**Name of Journal: *World Journal of Diabetes***

**ESPS Manuscript NO: 22050**

**Manuscript Type: REVIEW**

**­­­­Skeletal muscle as a therapeutic target for delaying type 1 diabetic complications**

Coleman *et al.*Skeletal muscle health in diabetes

**Samantha K Coleman, Irena A Rebalka, Donna M D’Souza, Thomas J Hawke**

**Samantha K Coleman, Irena A Rebalka, Donna M D’Souza, Thomas J Hawke,** Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON L8S 4L8, Canada

**Author contributions:** All authors equally contributed to the research, analysis, writing and editing of this report.

**Conflict-of-interest** **statement:** Authors declare no conflicts of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Thomas J Hawke, PhD,** Department of Pathology and Molecular Medicine, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada. hawke@mcmaster.ca

**Telephone**: +1-905-5259140-22372

**Received:** August 7, 2015

**Peer-review started:** August 21, 2015

**First decision:** September 30, 2015

**Revised:** October 1, 2015

**Accepted:** November 23, 2015

**Article in press:**

**Published online:**

**Abstract**

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease targeting the pancreatic beta-cells and rendering the person hypoinsulinemic and hyperglycemic. Despite exogenous insulin therapy, individuals with T1DM will invariably develop long-term complications such as blindness, kidney failure and cardiovascular disease. Though often overlooked, skeletal muscle is also adversely affected in T1DM, with both physical and metabolic derangements reported. As the largest metabolic organ in the body, impairments to skeletal muscle health in T1DM would impact insulin sensitivity, glucose/lipid disposal and basal metabolic rate and thus affect the ability of persons with T1DM to manage their disease. In this review, we discuss the impact of T1DM on skeletal muscle health with a particular focus on the proposed mechanisms involved. We then identify and discuss established and potential adjuvant therapies which, in association with insulin therapy, would improve the health of skeletal muscle in those with T1DM and thereby improve disease management- ultimately delaying the onset and severity of other long-term diabetic complications.

**Key words:** Type 1 diabetes mellitus; Skeletal muscle; Exercise; Myostatin; Leptin; Adiponectin; Metabolism

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Skeletal muscle is adversely affected in type 1 diabetes mellitus and strategies to maintain/improve muscle health will positively impact disease management and delay diabetic complications.

Coleman SK, Rebalka IA, D’Souza DM, Hawke TJ. Skeletal muscle as a therapeutic target for delaying type 1 diabetic complications. *World J Diabetes* 2015; In press

**INTRODUCTION**

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by the autoimmune destruction of the pancreatic beta cells. Without the insulin produced by these cells, the body is no longer able to manage blood glucose, leading to hyperglycemia. Even in the case of tightly regulated insulin therapy, it is extremely difficult to maintain blood glucose levels within an acceptable range[1]. Complications, such as blindness (retinopathy), kidney failure (nephropathy), peripheral nerve damage (neuropathy), cardiovascular disease and impairments to muscle health (myopathy), invariably arise as a direct/indirect result of the inability to manage blood glucose.

In healthy individuals, insulin is typically released postprandially and is responsible for promoting an influx of glucose into adipose, hepatic and skeletal muscle cells for storage or metabolism. Of these insulin-sensitive cells, skeletal muscle is the largest of these organs by mass in the body[2,3] and thus plays a prominent role in glucose homeostasis. Skeletal muscle is also capable of uptaking large amounts of glucose in a non-insulin mediated manner[4] such as is seen during muscle contraction. Not surprisingly then, if the health of skeletal muscle is sub-optimal, management of blood glucose will also be sub-optimal. Despite the vital role played by skeletal muscle in whole body metabolic control and blood glucose management, our understanding of changes to the health of this organ system in both acute and long-term T1DM is still in its infancy. Much of our current knowledge is derived from rodent models with uncontrolled hyperglycemia for a period of weeks or months. The resultant impairments to skeletal muscle health, referred to as ‘diabetic myopathy’ manifests as impaired muscle growth and strength[5-8], altered metabolic capacity[5-7] and reduced regenerative and stem cell capacities[9-15]. Though human studies investigating diabetic myopathy are sparse, the results to date suggest consistency in the observations with rodent models[6]. Specifically, reductions in muscle mass, fiber size, work capacity and maximal force production[6] are seen in persons with T1DM.

In this review, we will introduce some of the key factors impacting skeletal muscle health in those with T1DM and then discuss established and possible therapeutic strategies focused on improving skeletal muscle health as a means improve skeletal muscle health with the ultimate goal of attenuating the development of other diabetic complications.

**METABOLIC STRESS**

In a state such as T1DM, excessive accumulation of glucose in the blood incites excessive stress on the entire body. Specifically within the muscle, damaging metabolites, such as reactive oxygen species (ROS), wreak havoc within the tissue causing damage to cellular structures with resultant functional impairments. The oxidative capacity of T1DM skeletal muscle is altered when compared to healthy, non-diabetic muscle. In the *Ins2*Akita+/- model of T1DM, glycolytic fibers exhibit atrophy, as demonstrated through a decreased proportion of type IIB/X fibers, as well as a decrease in type IIA and IIB/X fiber area[5]. Studies in human T1DM populations also displayed alterations in fiber type variability through an increased proportion of fast glycolytic fibers, and an increased amount of glycolytic enzyme activity[16,17]. Correspondingly, changes in the normal fiber type distribution are accompanied by changes in fuel oxidation and metabolic capacity of the muscle. Due to the reduced ability of skeletal muscle to access carbohydrates in times of inadequate/low insulin, diabetic skeletal muscle must promote the use of other fuel sources. Skeletal muscle of individuals with T1DM is associated with the excessive deposition of intramyocellular lipids (IMCL)[5,18]. This high level of IMCLs is noted in the muscle following food consumption, and very low levels in the fasted state, as this fuel source is heavily relied upon. Muscle from the streptozotocin (STZ) T1DM mouse model also demonstrates increased acetyl CoA/CoA ratio, hypothesized to be due to increased fatty acid oxidation[19], as well as increased fat utilization and mobilization[20], as the muscle tries to deal with the increased fat content. Along with these changes in the skeletal muscle of both the *Ins2Akita+/-* and STZ models, there is an upregulation of CD36, a fatty acid transporter[5,21–23]. The alloxan-induced T1DM model similarly demonstrates an increase in free fatty acid levels in cardiac and skeletal muscle tissues[24]. It is believed that as the levels of IMCL deposition increase, lipotoxicity ensues[25], enhancing stress to the tissue. Despite a heavier reliance on triglycerides, diabetic myopathy is accompanied with decreased activity of lipid metabolism enzymes citrate synthase[5,26,27], β-hydroxybutyrate[5], and 3-hydroxybutyrate dehydrogenase[26]. The trend of increased IMCL persists in human populations of T1DM, and is correlated with the degree of insulin resistance observed in these subjects[28]. Contrarily, the *Ins2Akita+/-* mouse model does not show the same increase in intramuscular triglyceride content[5,29] seen in the (disease duration-matched) STZ model, and does not demonstrate a decrease in citrate synthase or β-hydroxybutyrate activity[5]. It is worth noting, however, in the case of the STZ-induced diabetic model, that STZ itself has been implicated in the generation of oxidative stress within muscle cells, even in the absence of hyperglycemia[30]. Thus the STZ model could be held to represent a much more severe model of T1DM due to the elevated levels of oxidative stress than may be seen in diabetes alone.

Studies have shown that hyperglycemia and T1DM specifically display elevated markers of oxidative stress in the skeletal muscle[31,32], resulting in insulin resistance[33]. Accumulation of damaging ROS in skeletal muscle has been linked with a loss of protein mass[34] and disrupted protein turnover[35]. This oxidative stress has an effect on transcription of glucose transporters which contributes to the development of insulin resistance[32]. Specifically in STZ rats, oxidative stress was seen to upregulate atrogin-1 and MuRF-1, markers of muscle atrophy, and downregulate MyoD, Myogenin and JunD, genes required for normal muscle growth and repair[15]. Though there is clear evidence that accumulation of IMCL deposits causes dysfunctional fatty acid oxidation, generation of ROS, and stress on the muscle, future studies are needed in other diabetic models to more fully elucidate the contribution(s) of these stressors to diabetic myopathy development and progression.

**VASCULAR DYSFUNCTION**

An intricate network of vasculature supplying the skeletal muscle with adequate blood supply is required for optimal muscle performance. In T1DM, however, there is dysfunction of the capillary network and endothelial cells. Hyperglycemia has been found to alter the capillary bed, reducing capillary diffusing capacity and disrupting hemodynamic regulation to skeletal muscle[36,37]. T1DM mice demonstrate both a decrease in capillary-to-fiber ratio[5,38] and dysregulated angiogenesis[38]. Moreover, thickening of the basement membrane of skeletal muscle blood vessels in T1DM rats has been found to be positively related to their level of dysglycemia[39-41]. Thickening of the basement membrane in skeletal muscle capillaries is also greater in patients experiencing worsening retinopathy, a serious complication of T1DM[42]. Furthermore, studies show that peripheral microvascular dysfunction could also be seen as an indicator of atherosclerotic damage in individuals with T1DM[43]. In the case of ApoE-/- STZ mice, a T1DM rodent model which mimics macrovascular complications, mice which were returned to normoglycemia exhibited expansion of the vasa vasorum microvascular network[44]. This expansion was directly correlated with attenuation of atherogenesis[44]. Overall, early attenuation of vascular dysfunction within the skeletal muscle would help prevent further long-term complications.

