^{+/-}$ and streptozotocin-induced Type 1 diabetic models. *J Appl Physiol* 106: 1650-1659, 2009.
184. Krause MP, Riddell MC, Hawke TJ. Effects of Type 1 Diabetes Mellitus on Skeletal Muscle: Clinical Observations and Physiological Mechanisms. *Pediatr Diabetes* 2010.
185. Larsen S, Brynjolf I, Birch K, Munck O, Sestoft L. The effect of continuous subcutaneous insulin infusion on cardiac performance during exercise in insulin-dependent diabetics. *Scand J Clin Lab Invest* 44: 683-691, 1984.
186. Larsson Y, Persson B, Sterky G, Thoren C. Functional adaptation to rigorous training and exercise in diabetic and nondiabetic adolescents. *J Appl Physiol* 19: 629-635, 1964.
187. Larsson YA, Sterky GC, Ekengren ke, Moller TG. Physical fitness and the influence of training in diabetic adolescent girls. *Diabetes March-April*; 11: 109-117, 1962.
188. Lassarre C, Girard F, Durand J, Raynaud J. Kinetics of human growth hormone during submaximal exercise. *J Appl Physiol* 37: 826-830, 1974.
189. Lee AY, Chung SS. Contributions of polyol pathway to oxidative stress in diabetic cataract. *FASEB J* 13: 23-30, 1999.

190. Lehmann R, Kaplan V, Bingisser R, Bloch KE, Spinass GA. Impact of physical activity on cardiovascular risk factors in IDDM. *Diabetes Care* 20: 1603-1611, 1997.
191. Locard E, David L, Ruitton A, de Chabanolle F, Francois R. Studies of growth hormone secretion in juvenile diabetes. *Horm Res* 11: 29-40, 1979.
192. Luger A, Watschinger B, Deuster P, Svoboda T, Clodi M, Chrousos GP. Plasma growth hormone and prolactin responses to graded levels of acute exercise and to a lactate infusion. *Neuroendocrinology* 56: 112-117, 1992.
193. Lumb AN, Gallen IW. Diabetes management for intense exercise. *Curr Opin Endocrinol Diabetes Obes* 16: 150-155, 2009.
194. Luzi L, Castellino P, Simonson DC, Petrides AS, DeFronzo RA. Leucine metabolism in IDDM. Role of insulin and substrate availability. *Diabetes* 39: 38-48, 1990.
195. Magee MF, Bhatt BA. Management of decompensated diabetes. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. *Crit Care Clin* 17: 75-106, 2001.
196. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: Implications for diabetes. *Diabetes* 51(Suppl 1): S271-S283, 2002.
197. Marshall S, Bacote V, Traxinger RR. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Role of hexosamine biosynthesis in the induction of insulin resistance. *J Biol Chem* 266: 4706-4712, 1991.
198. Marzban L, Bhanot S, McNeill JH. In vivo effects of insulin and bis(maltolato)oxovanadium (IV) on PKB activity in the skeletal muscle and liver of diabetic rats. *Mol Cell Biochem* 223: 147-157, 2001.
199. McCrimmon RJ, Evans ML, Jacob RJ, Fan X, Zhu Y, Shulman GI, Sherwin RS. AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. *Am J Physiol Endocrinol Metab* 283: E1076-E1083, 2002.
200. McKewen MW, Rehner NJ, Cox C, Mann J. Glycaemic control, muscle glycogen and exercise performance in IDDM athletes on diets of varying carbohydrate content. *Int J Sports Med* 20: 349-353, 1999.
201. McMahon SK, Ferreira LD, Ratnam N, Davey RJ, Youngs LM, Davis EA, Fournier PA, Jones TW. 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, 2007.
202. Mena P, Maynar M, Gutierrez JM, Maynar J, Timon J, Campillo JE. Erythrocyte free radical scavenger enzymes in bicycle professional racers. Adaptation to training. *Int J Sports Med* 12: 563-566, 1991.
203. Mitchell TH, Abraham G, Schiffrin A, Leiter LA, Marliss EB. Hyperglycemia after intense exercise in IDDM subjects during continuous subcutaneous insulin infusion. *Diabetes Care* 11: 311-317, 1988.
204. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 329: 1677-1683, 1993.