**INSULIN RESISTANCE**

Brownlee[31], in his unifying theory of diabetic complications, has suggested that a large part of cardiovascular disease risk in those with diabetes is due to insulin resistance. Though insulin resistance is more commonly associated with the development of Type 2 diabetes, individuals with T1DM also demonstrate insulin resistance[29,45,46]. In fact, insulin resistance has been observed in T1DM youth[45] and long-duration Type 1 diabetics[47,48], and occurs independent of glycemic control[49]. Impairment of glucose transporters[50] and glucose transport following exercise[51] have been observed in insulin resistant T1DM, further enhancing the diabetic phenotype. Insulin resistance in T1DM has been linked directly with skeletal muscle pathology[52]¸ through increased IMCL deposition and dysregulation of fatty acid oxidation[53].

Interestingly, exposure to a long-acting human insulin analogue, Insulin Detemir, has been shown to result in more significant insulin resistance, oxidative stress, skeletal muscle ectopic fat accumulation and mitochondrial impairments compared to hyperglycemia alone[54]. These results indicate that insulin resistance may in fact be a response to insulin treatment as opposed to hyperglycemia. Therapeutic strategies targeting an improvement in peripheral insulin sensitivity would reduce exogenous insulin needs, preventing insulin resistance and thus delaying the onset of diabetic complications[55].

In response to T1DM, skeletal muscle is negatively impacted, as is evidenced by increased metabolic stress, vascular impairments and insulin resistance (Figure 1). With all of these decrements, muscle is not able to respond optimally to stressors or combat the elevated glycemic and lipid loads frequently experienced in T1DM. It is believed that maintaining or improving skeletal muscle health in T1DM can contribute significantly to delaying diabetic complications. For example, improving muscle metabolic health would reduce oxidative stress, and increasing insulin sensitivity would have the combined effect of improving glycemic control and reducing exogenous insulin needs. In the following section we propose a variety of skeletal muscle-centric therapeutic strategies as a means to both improve the overall health of those with diabetes mellitus and reduce the complications associated with this disease state.

**EXERCISE TRAINING**

Exercise therapy is now being regarded as an important component in the management of T1DM due to its resultant improvements towards attenuation of microvascular complications and improvements of insulin sensitivity[56]. In a variety of metabolic disorders (independent of T1DM) exercise is associated with improvements in glucose and lipid metabolism[57–59], enhanced glucose transport[60], increased insulin sensitivity[61,62], reductions in daily insulin requirement, and a decreased risk of related co-morbidities[63,64]. Accordingly, it is predicted that improvements in skeletal muscle health, by way of exercise, would promote a greater state of well-being in individuals with T1DM.

Due to the onset of myopathy with T1DM disease advancement[6], as well as the presence of disease onset during the critical growth period, it is not surprising that the physical fitness of T1DM children is often observed to be reduced when compared to their healthy age-matched counterparts[6,65]. This disparity has been attributed, in part, to the inverse association between glycemic control and skeletal muscle function, resulting in reduced aerobic fitness. As mentioned, T1DM individuals commonly experience both functional and growth impairments[5–8]. A decrease in cardiorespiratory fitness has similarly been observed in T1DM adolescents and adults with poor glycemic control[66,67]. Based on these data, the implementation of an exercise training program would be considered an effective therapeutic strategy to improve muscle health and delay the onset and progression of diabetic complications.

A primary clinical measure to define the risk for complications development in those with T1DM is glycosylated haemoglobin (HbA1c). Changes to long term glycemic control (measured by HbA1c) are a contributing factor to disease progression, and it has been shown that hyperglycemia is prone to induce an assortment of co-morbidities that further perpetuate the disease state[68] including muscle morphology and function[69–71]. Many studies investigating the therapeutic benefit of exercise on the overall health of those with T1DM have relied on HbA1c as a primary outcome measure. Indeed, while exercise has been shown to increase glucose uptake and improve insulin sensitivity, information on changes to HbA1c remains largely controversial. Studies assessing the impact of either aerobic and/or strength training protocols in T1DM rodents and humans fail to establish a consensus on whether or not increasing physical activity improves glycemic control. For instance, a number of studies have reported a decrease in HbA1c levels following a period of aerobic training[72,73], while others report no difference in HbA1c following a period of comparable training volume[74-76]. Similarly, investigations incorporating strength training protocols have reported no effect on HbA1c levels[77,78], while others indicate beneficial effects incorporating both strength and aerobic exercise[79]. Nevertheless, longitudinal data suggests that improvements in glycemic control are still observed despite minimal improvements in HbA1c levels following aerobic training[80,81]. Discrepancies in HbA1c improvements amongst the studies reported are thought to be a result of variations in insulin dosage (reducing dosages as a means to prevent exercise-induced hypoglycaemia) and carbohydrate uptake, which override any quantifiable changes in glucose disposal. Although increased fitness may not dramatically improve glycemic control, physical activity is still encouraged for all T1DM individuals due to the additional skeletal muscle health benefits incurred, including the attenuation in microvascular complications, improved insulin sensitivity, reductions in inflammation, and enhanced muscle growth and repair. For a thorough review on exercise and T1DM, see[56].

As noted previously, the progression of T1DM promotes the onset of various microvascular complications. These complications not only promote a worsened disease state, but may also interfere with the individual’s physical capacity[82]. It is critical to address the role of vascular complications in the skeletal muscle in T1DM, as maladaptive changes to the diabetic muscle often precede the advancement of other complications[6,69,83]. The effect of exercise therapy on skeletal muscle vasculature is largely positive, with many studies reporting increases in angiogenesis-related genes[38], and enhanced vascular function[84,85]. In humans, an inverse correlation exists between physical activity and the development of macro-and micro-vascular complications in long-standing T1DM[86], however specific adaptions in skeletal muscle vasculature following exercise training remain largely unknown.

Elevations in markers of inflammatory and oxidative stress have also been identified in T1DM patients[87-89]. Inflammation is known to negatively impact skeletal muscle health, as observed by the positive correlation between inflammatory factors and muscle wasting[90,91]. Skeletal muscle from T1DM mice show an increased expression of inflammatory-related factors[92,93]. Exercise does elicit anti-inflammatory effects[94,95], which are dependent on exercise type, duration, intensity, endurance capacity and muscle morphology[96-98]. Recently, diabetic rats demonstrated reductions in inflammatory cytokine levels (*i.e.*, IL-1B, IL-4, *etc*.) following exercise intervention[99]. Furthermore, T1DM children subjected to an acute bout of exercise demonstrated dysregulation in the expression of inflammatory and oxidative stress variables[100], thereby providing evidence for the importance of exercise training in the reduction of inflammation associated with T1DM disease progression. While exercise reduces pro-inflammatory cytokines, it has also been found to promote the expression of anti-inflammatory cytokines that enhance muscle health. For instance, STZ rats subjected to a 5-wk resistance exercise training regimen displayed an increase in IL-15, an anabolic cytokine that is known to induce hypertrophy in skeletal muscle[101,102], while hindering apoptosis[103]. The cytokine IL-6, while primarily believed to be pro-inflammatory in nature, is also known to exert beneficial effects on skeletal muscle following training. Specifically, increased IL-6 production promoted greater glucose uptake during exercise[104] and an up-regulation of additional anti-inflammatory cytokines[105]. These data, while not explicitly investigated within the context of T1DM, suggests a protective role of IL-6 release from skeletal muscle following exercise. While these studies implicate exercise in the support of muscle health *via* attenuation of the inflammatory state associated with T1DM development, future work using human data is needed to further delineate the role of exercise training in the regulation of chronic inflammation in T1DM.

Overall physical capacity is negatively affected by the presence of T1DM, particularly in those with long-standing disease, and thus it is predicted that any form of activity (endurance, resistance, *etc*.) will benefit the individual by maintaining and/or enhancing skeletal muscle health and the benefits therein. The literature to date makes a clear case that exercise training can positively affect the skeletal muscle of those with T1DM through its influence on skeletal muscle endothelial cell function, inflammation and insulin sensitivity. What remains to be clearly elucidated is the impact of exercise training on the modulation of long-term glycemic control; a measure hampered by subject variability in insulin dosage, intensity of exercise training, and degree of disease advancement between studies.

**MYOSTATIN**

Myostatin (GDF-8), primarily synthesized by skeletal muscle and a negative regulator of muscle growth, was originally discovered in 1997 when a mutation in the myostatin gene was shown to be responsible for phenotypically hypermuscular cattle[106]. In the case of myostatin deficiency, muscle growth was observed to reach 2-3 times that of typical muscle size[106]. Instances of loss-of-function myostatin mutation have been observed in human populations to the same effect[107].

Myostatin levels have been measured in the STZ-diabetic mouse, and consistently show elevated protein[108] and gene expression[109,110]. Human populations of T2DM also demonstrate increased levels of myostatin[111-113]. This increase in myostatin in T1DM is consistent with the decreased muscle mass and myopathic phenotype observed. In a study of food deprivation, a state similar to that as found in uncontrolled T1DM, increased expression of myostatin was found to contribute to the observed muscle atrophy[114].

Methods of inhibiting or knocking down elements of the myostatin pathway have been, and are currently being investigated in a variety of disease states. Naturally, myostatin inhibition therapy *via* MYO-029[115], PF-06252616[116] and ACE-031[117], amongst others, was originally investigated in patient populations with genetic muscular diseases and muscle wasting disorders (*e.g.*, cancer cachexia). More recently, blockade of the myostatin pathway has been linked to improvements of metabolic pathologies in animal studies. For instance, high-fat diet fed mice with myostatin reduction therapy did not gain weight as wildtype counterparts did[118–120] and myostatin inhibition is seen to prevent diabetes development in a model of lipodystrophy[121]. Furthermore, in the case of T1DM specifically, STZ animals treated with follistatin, a known inhibitor of myostatin, demonstrate improvements in the regenerative capacity of skeletal muscle[14].

In the case of other metabolic diseases, increased myostatin expression has been implicated in the development of insulin resistance[122] and reduction or inhibition of myostatin has been seen to improve insulin sensitivity[119,123–126]. It is clear that myostatin plays a role in glycemic control of skeletal muscle. Models examining mutated myostatin or myostatin inhibition coincide with significantly elevated levels of GLUT4[127,128] and GLUT1[128], resulting in increased glucose uptake[127]. This evidence demonstrates how myostatin plays an important role in increasing glucose disposal both dependent and independent of insulin. Reductions in circulating myostatin in T1DM may therefore aid in both reducing exogenous insulin needs and preventing the insulin resistance which may develop as a result.

Increased levels of myostatin may contribute to the elevated oxidative stress noted in diabetic myopathy. Myostatin is thought to operate both through[129] and independent[130] of the NF-кB pathway to produce ROS, leading to muscle atrophy. In STZ-induced T1DM, myostatin was shown to contribute to oxidative stress leading to DNA damage[131]. Since myostatin contributes to oxidative stress, it is possible that in the case of myostatin inhibition, decreased oxidative stress (ROS production) could lead to functional problems as have been reported in rodents without myostatin[132]. It is important to remember however that in T1DM the fulcrum is already shifted towards increased ROS levels. Thus, reductions in myostatin could serve to restore balance resulting in healthier muscle and the associated benefits therein.

Myostatin inhibition has more recently been linked to the “browning” of white adipose tissue[133–136]. One study has postulated this effect is mediated through the AMPK-PGC1α-Fndc5 pathway originating in skeletal muscle[137]. While this is an indirect positive effect of myostatin inhibition (*i.e*., not specifically related to skeletal muscle), it would also provide benefits in reducing the diabetic condition. Gunawardana and Piston have shown that a transplant of brown adipose tissue into STZ-diabetic mice resulted in normalization of glucose and attenuation of the diabetic state[138]. This effect is thought to occur through recovery of subcutaneous white adipose tissue, resulting in the normalization of adipokines leptin, adiponectin and IGF-1.

Although downregulation of myostatin shows promise in the treatment of T1DM *via* decreasing oxidative stress, upregulating glucose transporters, preventing insulin resistance and browning white adipose tissue, there are still many areas left to be explored. Production of ROS is a delicate balance, and a drastic decrease in ROS levels can cause harm to an organism as well. Further, McPherron *et al*[139] explored a soluble myostatin receptor to downregulate the effects of myostatin in conjunction with STZ diabetes, and saw worsened hyperglycemia. Authors of this study observed severely low insulin levels and significantly elevated glucocorticoid levels, common to the STZ rodent model[139]. The lack of effect of myostatin reduction therapy may be the result of the rise in glucocorticoids (resulting in elevated blood glucose) or the absence of circulating insulin. Since the inhibition of myostatin may have its greatest metabolic effects *via* increasing insulin sensitivity, the lack of insulin seen in the STZ model may have been detrimental to any potential blood glucose lowering capacity of myostatin inhibition[139]. Overall, there is certainly enough compelling evidence to further investigate myostatin inhibition strategies as an adjuvant therapeutic strategy for T1DM.

**LEPTIN**

Leptin, a hormone predominantly produced by adipose tissue, has been heavily implicated in metabolism. First unwittingly examined in the 1950s, the leptin knockout mouse (ob/ob mouse) demonstrated excessive hyperphagia and in turn, excessive weight gain[140]. The discovery of leptin itself in 1994 led to the understanding of leptin as an important hormone with regard to appetite control[141], and has further been implicated in reproductive health[142], bone metabolism[143], the immune response[144], and importantly in regulating fat metabolism, insulin resistance and overall metabolism. The identification of leptin brought about an understanding that adipose tissue was an endocrine organ. Currently, more than 19 different adipocyte-derived cell-signaling proteins, termed adipokines, have been identified[145]. Adipokines include inflammatory mediators, angiogenic proteins, and metabolic regulators. With the global rise in obesity, the relationship between adipose tissue and its systemic effects has attracted much interest. Adipokines are thought to influence multiple processes, including glucose and fatty acid metabolism, and insulin sensitivity.

It has been noted that children and adults with poorly controlled T1DM demonstrate low levels of leptin regardless of gender[23,146]. Leptin levels can be normalized *via* insulin treatment in T1DM children[146], but not in adults[23]. Furthermore, poorly managed diabetes has been associated with an increase in the soluble leptin receptor, leading to leptin resistance[147]. This same trend is seen in STZ diabetic rodents, in which the induction of T1DM caused a decrease in circulating leptin, which was reversed by insulin therapy[148,149].

Leptin therapy has been found to attenuate many of the effects of T1DM, most notably restoring euglycemia[150-153]. Considering the restoration of euglycemia coupled with leptin’s ties to appetite control, leptin treated STZ diabetic rodents demonstrate diminished hyperphagia[154]. While Fujikawa *et al*[155] have hypothesized that the improvements observed in T1DM *via* leptin treatment occur *via* CNS-dependent mechanisms, and Unger’s group has targeted leptins ability to decrease plasma glucagon levels[152,156-158], there is growing evidence that leptin therapy provides benefits through skeletal muscle as well. Leptin treatment has been found to increase insulin sensitivity and glucose uptake in skeletal muscle specifically[159-161]. Yu and colleagues demonstrate that hyperleptinemia leads to euglycemia independent of insulin. This causes an upregulation of IGF-1 and pIGF-1 receptor, which further leads to increases in skeletal muscle IRS-1, P13K and ERK phosphorylation[162]. Specifically in the soleus muscle, leptin was implicated to act in an insulin-like fashion, leading to increases in a variety of muscle metabolic factors including glucose uptake, glycogen synthesis, lactate formation and glucose oxidation[163].

Leptin has also been demonstrated to play a role in both regulating fatty acid oxidation and preventing insulin resistance in skeletal muscle. Skeletal muscle of STZ diabetic animals treated with leptin exhibit evidence of restored glucose uptake, but also enhanced skeletal muscle markers of fatty acid utilization and oxidation, notably independent of differences in food consumption[164]. Leptin has also been seen to direct lipids towards the muscle to be burned rather than stored[165], as well as increase fatty acid oxidation in the skeletal muscle[166]. These metabolic benefits are thought to occur through the activation of AMPK and the inhibition of ACC[167]. Insulin resistance in T1DM has also been found to be reversed through leptin therapy[168]. Interestingly, however, this was thought to occur in a method independent of skeletal muscle[168]. Kusakabe *et al*[169] found that leptin treated STZ mice fed high fat diet to induce insulin resistance demonstrated enhanced insulin sensitivity. This was again seen by Lin *et al*[170], although was attributed to neurological changes. Although leptin’s role in diminishing insulin resistance is clear, further work is necessary to elucidate the mechanism of its action in this role.

As leptin appears to mimic many of the effects of insulin, leptin may indeed be used as an adjuvant therapy to insulin[152,171]. When leptin and insulin were given in conjunction to STZ rodents, much smaller doses of insulin were required to achieve normoglycemia than would be required with each treatment alone[172]. Metreleptin, a leptin analogue, is currently under clinical trials (NCT01268644) in conjunction with insulin therapy in order to investigate the effectiveness of this combination seen in the literature. Considering both the prevalent development of insulin resistance and the difficulty in maintaining normoglycemia in T1DM patients, even in the presence of insulin therapy, this adjuvant therapy warrants further investigation in the human T1DM population.