205. Miyazaki H, Oh-ishi S, Ookawara T, Kizaki T, Toshinai K, Ha S, Haga S, Ji LL, Ohno H. Strenuous endurance training in humans reduces oxidative stress following exhausting exercise. *Eur J Appl Physiol* 84: 1-6, 2001.
206. Mohamed-Ali V, Armstrong L, Clarke D, Bolton CH, Pinkney JH. Evidence for the regulation of levels of plasma adhesion molecules by proinflammatory cytokines and their soluble receptors in type 1 diabetes. *J Intern Med* 250: 415-421, 2001.
207. Moore K, Vizzard N, Coleman C, McMahon J, Hayes R, Thompson CJ. Extreme altitude mountaineering and Type 1 diabetes; the Diabetes Federation of Ireland Kilimanjaro Expedition. *Diabet Med* 18: 749-755, 2001.
208. Mora S, Gilsanz V. Establishment of peak bone mass. *Endocrinol Metab Clin North Am* 32: 39-63, 2003.
209. Moy CS, Songer TJ, LaPorte RE, Dorman JS, Kriska AM, Orchard TJ, Becker DJ, Drash AL. Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol* 137: 74-81, 1993.
210. Mylona-Karayanni C, Gourgoutis D, Bossios A, Kamper EF. Oxidative stress and adhesion molecules in children with type 1 diabetes mellitus: A possible link. *Pediatr Diabetes* 7: 51-59, 2006.
211. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J. Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients. *J Clin Invest* 95: 2926-2937, 1995.
212. Nair KS, Ford GC, Halliday D. Effect of intravenous insulin treatment on in vivo whole body leucine kinetics and oxygen consumption in insulin-deprived type I diabetic patients. *Metabolism* 36: 491-495, 1987.
213. Nair KS, Garrow JS, Ford C, Mahler RF, Halliday D. Effect of poor diabetic control and obesity on whole body protein metabolism in man. *Diabetologia* 25: 400-403, 1983.
214. Nair KS, Halliday D, Matthews DE, Welle SL. Hyperglucagonemia during insulin deficiency accelerates protein catabolism. *Am J Physiol* 253: E208-E213, 1987.
215. Nareika A, Im YB, Game BA, Slate EH, Sanders JJ, London SD, Lopes-Virella MF, Huang Y. High glucose enhances lipopolysaccharide-stimulated CD14 expression in U937 mononuclear cells by increasing nuclear factor kappaB and AP-1 activities. *J Endocrinol* 196: 45-55, 2008.
216. Naveri H. Blood hormone and metabolite levels during graded cycle ergometer exercise. *Scand J Clin Lab Invest* 45: 599-603, 1985.
217. Naveri H, Kuoppasalmi K, Harkonen M. Metabolic and hormonal changes in moderate and intense long-term running exercises. *Int J Sports Med* 6: 276-281, 1985.
218. Nemet D, Hong S, Mills PJ, Ziegler MG, Hill M, Cooper DM. Sysemic vs. local cytokine and leukocyte responses to unilateral wrist flexion exercise. *J Appl Physiol* 93: 546-554, 2002.
219. Nemet D, Oh Y, Kim H-S, Hill MA, Cooper DM. The effect of intense exercise on inflammatory cytokines and growth mediators in adolescent boys. *Pediatrics* 110: 681-689, 2002.
220. Nicolls MR, Haskins K, Flores SC. Oxidant stress, immune dysregulation, and vascular function in type I diabetes. *Antiox Redox Sign* 9: 879-889, 2007.
221. Nieman DC, Miller AR, Henson DA, Warren BJ, Gusewitch G, Johnson RL, Davis JM, Butterworth DE, Herring JL, Nehlsen-Cannarella SL. Effect of high- versus moderate-intensity exercise on lymphocyte subpopulations and proliferative response. *Int J Sports Med* 15: 199-206, 1994.
222. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giordino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 404: 787-790, 2000.
223. Nugent A-M, Steele IC, Al-Modaris F, Valley S, Moore A, Campbell NPS, Bell PM, Buchanan KD, Trimble ER, Nicholls DP. Exercise responses in patients with IDDM. *Diabetes Care* 20: 1814-1821, 1997.
224. Orchard TJ, Costacou T. When are type 1 diabetic patients at risk for cardiovascular disease? *Curr Diab Rep* 10: 48-54, 2010.
225. Pain VM, Albertse EC, Garlick PJ. Protein metabolism in skeletal muscle, diaphragm, and heart of diabetic rats. *Am J Physiol* 245: E604-E610, 1983.
226. Pain VM, Garlick PJ. Effect of streptozotocin diabetes and insulin treatment on the rate of protein synthesis in tissues of the rat in vivo. *J Biol Chem* 249: 4510-4514, 1974.
227. Pavan P, Sarto P, Merlo L, Casara D, Ponchia A, Biasin R, Noventa D, Avogaro A. Metabolic and cardiovascular parameters in type 1 diabetes at extreme altitude. *Med Sci Sports Exerc* 36: 1283-1289, 2004.
228. Pavan P, Sarto P, Merlo L, Casara D, Ponchia A, Biasin R, Noventa D, Avogaro A. Extreme altitude mountaineering and type 1 diabetes: The Cho Oyu alpinists in Alta Quota expedition. *Diabetes Care* 26: 3196-3197, 2003.
229. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, Febbraio M, Saltin B. Searching for the exercise factor: Is IL-6 a candidate? *J Muscle Res Cell Motil* 24: 113-119, 2003.
230. Perez CJ, Nemet D, Mills PJ, Scheet TP, Ziegler MG, Cooper DM. Effects of laboratory versus field exercise on leukocyte subsets and cell adhesion molecule expression in children. *Eur J Appl Physiol* 86: 34-39, 2001.
231. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 98: 1154-1162, 2005.
232. Petersen KF, Price TB, Bergeron R. Regulation of net hepatic glycogenolysis and gluconeogenesis during exercise: Impact of type 1 diabetes. *J Clin Endocrinol Metab* 89: 4656-4664, 2004.
233. Pieper GM, Riaz uH. Activation of nuclear factor-kappaB in cultured endothelial cells by increased glucose concentration: Prevention by calphostin C. *J Cardiovasc Pharmacol* 30: 528-532, 1997.
234. Poehlman ET, Copeland KC. Influence of physical activity on insulin-like growth factor-I in healthy younger and older men. *J Clin Endocrinol Metab* 71: 1468-1473, 1990.
235. Poortmans JR, Saerens P, Edelman R, Vertongen F, Dorchy H. Influence of the degree of metabolic control on physical fitness in type I diabetic adolescents. *Int J Sports Med* 7: 232-235, 1986.
236. Pritzlaff CJ, Wideman L, Weltman JY, Abbott RD, Gutgesell ME, Hartman ML, Veldhuis JD, Weltman A. Impact of acute exercise intensity on pulsatile growth hormone release in men. *J Appl Physiol* 87: 498-504, 1999.
237. Pyke S, Lew H, Quintanilha A. Severe depletion in liver glutathione during physical exercise. *Biochem Biophys Res Commun* 139: 926-931, 1986.
238. Rabinovich A. An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus. *Diabetes Metab Rev* 14: 129-151, 1998.
239. Radom-Aizik S, Zaldivar F, Jr., Leu SY, Galassetti P, Cooper DM. Effects of 30 min of aerobic exercise on gene expression in human neutrophils. *J Appl Physiol* 104: 236-243, 2008.

240. Radom-Aizik S, Zaldivar F, Leu SY, Cooper DM. Brief bout of exercise alters gene expression in peripheral blood mononuclear cells of early- and late-pubertal males. *Pediatr Res* Apr;65(4): 447-452, 2009.
241. Ramalho AC, de Lourdes LM, Nunes F, Cambui Z, Barbosa C, Andrade A, Viana A, Martins M, Abrantes V, Aragao C, Temistocles M. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. *Diabetes Res Clin Pract* 72: 271-276, 2006.
242. Ramasamy R, Vannucci SJ, Yan SS, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: A common thread in aging, diabetes, neurodegeneration, and inflammation. *Glycobiology* 15: 16R-28R, 2005.
243. Ramires PR, Forjaz CL, Silva ME. Exercise tolerance is lower in type 1 diabetics compared with normal young men. *Metabolism* 42: 191-195, 1993.
244. Rask-Madsen C, King GL. Proatherosclerotic mechanisms involving protein kinase C in diabetes and insulin resistance. *Arterioscler Thromb Vasc Biol* 25: 487-496, 2005.
245. Raynaud J, Capderou A, Martineaud JP, Bordachar J, Durand J. Inter-subject viability in growth hormone time course during different types of work. *J Appl Physiol* 55: 1682-1687, 1983.