**ADIPONECTIN**

Adiponectin, first characterized in 1995[173], is an insulin-sensitizing adipokine; capable of increasing both insulin-mediated uptake of glucose and β-oxidation of lipids[174-177]. Individuals with T2DM exhibit significantly lower levels of circulating adiponectin than healthy, non-diabetic individuals[178]. With adiponectin behaving as an insulin sensitizing factor, it is not surprising that this deficiency in adiponectin closely correlates with an individuals’ degree of insulin resistance[179]. Systemic injection of adiponectin has been shown to decrease resting blood glucose levels and attenuate insulin resistance[174,175,180]. Furthermore, stimulation of adiponectin production in an animal model of T2DM improves skeletal muscle insulin sensitivity[181]. Paradoxically, when compared to healthy non-diabetic subjects, adiponectin is present in elevated levels in individuals with T1DM, regardless of their level of glycemic control[28,182,183] and these elevations are positively correlated with duration of T1DM[184,185].

The presence of metabolic syndrome in patients with T1DM has previously been associated with insulin resistance[186]. Interestingly, T1DM patients with metabolic syndrome present with significantly lower levels of serum adiponectin than T1DM patients that do not present with metabolic syndrome[186]. Similar to the relationship between insulin sensitivity and adiponectin in non-diabetic individuals, levels of adiponectin are positively correlated with insulin sensitivity in T1DM[184]. Insulin sensitivity in T1DM individuals, however, is lower than in non-diabetic subjects at any given level of circulating adiponectin[184]. The preservation of the positive relationship between adiponectin and insulin sensitivity in T1DM coupled with the overall decrease in insulin sensitivity in T1DM individuals suggests a modification in the homeostatic regulation of adiponectin in the T1DM state[184].

Upon binding to adiponectin receptors in the pancreatic beta cells, adiponectin increases insulin gene expression and secretion[187]. The presence of insulin, on the other hand, has been shown to downregulate adiponectin gene expression[188]. In this light, it is possible that the overabundance of adiponectin in the T1DM state is a compensatory mechanism; an attempt at upregulating insulin production. As previously mentioned, however, despite higher levels of adiponectin being associated with insulin sensitivity, individuals with T1DM still have a lower insulin sensitivity than non-diabetic individuals[184].

Adult T1DM human and rodent muscle has been observed to have higher levels of intramyocellular lipids (IMCL) than muscle of healthy, non-diabetic subjects[5,28,189]. This accretion of IMCLs has been associated with insulin resistance in T1DM[189]. Interestingly, previous reports indicate no differences in IMCL content between T1DM and non-diabetic children[190], potentially indicating that, similar to circulating levels of adiponectin, IMCL content is affected by, and positively associated with T1DM disease duration. Furthermore, Krause and colleagues found a positive correlation between intramyocellular adiponectin expression and IMCL density in non-diabetic mice; elevated levels of adiponectin were detected in muscle fibers displaying a greater IMCL density, while adiponectin was virtually undetectable in muscle fibers with a low IMCL content[191]. In the T1DM disease state, however, it is possible that this positive relationship may be a compensatory mechanism to remove lipid from circulation, and further investigation into this relationship in the diabetic state must be conducted. In 2007, Behre proposed that adiponectin may in fact be a defense mechanism of the body in response to starvation (as can be compared to overt T1DM), resulting in increased fatty acid oxidation and glucose uptake *via* activation of AMPK and PPAR-α[192].

Overall, a great deal of research must still be conducted to elucidate the role of adiponectin in both overall health and skeletal muscle health in T1DM. While adiponectin levels are elevated in the T1DM state, adiponectin appears to act in a compensatory mechanism to improve insulin sensitivity in the absence of insulin. As insulin resistance develops in T1DM individuals that develop metabolic syndrome, adiponectin levels demonstrate a decline. Evidence suggests that it may be beneficial to supplement adiponectin in the T1DM disease state in order to boost insulin production and increase insulin sensitivity in order to prevent this insulin resistance.

**CONCLUDING THOUGHTS**

The presence of insulin resistance, altered lipid metabolism, impaired vascularization and oxidative stresses are clear indicators of the presence of pathology in T1DM skeletal muscle. Exercise training, myostatin, leptin and adiponectin have been identified as potential therapeutic avenues to investigate with regard to improving skeletal muscle health (Figure 1). It is our hypothesis that, by improving skeletal muscle health in T1DM, the muscle will be better able to contribute to the reduction of diabetic symptoms. This would, in turn, lead to systemic benefits and delayed diabetic complications, increasing the quality and quantity of life of individuals with T1DM.

**REFERENCES**

1 **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* 2006; **8**: 627-635 [PMID: 17109594 DOI: 10.1089/dia.2006.8.627]

2 **Katz LD**, Glickman MG, Rapoport S, Ferrannini E, DeFronzo RA. Splanchnic and peripheral disposal of oral glucose in man. *Diabetes* 1983; **32**: 675-679 [PMID: 6862113 DOI: 10.2337/diab.32.7.675]

3 **Kraegen EW**, James DE, Jenkins AB, Chisholm DJ. Dose-response curves for in vivo insulin sensitivity in individual tissues in rats. *Am J Physiol* 1985; **248**: E353-E362 [PMID: 3883806]

4 **Baron AD**, Brechtel G, Wallace P, Edelman SV. Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol* 1988; **255**: E769-E774 [PMID: 3059816]

5 **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* (1985) 2009; **106**: 1650-1659 [PMID: 19246652 DOI: 10.1152/japplphysiol.91565.2008]

6 **Krause MP**, Riddell MC, Hawke TJ. Effects of type 1 diabetes mellitus on skeletal muscle: clinical observations and physiological mechanisms. *Pediatr Diabetes* 2011; **12**: 345-364 [PMID: 20860561 DOI: 10.1111/j.1399-5448.2010.00699.x]

7 **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* 2010; **5**: e14032 [PMID: 21103335 DOI: 10.1371/journal.pone.0014032]

8 **Fricke O**, Seewi O, Semler O, Tutlewski B, Stabrey A, Schoenau E. The influence of auxology and long-term glycemic control on muscle function in children and adolescents with type 1 diabetes mellitus. *J Musculoskelet Neuronal Interact* 2008; **8**: 188-195 [PMID: 18622088]

9 **Gulati AK**, Swamy MS. Regeneration of skeletal muscle in streptozotocin-induced diabetic rats. *Anat Rec* 1991; **229**: 298-304 [PMID: 2024774]

10 **Jerković R**, Bosnar A, Jurisić-Erzen D, Azman J, Starcević-Klasan G, Peharec S, Coklo M. The effects of long-term experimental diabetes mellitus type I on skeletal muscle regeneration capacity. *Coll Antropol* 2009; **33**: 1115-1119 [PMID: 20102056]

11 **Vignaud A**, Ramond F, Hourdé C, Keller A, Butler-Browne G, Ferry A. Diabetes provides an unfavorable environment for muscle mass and function after muscle injury in mice. *Pathobiology* 2007; **74**: 291-300 [PMID: 17890896 DOI: 10.1159/000105812]

12 **Krause MP**, Moradi J, Nissar AA, Riddell MC, Hawke TJ. Inhibition of plasminogen activator inhibitor-1 restores skeletal muscle regeneration in untreated type 1 diabetic mice. *Diabetes* 2011; **60**: 1964-1972 [PMID: 21593201 DOI: 10.2337/db11-0007]

13 **Krause MP**, Al-Sajee D, D'Souza DM, Rebalka IA, Moradi J, Riddell MC, Hawke TJ. Impaired macrophage and satellite cell infiltration occurs in a muscle-specific fashion following injury in diabetic skeletal muscle. *PLoS One* 2013; **8**: e70971 [PMID: 23951058 DOI: 10.1371/journal.pone.0070971]

14 **Jeong J**, Conboy MJ, Conboy IM. Pharmacological inhibition of myostatin/TGF-β receptor/pSmad3 signaling rescues muscle regenerative responses in mouse model of type 1 diabetes. *Acta Pharmacol Sin* 2013; **34**: 1052-1060 [PMID: 23770987 DOI: 10.1038/aps.2013.67]

15 **Aragno M**, Mastrocola R, Catalano MG, Brignardello E, Danni O, Boccuzzi G. Oxidative stress impairs skeletal muscle repair in diabetic rats. *Diabetes* 2004; **53**: 1082-1088 [PMID: 15047625 DOI: 10.2337/diabetes.53.4.1082]

16 **Fritzsche K**, Blüher 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* 2008; **116**: 606-613 [PMID: 18465682 DOI: 10.1055/s-2008-1073126]

17 **Crowther GJ**, Milstein JM, Jubrias SA, 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* 2003; **284**: E655-E662 [PMID: 12626321 DOI: 10.1152/ajpendo.00343.2002]