246. Raynaud J, Drouet L, Martineaud JP, Bordachar J, Coudert J, Durand J. Time course of plasma growth hormone during exercise in humans at altitude. *J Appl Physiol* 50: 229-233, 1981.
247. Reddigan JI, Riddell MC, Kuk JL. The joint association of physical activity and glycaemic control in predicting cardiovascular death and all-cause mortality in the US population. *Diabetologia* 55: 632-635, 2012.
248. Reske-Nielsen E, Harmsen A, Vorre P. Ultrastructure of muscle biopsies in recent, short-term and long-term juvenile diabetes. *Acta Neurol Scand* 55: 345-362, 1977.
249. Richter EA. Glucose utilization. In: Rowell LB, Shepherd JT, editors. *Handbook of Physiology*. Oxford, UK: Oxford University Press, 1996, pp. 912-951.
250. Riddell MC, Perkins BA. Type 1 diabetes and exercise-part I: Applications of exercise physiology to patient management during vigorous activity. *Can J Diabet* 30: 63-71, 2006.
251. Riddell M, Perkins BA. Exercise and glucose metabolism in persons with diabetes mellitus: Perspectives on the role for continuous glucose monitoring. *J Diabetes Sci Technol* 3: 914-923, 2009.
252. Riddell MC, Bar-Or O, Ayub BV, Calvert RE, Heil BV. Glucose ingestion matched with total carbohydrate utilization attenuates hypoglycemia during exercise in adolescents with IDDM. *Int J Sports Nutr* 9: 24-34, 1999.
253. Riddell MC, Bar-Or O, Gerstein HC, Heigenhauser GJ. Perceived exertion with glucose ingestion in adolescent males with IDDM. *Med Sci Sports Exerc* 32: 167-173, 2000.
254. Riddell MC, Burr J. Evidence-based risk assessment and recommendations for physical activity clearance: Diabetes mellitus and related comorbidities. This paper is one of a selection of papers published in this Special Issue, entitled Evidence-based risk assessment and recommendations for physical activity clearance, and has undergone the Journal's usual peer review process. *Appl Physiol Nutr Metab* 36(Suppl 1): S154-S189, 2011.
255. Riddell MC, Iscoe KE. Physical activity, sport, and pediatric diabetes. *Pediatr Diabetes* 7: 60-70, 2006.
256. Riddell M, Ruderman NB, Berger M, Vranic M. Exercise Physiology and Diabetes: From Antiquity to the Age of Exercise Sciences. In: Ruderman NB, Devlin JT, Schneider S, Kriska A, editors. *Handbook of Exercise and Diabetes*. Alexandria, VA: American Diabetes Association, 2002, pp. 3-15.
257. Rizza RA, Cryer PE, Gerich JE. Role of glucagon, catecholamines, and growth hormone in human glucose counterregulation. *J Clin Invest* 64: 62-71, 1979.
258. Roberts L, Jones TW, Fournier PA. Exercise training and glycaemic control in adolescents with poorly controlled type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 15: 621-627, 2002.
259. Robertson K, Adolfsson P, Schneider G, Hanas R, Riddell MC. Exercise in children and adolescents with diabetes. *Pediatr Diabetes* 10: 154-168, 2009.
260. Robitaille M, Dube MC, Weisnagel SJ, Prud'homme D, Massicotte D, Peronnet F, Lavoie C. Substrate source utilization during moderate intensity exercise with glucose ingestion in Type 1 diabetic patients. *J Appl Physiol* 103: 119-124, 2007.
261. Rosa JS, Flores RL, Oliver SR, Pontello AM, Zaldivar FP, Galassetti PR. Resting and exercise-induced IL-6 levels in children with Type 1 diabetes reflect hyperglycemic profiles during the previous 3 days. *J Appl Physiol* 108: 334-342, 2010.
262. Rosa JS, Flores RL, Oliver SR, Pontello AM, Zaldivar FP, Galassetti PR. Sustained IL-1 α , IL-4, and IL-6 elevations following correction of hyperglycemia in children with type 1 diabetes mellitus. *Pediatr Diabetes* 9: 9-16, 2008.