18 **Chao TT**, Ianuzzo CD, Armstrong RB, Albright JT, Anapolle SE. Ultrastructural alterations in skeletal muscle fibers of streptozotocin-diabetic rats. *Cell Tissue Res* 1976; **168**: 239-246 [PMID: 131648 DOI: 10.1007/BF00215880]

19 **Goodman MN**, Berger M, Ruderman NB. Glucose metabolism in rat skeletal muscle at rest. Effect of starvation, diabetes, ketone bodies and free fatty acids. *Diabetes* 1974; **23**: 881-888 [PMID: 4279193 DOI: 10.2337/diab.23.11.881]

20 **Stearns SB**, Tepperman HM, Tepperman J. Studies on the utilization and mobilization of lipid in skeletal muscles from streptozotocin-diabetic and control rats. *J Lipid Res* 1979; **20**: 654-662 [PMID: 490043]

21 **Bonen A**, Benton CR, Campbell SE, Chabowski A, Clarke DC, Han XX, Glatz JF, Luiken JJ. Plasmalemmal fatty acid transport is regulated in heart and skeletal muscle by contraction, insulin and leptin, and in obesity and diabetes. *Acta Physiol Scand* 2003; **178**: 347-356 [PMID: 12864739 DOI: 10.1046/j.1365-201X.2003.01157.x]

22 **Chen M**, Yang YK, Loux TJ, Georgeson KE, Harmon CM. The role of hyperglycemia in FAT/CD36 expression and function. *Pediatr Surg Int* 2006; **22**: 647-654 [PMID: 16838191 DOI: 10.1007/s00383-006-1704-x]

23 **Attia N**, Caprio S, Jones TW, Heptulla R, Holcombe J, Silver D, Sherwin RS, Tamborlane WV. Changes in free insulin-like growth factor-1 and leptin concentrations during acute metabolic decompensation in insulin withdrawn patients with type 1 diabetes. *J Clin Endocrinol Metab* 1999; **84**: 2324-2328 [PMID: 10404797 DOI: 10.1210/jcem.84.7.5861]

24 **Garland PB**, Randle PJ. Regulation of glucose uptake by muscles. 10. Effects of alloxan-diabetes, starvation, hypophysectomy and adrenalectomy, and of fatty acids, ketone bodies and pyruvate, on the glycerol output and concentrations of free fatty acids, long-chain fatty acyl-coenzyme A, glycerol phosphate and citrate-cycle intermediates in rat heart and diaphragm muscles. *Biochem J* 1964; **93**: 678-687 [PMID: 5839199 DOI: 10.1042/bj0930678]

25 **van Herpen NA**, Schrauwen-Hinderling VB. Lipid accumulation in non-adipose tissue and lipotoxicity. *Physiol Behav* 2008; **94**: 231-241 [PMID: 18222498 DOI: 10.1016/j.physbeh.2007.11.049]

26 **Fewell JG**, Moerland TS. Responses of mouse fast and slow skeletal muscle to streptozotocin diabetes: myosin isoenzymes and phosphorous metabolites. *Mol Cell Biochem* 1995; **148**: 147-154 [PMID: 8594419 DOI: 10.1007/BF00928152]

27 **Noble EG**, Ianuzzo CD. Influence of training on skeletal muscle enzymatic adaptations in normal and diabetic rats. *Am J Physiol* 1985; **249**: E360-E365 [PMID: 2931994]

28 **Perseghin G**, Lattuada G, Danna M, Sereni LP, Maffi P, De Cobelli F, Battezzati A, Secchi A, Del Maschio A, Luzi L. Insulin resistance, intramyocellular lipid content, and plasma adiponectin in patients with type 1 diabetes. *Am J Physiol Endocrinol Metab* 2003; **285**: E1174-E1181 [PMID: 12933352 DOI: 10.1152/ajpendo.00279.2003]

29 **Hong EG**, Jung DY, Ko HJ, Zhang Z, Ma Z, Jun JY, Kim JH, Sumner AD, Vary TC, Gardner TW, Bronson SK, Kim JK. Nonobese, insulin-deficient Ins2Akita mice develop type 2 diabetes phenotypes including insulin resistance and cardiac remodeling. *Am J Physiol Endocrinol Metab* 2007; **293**: E1687-E1696 [PMID: 17911348 DOI: 10.1152/ajpendo.00256.2007]

30 **Johnston AP**, Campbell JE, Found JG, Riddell MC, Hawke TJ. Streptozotocin induces G2 arrest in skeletal muscle myoblasts and impairs muscle growth in vivo. *Am J Physiol Cell Physiol* 2007; **292**: C1033-C1040 [PMID: 17092995 DOI: 10.1152/ajpcell.00338.2006]

31 **Brownlee M**. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; **54**: 1615-1625 [PMID: 15919781 DOI: 10.2337/diabetes.54.6.1615]

32 **Bloch-Damti A**, Bashan N. Proposed mechanisms for the induction of insulin resistance by oxidative stress. *Antioxid Redox Signal* 2005; **7**: 1553-1567 [PMID: 16356119 DOI: 10.1089/ars.2005.7.1553]

33 **Haber CA**, Lam TK, Yu Z, Gupta N, Goh T, Bogdanovic E, Giacca A, Fantus IG. N-acetylcysteine and taurine prevent hyperglycemia-induced insulin resistance in vivo: possible role of oxidative stress. *Am J Physiol Endocrinol Metab* 2003; **285**: E744-E753 [PMID: 12799318 DOI: 10.1152/ajpendo.00355.2002]

34 **Li YP**, Schwartz RJ, Waddell ID, Holloway BR, Reid MB. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. *FASEB J* 1998; **12**: 871-880 [PMID: 9657527]

35 **Zhou LZ**, Johnson AP, Rando TA. NF kappa B and AP-1 mediate transcriptional responses to oxidative stress in skeletal muscle cells. *Free Radic Biol Med* 2001; **31**: 1405-1416 [PMID: 11728812 DOI: 10.1016/S0891-5849(01)00719-5]

36 **Sexton WL**, Poole DC, Mathieu-Costello O. Microcirculatory structure-function relationships in skeletal muscle of diabetic rats. *Am J Physiol* 1994; **266**: H1502-H1511 [PMID: 8184927]

37 **Kindig CA**, Sexton WL, Fedde MR, Poole DC. Skeletal muscle microcirculatory structure and hemodynamics in diabetes. *Respir Physiol* 1998; **111**: 163-175 [PMID: 9574868 DOI: 10.1016/S0034-5687(97)00122-9]

38 **Kivelä R**, Silvennoinen M, Touvra 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* 2006; **20**: 1570-1572 [PMID: 16816123 DOI: 10.1096/fj.05-4780fje]

39 **Raskin P**, Pietri AO, Unger R, Shannon WA. The effect of diabetic control on the width of skeletal-muscle capillary basement membrane in patients with Type I diabetes mellitus. *N Engl J Med* 1983; **309**: 1546-1550 [PMID: 6361554 DOI: 10.1056/NEJM198312223092504]

40 **Sosenko JM**, Miettinen OS, Williamson JR, Gabbay KH. Muscle capillary basement-membrane thickness and long-term glycemia in type I diabetes mellitus. *N Engl J Med* 1984; **311**: 694-698 [PMID: 6472356 DOI: 10.1056/NEJM198409133111102]

41 **Rosenstock J**, Challis P, Strowig S, Raskin P. Improved diabetes control reduces skeletal muscle capillary basement membrane width in insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 1988; **4**: 167-175 [PMID: 3359916 DOI: 10.1016/S0168-8227(88)80014-7]

42 **Rosenstock J**, Friberg T, Raskin P. Effect of glycemic control on microvascular complications in patients with type I diabetes mellitus. *Am J Med* 1986; **81**: 1012-1018 [PMID: 3541587 DOI: 10.1016/0002-9343(86)90398-0]

43 **Rossi M**, Matteucci E, Pesce M, Consani C, Franzoni F, Santoro G, Giampietro O. Peripheral microvascular dysfunction as an independent predictor of atherosclerotic damage in type 1 diabetes patients: a preliminary study. *Clin Hemorheol Microcirc* 2013; **54**: 381-391 [PMID: 23089884 DOI: 10.3233/CH-2012-1628]

44 **Veerman KJ**, Venegas-Pino DE, Shi Y, Khan MI, Gerstein HC, Werstuck GH. Hyperglycaemia is associated with impaired vasa vasorum neovascularization and accelerated atherosclerosis in apolipoprotein-E deficient mice. *Atherosclerosis* 2013; **227**: 250-258 [PMID: 23411040 DOI: 10.1016/j.atherosclerosis.2013.01.018]

45 **Nadeau KJ**, Regensteiner JG, Bauer TA, Brown MS, Dorosz JL, Hull A, Zeitler P, Draznin B, Reusch JE. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. *J Clin Endocrinol Metab* 2010; **95**: 513-521 [PMID: 19915016 DOI: 10.1210/jc.2009-1756]

46 **Kilpatrick ES**, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: "double diabetes" in the Diabetes Control and Complications Trial. *Diabetes Care* 2007; **30**: 707-712 [PMID: 17327345 DOI: 10.2337/dc06-1982]

47 **Yki-Järvinen H**, Koivisto VA. Natural course of insulin resistance in type I diabetes. *N Engl J Med* 1986; **315**: 224-230 [PMID: 3523247 DOI: 10.1056/NEJM198607243150404]

48 **DeFronzo RA**, Hendler R, Simonson D. Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes* 1982; **31**: 795-801 [PMID: 6761214 DOI: 10.2337/diab.31.9.795]

49 **Schauer IE**, Snell-Bergeon JK, Bergman BC, Maahs DM, Kretowski A, Eckel RH, Rewers M. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: The CACTI study. *Diabetes* 2011; **60**: 306-314 [PMID: 20978091 DOI: 10.2337/db10-0328]

50 **Kahn BB**, Rosen AS, Bak JF, Andersen PH, Damsbo P, Lund S, Pedersen O. Expression of GLUT1 and GLUT4 glucose transporters in skeletal muscle of humans with insulin-dependent diabetes mellitus: regulatory effects of metabolic factors. *J Clin Endocrinol Metab* 1992; **74**: 1101-1109 [PMID: 1569156 DOI: 10.1210/jcem.74.5.1569156]

51 **Peltoniemi P**, Yki-Järvinen H, Oikonen V, Oksanen A, Takala TO, Rönnemaa T, Erkinjuntti M, Knuuti MJ, Nuutila P. Resistance to exercise-induced increase in glucose uptake during hyperinsulinemia in insulin-resistant skeletal muscle of patients with type 1 diabetes. *Diabetes* 2001; **50**: 1371-1377 [PMID: 11375338 DOI: 10.2337/diabetes.50.6.1371]

52 **Nuutila P**, Knuuti J, Ruotsalainen U, Koivisto VA, Eronen E, Teräs M, Bergman J, Haaparanta M, Voipio-Pulkki LM, Viikari J. Insulin resistance is localized to skeletal but not heart muscle in type 1 diabetes. *Am J Physiol* 1993; **264**: E756-E762 [PMID: 8498497]

53 **Kelley DE**, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. *Am J Physiol* 1999; **277**: E1130-E1141 [PMID: 10600804]

54 **Liu HY**, Cao SY, Hong T, Han J, Liu Z, Cao W. Insulin is a stronger inducer of insulin resistance than hyperglycemia in mice with type 1 diabetes mellitus (T1DM). *J Biol Chem* 2009; **284**: 27090-27100 [PMID: 19654321 DOI: 10.1074/jbc.M109.016675]

55 **Fourlanos S**, Narendran P, Byrnes GB, Colman PG, Harrison LC. Insulin resistance is a risk factor for progression to type 1 diabetes. *Diabetologia* 2004; **47**: 1661-1667 [PMID: 15480539 DOI: 10.1007/s00125-004-1621-2]

56 **Galassetti P**, Riddell MC. Exercise and type 1 diabetes (T1DM). *Compr Physiol* 2013; **3**: 1309-1336 [PMID: 23897688 DOI: 10.1002/cphy.c110040]

57 **Goodyear LJ**, Kahn BB. Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med* 1998; **49**: 235-261 [PMID: 9509261 DOI: 10.1146/annurev.med.49.1.235]

58 **Hayashi T**, Wojtaszewski JF, Goodyear LJ. Exercise regulation of glucose transport in skeletal muscle. *Am J Physiol* 1997; **273**: E1039-E1051 [PMID: 9435517]

59 **Henriksen EJ**, Halseth AE. Adaptive responses of GLUT-4 and citrate synthase in fast-twitch muscle of voluntary running rats. *Am J Physiol* 1995; **268**: R130-R134 [PMID: 7840312]

60 **Rodnick KJ**, Henriksen EJ, James DE, Holloszy JO. Exercise training, glucose transporters, and glucose transport in rat skeletal muscles. *Am J Physiol* 1992; **262**: C9-14 [PMID: 1733237]

61 **James DE**, Kraegen EW, Chisholm DJ. Effects of exercise training on in vivo insulin action in individual tissues of the rat. *J Clin Invest* 1985; **76**: 657-666 [PMID: 3897288 DOI: 10.1172/JCI112019]

62 **Berger M**, Kemmer FW, Becker K, Herberg L, Schwenen M, Gjinavci A, Berchtold P. Effect of physical training on glucose tolerance and on glucose metabolism of skeletal muscle in anaesthetized normal rats. *Diabetologia* 1979; **16**: 179-184 [PMID: 428688 DOI: 10.1007/BF01219795]

63 **Rachmiel M**, Buccino J, Daneman D. Exercise and type 1 diabetes mellitus in youth; review and recommendations. *Pediatr Endocrinol Rev* 2007; **5**: 656-665 [PMID: 18084160]

64 **Aouadi R**, Khalifa R, Aouidet A, Ben Mansour A, Ben Rayana M, Mdini F, Bahri S, Stratton G. Aerobic training programs and glycemic control in diabetic children in relation to exercise frequency. *J Sports Med Phys Fitness* 2011; **51**: 393-400 [PMID: 21904277]

65 **Nguyen T**, Obeid J, Walker RG, Krause MP, Hawke TJ, McAssey K, Vandermeulen J, Timmons BW. Fitness and physical activity in youth with type 1 diabetes mellitus in good or poor glycemic control. *Pediatr Diabetes* 2015; **16**: 48-57 [PMID: 24444038 DOI: 10.1111/pedi.12117]

66 **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* 2005; **6**: 145-149 [PMID: 16109070 DOI: 10.1111/j.1399-543X.2005.00120.x]

67 **Baldi JC**, Cassuto NA, Foxx-Lupo WT, Wheatley CM, Snyder EM. Glycemic status affects cardiopulmonary exercise response in athletes with type I diabetes. *Med Sci Sports Exerc* 2010; **42**: 1454-1459 [PMID: 20139786 DOI: 10.1249/MSS.0b013e3181d1fdb3]

68 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414 DOI: 10.1038/414813a]

69 **Reske-Nielsen E**, Harmsen A, Vorre P. Ultrastructure of muscle biopsies in recent, short-term and long-term juvenile diabetes. *Acta Neurol Scand* 1977; **55**: 345-362 [PMID: 857576 DOI: 10.1111/j.1600-0404.1977.tb05654.x]

70 **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* 2008; **37**: 231-240 [PMID: 18041050 DOI: 10.1002/mus.20919]

71 **Andersen H**, Schmitz O, Nielsen S. Decreased isometric muscle strength after acute hyperglycaemia in Type 1 diabetic patients. *Diabet Med* 2005; **22**: 1401-1407 [PMID: 16176203 DOI: 10.1111/j.1464-5491.2005.01649.x]

72 **Campaigne BN**, Gilliam TB, Spencer ML, Lampman RM, Schork MA. Effects of a physical activity program on metabolic control and cardiovascular fitness in children with insulin-dependent diabetes mellitus. *Diabetes Care* 1984; **7**: 57-62 [PMID: 6705666 DOI: 10.2337/diacare.7.1.57]

73 **Dahl-Jørgensen K**, Meen HD, Hanssen KF, Aagenaes O. The effect of exercise on diabetic control and hemoglobin A1 (HbA1) in children. *Acta Paediatr Scand Suppl* 1980; **283**: 53-56 [PMID: 6938115 DOI: 10.1111/j.1651-2227.1980.tb15313.x]

74 **Landt KW**, Campaigne BN, James FW, Sperling MA. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. *Diabetes Care* 1985; **8**: 461-465 [PMID: 4053932 DOI: 10.2337/diacare.8.5.461]

75 **Wallberg-Henriksson H**. Exercise and diabetes mellitus. *Exerc Sport Sci Rev* 1992; **20**: 339-368 [PMID: 1623892]

76 **Zinman B**, Zuniga-Guajardo S, Kelly D. Comparison of the acute and long-term effects of exercise on glucose control in type I diabetes. *Diabetes Care* 1984; **7**: 515-519 [PMID: 6439529 DOI: 10.2337/diacare.7.6.515]

77 **Ramalho AC**, de Lourdes Lima M, Nunes F, Cambuí Z, Barbosa C, Andrade A, Viana A, Martins M, Abrantes V, Aragão C, Temístocles M. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. *Diabetes Res Clin Pract* 2006; **72**: 271-276 [PMID: 16406128 DOI: 10.1016/j.diabres.2005.11.011]

78 **Heyman E**, Toutain C, Delamarche P, Berthon P, Briard D, Youssef H, Dekerdanet M, Gratas-Delamarche A. Exercise training and cardiovascular risk factors in type 1 diabetic adolescent girls. *Pediatr Exerc Sci* 2007; **19**: 408-419 [PMID: 18089908]