263. Rosa JS, Oliver SR, Flores RL, Graf SC, Pontello AM, Lbardolaza M, Zaldivar FP, Galassetti PR. Kinetic profiles of 18 systemic pro- and anti-inflammatory mediators during and following exercise in children. *J Pediatr Endocrinol Metab* 20: 1293-1305, 2007.
264. Rosa JS, Oliver SR, Mitsuhashi M, Flores RL, Pontello AM, Zaldivar FP, Galassetti PR. Altered kinetics of interleukin-6 and other inflammatory mediators during exercise in children with type 1 diabetes. *J Invest Med* 56: 701-713, 2008.
265. Rosen P, Nawroth PP, King G, Moller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: A summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes Metab Res Rev* 17: 189-212, 2001.
266. Ross LA, Warren RE, Kelnar CJ, Frier BM. Pubertal stage and hypoglycaemia counterregulation in type 1 diabetes. *Arch Dis Child* 90: 190-194, 2005.
267. Roth J, Glick SM, Yalow RS and Berson SA. Secretion of human growth hormone: Physiologic and experimental modification. *Metabolism* 12: 577-579, 1963.
268. Roubenoff R. Sarcopenia: Effects on body composition and function. *J Gerontol A Biol Sci Med Sci* 58: 1012-1017, 2003.
269. Sampson MJ, Gopaul N, Davies IR, Hughes DA, Carrier MJ. Plasma F2-isoprostanes - direct evidence of increased free radical damage during acute hyperglycemia in type 2 diabetes. *Diabetes Care* 25: 537-541, 2002.
270. Sandoval DA, Guy DL, Richardson MA, Ertl AC, Davis SN. Effects of low and moderate antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes. *Diabetes* 53: 1798-1806, 2004.
271. Sane T, Helve E, Pelkonen R, Koivisto VA. The adjustment of diet and insulin dose during long-term endurance exercise in type 1 (insulin-dependent) diabetic men. *Diabetologia* 31: 35-40, 1988.
272. Schmidt AM, Hori O, Chen JX, Li JF, Crandall J, Zhang J, Cao R, Yan SD, Brett J, Stern D. Advanced glycation endproducts interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. A potential mechanism for the accelerated vasculopathy of diabetes. *J Clin Invest* 96: 1395-1403, 1995.
273. Schwindt CD, Zaldivar F, Wilson L, Leu SY, Wang-Rodriguez J, Mills PJ, Cooper DM. Do circulating leucocytes and lymphocyte subtypes increase in response to brief exercise in children with and without asthma? *Br J Sports Med* 41: 34-40, 2007.
274. Segel SA, Fanelli CG, Dence CS, Markham J, Videen TO, Paramore DS, Powers WJ, Cryer PE. Blood-to-brain glucose transport, cerebral glucose metabolism, and cerebral blood flow are not increased after hypoglycemia. *Diabetes* 50: 1911-1917, 2001.
275. Sen CK. Oxidants and antioxidants in exercise. *J Appl Physiol* 79: 675-686, 1995.
276. Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. *Am J Clin Nutr* 72: 653S-669S, 2000.
277. Serino AS, Adegoke OA, Zargar S, Gordon CS, Szigiato AA, Hawke TJ, Riddell MC. Voluntary physical activity and leucine correct impairments in muscle protein synthesis in partially pancreatectomised rats. *Diabetologia* 54: 3111-3120, 2011.
278. Severinsen K, Obel A, Jakobsen J, Andersen H. Atrophy of foot muscles in diabetic patients can be detected with ultrasonography. *Diabetes Care* 30: 3053-3057, 2007.
279. Shen WH, Boyle DW, Wisniewski P, Bade A, Liechty EA. Insulin and IGF-I stimulate the formation of the eukaryotic initiation factor 4F complex and protein synthesis in C2C12 myotubes independent of availability of external amino acids. *J Endocrinol* 185: 275-289, 2005.
280. Shephard RJ. Cytokine responses to physical activity, with particular reference to IL-6: Sources, actions, and clinical implications. *Crit Rev Immunol* 22: 165-182, 2002.
281. Sigal R, Kenny G, Oh P, Perkins BA, Plotnikoff RC, Prud'homme D, Riddell MC. Physical activity and diabetes. Canadian diabetes clinical practice guidelines expert committee. Canadian diabetes association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabet* 32: S37-S39, 2008.