79 **Mosher PE**, Nash MS, Perry AC, LaPerriere AR, Goldberg RB. Aerobic circuit exercise training: effect on adolescents with well-controlled insulin-dependent diabetes mellitus. *Arch Phys Med Rehabil* 1998; **79**: 652-657 [PMID: 9630144 DOI: 10.1016/S0003-9993(98)90039-9]

80 **Roberts L**, Jones TW, Fournier PA. Exercise training and glycemic control in adolescents with poorly controlled type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002; **15**: 621-627 [PMID: 12014521 DOI: 10.1515/JPEM.2002.15.5.621]

81 **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 I diabetics after physical training. *Diabetes* 1982; **31**: 1044-1050 [PMID: 6757018 DOI: 10.2337/diacare.31.12.1044]

82 **Wadén J**, Forsblom C, Thorn LM, Saraheimo M, Rosengård-Bärlund M, Heikkilä O, Lakka TA, Tikkanen H, Groop PH. Physical activity and diabetes complications in patients with type 1 diabetes: the Finnish Diabetic Nephropathy (FinnDiane) Study. *Diabetes Care* 2008; **31**: 230-232 [PMID: 17959867 DOI: 10.2337/dc07-1238]

83 **Jakobsen J**, Reske-Nielsen E. Diffuse muscle fiber atrophy in newly diagnosed diabetes. *Clin Neuropathol* 1986; **5**: 73-77 [PMID: 3708956]

84 **Fuchsjäger-Mayrl G**, Pleiner J, Wiesinger GF, Sieder AE, Quittan M, Nuhr MJ, Francesconi C, Seit HP, Francesconi M, Schmetterer L, Wolzt M. Exercise training improves vascular endothelial function in patients with type 1 diabetes. *Diabetes Care* 2002; **25**: 1795-1801 [PMID: 12351480 DOI: 10.2337/diacare.25.10.1795]

85 **Mason NJ**, Jenkins AJ, Best JD, Rowley KG. Exercise frequency and arterial compliance in non-diabetic and type 1 diabetic individuals. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 598-603 [PMID: 16874151 DOI: 10.1097/01.hjr.0000216546.07432.b2]

86 **Kriska AM**, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ. The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: the Epidemiology of Diabetes Complications Study--VII. *J Clin Epidemiol* 1991; **44**: 1207-1214 [PMID: 1941015 DOI: 10.1016/0895-4356(91)90153-Z]

87 **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* 2006; **55**: 774-779 [PMID: 16505242 DOI: 10.2337/diabetes.55.03.06.db05-1417]

88 **Giugliano D**, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care* 1996; **19**: 257-267 [PMID: 8742574 DOI: 10.2337/diacare.19.3.257]

89 **Nicolls MR**, Haskins K, Flores SC. Oxidant stress, immune dysregulation, and vascular function in type I diabetes. *Antioxid Redox Signal* 2007; **9**: 879-889 [PMID: 17508913 DOI: 10.1089/ars.2007.1631]

90 **Ladner KJ**, Caligiuri MA, Guttridge DC. Tumor necrosis factor-regulated biphasic activation of NF-kappa B is required for cytokine-induced loss of skeletal muscle gene products. *J Biol Chem* 2003; **278**: 2294-2303 [PMID: 12431991 DOI: 10.1074/jbc.M207129200]

91 **Melstrom LG**, Melstrom KA, Ding XZ, Adrian TE. Mechanisms of skeletal muscle degradation and its therapy in cancer cachexia. *Histol Histopathol* 2007; **22**: 805-814 [PMID: 17455154]

92 **Molanouri Shamsi M**, Hassan ZH, Gharakhanlou R, Quinn LS, Azadmanesh K, Baghersad L, Isanejad A, Mahdavi M. Expression of interleukin-15 and inflammatory cytokines in skeletal muscles of STZ-induced diabetic rats: effect of resistance exercise training. *Endocrine* 2014; **46**: 60-69 [PMID: 24006180 DOI: 10.1007/s12020-013-0038-4]

93 **Ono T**, Takada S, Kinugawa S, Tsutsui H. Curcumin ameliorates skeletal muscle atrophy in type 1 diabetic mice by inhibiting protein ubiquitination. *Exp Physiol* 2015; **100**: 1052-1063 [PMID: 25998196 DOI: 10.1113/EP085049]

94 **Lira FS**, Koyama CH, Yamashita AS, Rosa JC, Zanchi NE, Batista ML, Seelaender MC. Chronic exercise decreases cytokine production in healthy rat skeletal muscle. *Cell Biochem Funct* 2009; **27**: 458-461 [PMID: 19681095 DOI: 10.1002/cbf.1594]

95 **Zanchi NE**, Lira FS, de Siqueira Filho MA, Rosa JC, de Oliveira Carvalho CR, Seelaender M, Santos RV, Lancha AH. Chronic low frequency/low volume resistance training reduces pro-inflammatory cytokine protein levels and TLR4 mRNA in rat skeletal muscle. *Eur J Appl Physiol* 2010; **109**: 1095-1102 [PMID: 20369365 DOI: 10.1007/s00421-010-1456-0]

96 **Balducci S**, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, Fallucca S, Alessi E, Letizia C, Jimenez A, Fallucca F, Pugliese G. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis* 2010; **20**: 608-617 [PMID: 19695853 DOI: 10.1016/j.numecd.2009.04.015]

97 **Carmeli E**, Moas M, Lennon S, Powers SK. High intensity exercise increases expression of matrix metalloproteinases in fast skeletal muscle fibres. *Exp Physiol* 2005; **90**: 613-619 [PMID: 15833756 DOI: 10.1113/expphysiol.2004.029462]

98 **Yeghiazaryan M**, Żybura-Broda K, Cabaj A, Włodarczyk J, Sławińska U, Rylski M, Wilczyński GM. Fine-structural distribution of MMP-2 and MMP-9 activities in the rat skeletal muscle upon training: a study by high-resolution in situ zymography. *Histochem Cell Biol* 2012; **138**: 75-87 [PMID: 22419075 DOI: 10.1007/s00418-012-0940-5]

99 **Kim JS**, Lee YH, Kim JC, Ko YH, Yoon CS, Yi HK. Effect of exercise training of different intensities on anti-inflammatory reaction in streptozotocin-induced diabetic rats. *Biol Sport* 2014; **31**: 73-79 [PMID: 25187675 DOI: 10.5604/20831862.1093775]

100 **Rosa JS**, Oliver SR, Flores RL, Ngo J, Milne GL, Zaldivar FP, Galassetti PR. Altered inflammatory, oxidative, and metabolic responses to exercise in pediatric obesity and type 1 diabetes. *Pediatr Diabetes* 2011; **12**: 464-472 [PMID: 21443585 DOI: 10.1111/j.1399-5448.2010.00724.x]

101 **Quinn LS**, Anderson BG, Drivdahl RH, Alvarez B, Argilés JM. Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for treatment of muscle wasting disorders. *Exp Cell Res* 2002; **280**: 55-63 [PMID: 12372339 DOI: 10.1006/excr.2002.5624]

102 **Kim HC**, Cho HY, Hah YS. Role of IL-15 in Sepsis-Induced Skeletal Muscle Atrophy and Proteolysis. *Tuberc Respir Dis* (Seoul) 2012; **73**: 312-319 [PMID: 23319993 DOI: 10.4046/trd.2012.73.6.312]

103 **Figueras M**, Busquets S, Carbó N, Barreiro E, Almendro V, Argilés JM, López-Soriano FJ. Interleukin-15 is able to suppress the increased DNA fragmentation associated with muscle wasting in tumour-bearing rats. *FEBS Lett* 2004; **569**: 201-206 [PMID: 15225634 DOI: 10.1016/j.febslet.2004.05.066]

104 **Steensberg A**, Febbraio MA, Osada T, Schjerling P, van Hall G, Saltin B, Pedersen BK. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol* 2001; **537**: 633-639 [PMID: 11731593 DOI: 10.1111/j.1469-7793.2001.00633.x]

105 **Steensberg A**, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab* 2003; **285**: E433-E437 [PMID: 12857678 DOI: 10.1152/ajpendo.00074.2003]

106 **McPherron AC**, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature* 1997; **387**: 83-90 [PMID: 9139826 DOI: 10.1038/387083a0]

107 **Schuelke M**, Wagner KR, Stolz LE, Hübner C, Riebel T, Kömen W, Braun T, Tobin JF, Lee SJ. Myostatin mutation associated with gross muscle hypertrophy in a child. *N Engl J Med* 2004; **350**: 2682-2688 [PMID: 15215484 DOI: 10.1056/NEJMoa040933]

108 **Hulmi JJ**, Silvennoinen M, Lehti M, Kivelä R, Kainulainen H. Altered REDD1, myostatin, and Akt/mTOR/FoxO/MAPK signaling in streptozotocin-induced diabetic muscle atrophy. *Am J Physiol Endocrinol Metab* 2012; **302**: E307-E315 [PMID: 22068602 DOI: 10.1152/ajpendo.00398.2011]