282. Sigal RJ, Fisher S, Halter JB, Vranic M, Marliss EB. The roles of catecholamines in glucoregulation in intense exercise as defined by the islet clamp technique. *Diabetes* 45: 148-156, 1996.
283. Sigal RJ, Fisher SJ, Manzon A, Morais JA, Halter JB, Vranic M, Marliss EB. Glucoregulation during and after antense exercise: Effects of α -adrenergic blockade. *Metab Clin Exp* 49: 386-394, 2000.
284. Sigal RJ, Purdon C, Fisher SJ, Halter JB, Vranic M, Marliss EB. Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 79: 1049-1057, 1994.
285. Simsek M, Naziroglu M, Erdinc A. Moderate exercise with a dietary vitamin C and e combination protects against streptozotocin-induced

- oxidative damage to the kidney and lens in pregnant rats. *Exp Clin Endocrinol Diabetes* 113: 53-59, 2005.
286. Skatrud-Mickelson M, Benson J, Hannon JC, Askew EW. A comparison of subjective and objective measures of physical exertion. *J Sports Sci* 29: 1635-1644, 2011.
 287. Skolnik EY, Yang Z, Makita Z, Radoff S, Kirstein M, Vlassara H. Human and rat mesangial cell receptors for glucose-modified proteins: Potential role in kidney tissue remodelling and diabetic nephropathy. *J Exp Med* 174: 931-939, 1991.
 288. Snegovskaya V, Viru A. Elevation of cortisol and growth hormone levels in the course of further improvement of performance capacity in trained rowers. *Int J Sports Med* 14: 202-206, 1993.
 289. Somwar R, Sumitani S, Taha C, Sweeney G, Klip A. Temporal activation of p70 S6 kinase and Akt1 by insulin: PI 3-kinase-dependent and -independent mechanisms. *Am J Physiol* 275: E618-E625, 1998.
 290. Somwar R, Sweeney G, Ramlal T, Klip A. Stimulation of glucose and amino acid transport and activation of the insulin signaling pathways by insulin lispro in L6 skeletal muscle cells. *Clin Ther* 20: 125-140, 1998.
 291. Stettler C, Jenni S, Allemann S, Steiner R, Hoppeler H, Trepp R, Christ ER, Zwahlen M, Diem P. Exercise capacity in subjects with type 1 diabetes mellitus in eu- and hyperglycaemia. *Diabetes Metab Res Rev* 22: 300-306, 2006.
 292. Stitt AW, He C, Friedman S, Scher L, Rossi P, Ong L, Founds H, Li YM, Bucala R, Vlassara H. Elevated AGE-modified ApoB in sera of euglycemic, normolipidemic patients with atherosclerosis: Relationship to tissue AGEs. *Mol Med* 3: 617-627, 1997.
 293. Surridge DH, Erdahl DL, Lawson JS, Donald MW, Monga TN, Bird CE, Letemendia FJ. Psychiatric aspects of diabetes mellitus. *Br J Psychiatry* 145: 269-276, 1984.
 294. Sutton J, Lazarus L. Growth hormone in exercise: Comparison of physiological and pharmacological stimuli. *J Appl Physiol* 41: 523-527, 1976.
 295. Sutton JR. Hormonal and metabolic responses to exercise in subject of high and low work capacities. *Med Sci Sports* 10: 1-6, 1978.
 296. Tansey MJ, Tsalikian E, Beck RW, Mauras N, Buckingham BA, Weinzimer SA, Janz KF, Kollman C, Xing D, Ruedy KJ, Steffes MW, Borland TM, Singh RJ, Tamborlane WV. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care* 29: 20-25, 2006.
 297. Tapanainen P, Kaar ML, Leppaluoto J, Huttunen NP, Knip M. Normal stimulated growth hormone secretion but low peripheral levels of insulin-like growth factor I in prepubertal children with insulin-dependent diabetes mellitus. *Acta Paediatr* 84: 646-650, 1995.
 298. Targher G, Zenari L, Bertolini L, Muggeo M, Zoppini G. Elevated levels of interleukin-6 in young adults with type 1 diabetes without clinical evidence of microvascular and macrovascular complications. *Diabetes Care* 24: 956-957, 2001.
 299. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977-986, 1993.
 300. Thirunavukkarasu V, Balakrishnan SD, Ravichandran MK, Anuradha CV. Influence of 6-week exercise training on erythrocyte and liver antioxidant defense in hyperinsulinemic rats. *Comp Biochem Physiol Part C* 135: 31-37, 2003.
 301. Tiidus PM, Pushkarenko J, Houston ME. Lack of antioxidant adaptation to short-term aerobic training in human muscle. *Am J Physiol* 271: R832-R836, 1996.
 302. Tirakitsountorn P, Nussbaum E, Moser C, Hill M, Cooper DM. Fitness, acute exercise, and anabolic and catabolic mediators in cystic fibrosis. *Am J Resp Crit Care Med* 164: 1432-1437, 2001.
 303. Tsalikian E, Mauras N, Beck RW, Tamborlane WV, Janz KF, Chase HP, Wysocki T, Weinzimer SA, Buckingham BA, Kollman C, Xing D, Ruedy KJ. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. *J Pediatr* 147: 528-534, 2005.
 304. Tuominen JA, Karonen SL, Melamies L, Bolli G, Koivisto VA. Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue. *Diabetologia* 38: 106-111, 1995.
 305. Umpleby AM, Boroujerdi MA, Brown PM, Carson ER, Sonksen PH. The effect of metabolic control on leucine metabolism in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 29: 131-141, 1986.
 306. Valerio G, Spagnuolo MI, Lombardi F, Spadaro R, Siano M, Franzese A. Physical activity and sports participation in children and adolescents with type 1 diabetes mellitus. *Nutr Metab Cardiovasc Dis* 17: 376-382, 2007.
 307. Van der Does FE, De Neeling JN, Snoek FJ, Kostense PJ, Grooten-huis PA, Bouter LM, Heine RJ. Symptoms and well-being in relation to glycemic control in type II diabetes. *Diabetes Care* 19: 204-210, 1996.
 308. VanHelder WP, Casey K, Goode RC, Radomski WM. Growth hormone regulation in two types of aerobic exercise of equal oxygen uptake. *Eur J Appl Physiol Occup Physiol* 55: 236-239, 1986.
 309. Veldhuis JD, Iranmanesh A, Ho KK, Waters MJ, Johnson ML, Lizarralde G. Dual defects in pulsatile growth hormone secretion and clearance subserve the hypsomatotropism of obesity in man. *J Clin Endocrinol Metab* 72: 51-59, 1991.
 310. Veldhuis JD, Liem AY, South S, Weltman A, Weltman J, Clemmons DA, Abbott R, Mulligan T, Johnson ML, Pincus S. Differential impact of age, sex steroid hormones, and obesity on basal versus pulsatile growth hormone secretion in men as assessed in an ultrasensitive chemiluminescence assay. *J Clin Endocrinol Metab* 80: 3209-3222, 1995.
 311. Veves A, Saouaf R, Donaghue VM, Mullooly CA, Kistler JA, Giurini JM, Horton ES, Fielding RA. Aerobic exercise capacity remains normal despite impaired endothelial function in the micro- and macrocirculation of physically active IDDM patients. *Diabetes* 46: 1846-1852, 1997.
 312. Villa-Caballero L, Nava-Ocampo AA, Frati-Munari A, Ponce-Monter H. Oxidative stress, acute and regular exercise: Are they really harmful in the diabetic patient? *Med Hypotheses* 55: 43-46, 2000.
 313. Vina J, Gimeno A, Sastre J, Desco C, Asensi M, Pallardo FV, Cuesta A, Ferrero JA, Terada LS, Repine JE. Mechanism of free radical production in exhaustive exercise in humans and rats; role of xanthine oxidase and protection by allopurinol. *IUBMB Life* 49: 539-544, 2000.
 314. Vina J, Gomez-Cabrera MC, Lloret A, Marquez R, Minana JB, Pallardo FV, Sastre J. Free radical in exhaustive physical exercise: Mechanism of production. *IUBMB Life* 50: 271-277, 2000.
 315. Vina J, Sanchis-Gomar F, Martinez-Bello V, Gomez-Cabrera MC. Exercise acts as a drug; the pharmacological benefits of exercise. *Br J Pharmacol* 167: 1-12, 2012.
 316. Viru A, Karelson K, Smirnova T. Stability and variability in hormonal responses to prolonged exercise. *Int J Sports Med* 13: 230-235, 1992.
 317. Vlassara H, Brownlee M, Manogue KR, Dinarello CA, Pasagian A. Cachectin/TNF and IL-1 induced by glucose-modified proteins: Role in normal tissue remodeling. *Science* 240: 1546-1548, 1988.
 318. Waden J, Tikkanen H, Forsblom C, Fagerudd J, Pettersson-Fernholm K, Lakka T, Riska M, Groop PH. Leisure time physical activity is associated with poor glycemic control in type 1 diabetic women: The FinnDiane study. *Diabetes Care* 28: 777-782, 2005.
 319. Wallberg-Henriksson H, Gunnarsson R, Henriksson J, DeFronzo R, Felig P, Ostman J, Wahren J. Increased peripheral insulin sensitivity and muscle mitochondrial enzymes but unchanged blood glucose control in type 1 diabetes after physical training. *Diabetes* 31: 1044-1050, 1982.
 320. Wallymahmed ME, Morgan C, Gill GV, MacFarlane IA. Aerobic fitness and hand grip strength in Type 1 diabetes: Relationship to glycaemic control and body composition. *Diabet Med* 24: 1296-1299, 2007.
 321. Wang MY, Chen L, Clark GO, Lee Y, Stevens RD, Ilkayeva OR, Wenner BR, Bain JR, Charron MJ, Newgard CB, Unger RH. Leptin therapy in insulin-deficient type I diabetes. *Proc Natl Acad Sci U S A* 107: 4813-4819, 2010.
 322. Wanke T, Auinger M, Formanek D, Merkle M, Lahrman H, Ogris E, Zwisch H, Irsigler K. Defective endogenous opioid response to exercise in type I diabetic patients. *Metabolism* 45: 137-142, 1996.
 323. Wasserman DH. Four grams of glucose. *Am J Physiol Endocrinol Metab* 296: E11-E21, 2009.
 324. Wasserman DH, Cherrington AD. Hepatic fuel metabolism during muscular work: Role and regulation. *Am J Physiol* 260: E811-E824, 1991.
 325. Wasserman DH, Zinman B. Exercise in individuals with IDDM. *Diabetes Care* 17: 924-937, 1994.
 326. Weltman NY, Saliba SA, Barrett EJ, Weltman A. The use of exercise in the management of type 1 and type 2 diabetes. *Clin Sports Med* 28: 423-439, 2009.
 327. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: A meta-analysis of randomized, controlled trials. *Ann Intern Med* 136: 493-503, 2002.
 328. Wideman L, Consitt L, Patrie J, Swearingin B, Bloomer R, Davis P, Weltman A. The impact of sex and exercise duration on growth hormone secretion. *J Appl Physiol* 101: 1641-1647, 2006.
 329. Williams B, Gallacher B, Patel H, Orme C. Glucose-induced protein kinase C activation regulates vascular permeability factor mRNA expression and peptide production by human vascular smooth muscle cells in vitro. *Diabetes* 46: 1497-1503, 1997.
 330. Yardley JE, Iscoe KE, Sigal RJ, Kenny GP, Perkins BA, Riddell MC. Insulin pump therapy is associated with less post-exercise hyperglycemia than multiple daily injections: An observational study of physically active type 1 diabetes patients. *Diabetes Technol Ther* 15: 84-88, 2013.
 331. Yerneni KK, Bai W, Khan BV, Medford RM, Natarajan R. Hyperglycemia-induced activation of nuclear transcription factor kappa-paB in vascular smooth muscle cells. *Diabetes* 48: 855-864, 1999.

332. Yu X, Park BH, Wang MY, Wang ZV, Unger RH. Making insulin-deficient type 1 diabetic rodents thrive without insulin. *Proc Natl Acad Sci U S A* 105: 14070-14075, 2008.
333. Zaccaria M, Varnier M, Piazza P, Noventa D, Ermolao A. Blunted growth hormone response to maximal exercise in middle-aged versus young subjects and no effect of endurance training. *J Clin Endocrinol Metab* 84: 2303-2307, 1999.
334. Zaldivar F, Eliakim A, Radom-Aizik S, Cooper DM. The effect of brief exercise on circulating CD34+ stem cells in early and late pubertal boys. *Ped Res* Apr;61(4):491-495, 2007.
335. Zoppini G, Carlini M, Muggeo M. Self-reported exercise and quality of life in young type 1 diabetic subjects. *Diabetes Nutr Metab* 16: 77-80, 2003.