109 **Chen Y**, Cao L, Ye J, Zhu D. Upregulation of myostatin gene expression in streptozotocin-induced type 1 diabetes mice is attenuated by insulin. *Biochem Biophys Res Commun* 2009; **388**: 112-116 [PMID: 19646957 DOI: 10.1016/j.bbrc.2009.07.129]

110 **Wieteska-Skrzeczynska W**, Grzelkowska-Kowalczyk K, Jank M, Maciejewski H. Transcriptional dysregulation of skeletal muscle protein metabolism in streptozotocin-diabetic mice. *J Physiol Pharmacol* 2009; **60** Suppl 1: 29-36 [PMID: 19609011]

111 **Wang F**, Liao Y, Li X, Ren C, Cheng C, Ren Y. Increased circulating myostatin in patients with type 2 diabetes mellitus. *J Huazhong Univ Sci Technolog Med Sci* 2012; **32**: 534-539 [PMID: 22886966 DOI: 10.1007/s11596-012-0092-9]

112 **Brandt C**, Nielsen AR, Fischer CP, Hansen J, Pedersen BK, Plomgaard P. Plasma and muscle myostatin in relation to type 2 diabetes. *PLoS One* 2012; **7**: e37236 [PMID: 22615949 DOI: 10.1371/journal.pone.0037236]

113 **Hittel DS**, Berggren JR, Shearer J, Boyle K, Houmard JA. Increased secretion and expression of myostatin in skeletal muscle from extremely obese women. *Diabetes* 2009; **58**: 30-38 [PMID: 18835929 DOI: 10.2337/db08-0943]

114 **Allen DL**, Cleary AS, Lindsay SF, Loh AS, Reed JM. Myostatin expression is increased by food deprivation in a muscle-specific manner and contributes to muscle atrophy during prolonged food deprivation in mice. *J Appl Physiol* (1985) 2010; **109**: 692-701 [PMID: 20595541 DOI: 10.1152/japplphysiol.00504.2010]

115 **Wagner KR**, Fleckenstein JL, Amato AA, Barohn RJ, Bushby K, Escolar DM, Flanigan KM, Pestronk A, Tawil R, Wolfe GI, Eagle M, Florence JM, King WM, Pandya S, Straub V, Juneau P, Meyers K, Csimma C, Araujo T, Allen R, Parsons SA, Wozney JM, Lavallie ER, Mendell JR. A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy. *Ann Neurol* 2008; **63**: 561-571 [PMID: 18335515 DOI: 10.1002/ana.21338]

116 **Smith RC**, Lin BK. Myostatin inhibitors as therapies for muscle wasting associated with cancer and other disorders. *Curr Opin Support Palliat Care* 2013; **7**: 352-360 [PMID: 24157714 DOI: 10.1097/SPC.0000000000000013]

117 **Attie KM**, Borgstein NG, Yang Y, Condon CH, Wilson DM, Pearsall AE, Kumar R, Willins DA, Seehra JS, Sherman ML. A single ascending-dose study of muscle regulator ACE-031 in healthy volunteers. *Muscle Nerve* 2013; **47**: 416-423 [PMID: 23169607 DOI: 10.1002/mus.23539]

118 **McPherron AC**, Lee SJ. Suppression of body fat accumulation in myostatin-deficient mice. *J Clin Invest* 2002; **109**: 595-601 [PMID: 11877467 DOI: 10.1172/JCI0213562]

119 **Zhao B**, Wall RJ, Yang J. Transgenic expression of myostatin propeptide prevents diet-induced obesity and insulin resistance. *Biochem Biophys Res Commun* 2005; **337**: 248-255 [PMID: 16182246 DOI: 10.1016/j.bbrc.2005.09.044]

120 **Zhang C**, McFarlane C, Lokireddy S, Masuda S, Ge X, Gluckman PD, Sharma M, Kambadur R. Inhibition of myostatin protects against diet-induced obesity by enhancing fatty acid oxidation and promoting a brown adipose phenotype in mice. *Diabetologia* 2012; **55**: 183-193 [PMID: 21927895 DOI: 10.1007/s00125-011-2304-4]

121 **Guo T**, Bond ND, Jou W, Gavrilova O, Portas J, McPherron AC. Myostatin inhibition prevents diabetes and hyperphagia in a mouse model of lipodystrophy. *Diabetes* 2012; **61**: 2414-2423 [PMID: 22596054 DOI: 10.2337/db11-0915]

122 **Bonala S**, Lokireddy S, McFarlane C, Patnam S, Sharma M, Kambadur R. Myostatin induces insulin resistance via Casitas B-lineage lymphoma b (Cblb)-mediated degradation of insulin receptor substrate 1 (IRS1) protein in response to high calorie diet intake. *J Biol Chem* 2014; **289**: 7654-7670 [PMID: 24451368 DOI: 10.1074/jbc.M113.529925]

123 **Guo T**, Jou W, Chanturiya T, Portas J, Gavrilova O, McPherron AC. Myostatin inhibition in muscle, but not adipose tissue, decreases fat mass and improves insulin sensitivity. *PLoS One* 2009; **4**: e4937 [PMID: 19295913 DOI: 10.1371/journal.pone.0004937]

124 **Wilkes JJ**, Lloyd DJ, Gekakis N. Loss-of-function mutation in myostatin reduces tumor necrosis factor alpha production and protects liver against obesity-induced insulin resistance. *Diabetes* 2009; **58**: 1133-1143 [PMID: 19208906 DOI: 10.2337/db08-0245]

125 **Brandt C**, Hansen RH, Hansen JB, Olsen CH, Galle P, Mandrup-Poulsen T, Gehl J, Pedersen BK, Hojman P. Over-expression of Follistatin-like 3 attenuates fat accumulation and improves insulin sensitivity in mice. *Metabolism* 2015; **64**: 283-295 [PMID: 25456456 DOI: 10.1016/j.metabol.2014.10.007]

126 **Zhang C**, McFarlane C, Lokireddy S, Bonala S, Ge X, Masuda S, Gluckman PD, Sharma M, Kambadur R. Myostatin-deficient mice exhibit reduced insulin resistance through activating the AMP-activated protein kinase signalling pathway. *Diabetologia* 2011; **54**: 1491-1501 [PMID: 21347623 DOI: 10.1007/s00125-011-2079-7]

127 **Takahashi H**, Sato K, Yamaguchi T, Miyake M, Watanabe H, Nagasawa Y, Kitagawa E, Terada S, Urakawa M, Rose MT, McMahon CD, Watanabe K, Ohwada S, Gotoh T, Aso H. Myostatin alters glucose transporter-4 (GLUT4) expression in bovine skeletal muscles and myoblasts isolated from double-muscled (DM) and normal-muscled (NM) Japanese shorthorn cattle. *Domest Anim Endocrinol* 2014; **48**: 62-68 [PMID: 24906930 DOI: 10.1016/j.domaniend.2014.01.007]

128 **Cleasby ME**, Jarmin S, Eilers W, Elashry M, Andersen DK, Dickson G, Foster K. Local overexpression of the myostatin propeptide increases glucose transporter expression and enhances skeletal muscle glucose disposal. *Am J Physiol Endocrinol Metab* 2014; **306**: E814-E823 [PMID: 24473441 DOI: 10.1152/ajpendo.00586.2013]

129 **Sriram S**, Subramanian S, Sathiakumar D, Venkatesh R, Salerno MS, McFarlane CD, Kambadur R, Sharma M. Modulation of reactive oxygen species in skeletal muscle by myostatin is mediated through NF-κB. *Aging Cell* 2011; **10**: 931-948 [PMID: 21771249 DOI: 10.1111/j.1474-9726.2011.00734.x]

130 **Sriram S**, Subramanian S, Juvvuna PK, Ge X, Lokireddy S, McFarlane CD, Wahli W, Kambadur R, Sharma M. Myostatin augments muscle-specific ring finger protein-1 expression through an NF-kB independent mechanism in SMAD3 null muscle. *Mol Endocrinol* 2014; **28**: 317-330 [PMID: 24438338 DOI: 10.1210/me.2013-1179]

131 **Sriram S**, Subramanian S, Juvvuna PK, McFarlane C, Salerno MS, Kambadur R, Sharma M. Myostatin induces DNA damage in skeletal muscle of streptozotocin-induced type 1 diabetic mice. *J Biol Chem* 2014; **289**: 5784-5798 [PMID: 24425880 DOI: 10.1074/jbc.M113.483115]

132 **Ploquin C**, Chabi B, Fouret G, Vernus B, Feillet-Coudray C, Coudray C, Bonnieu A, Ramonatxo C. Lack of myostatin alters intermyofibrillar mitochondria activity, unbalances redox status, and impairs tolerance to chronic repetitive contractions in muscle. *Am J Physiol Endocrinol Metab* 2012; **302**: E1000-E1008 [PMID: 22318951 DOI: 10.1152/ajpendo.00652.2011]

133 **Fournier B**, Murray B, Gutzwiller S, Marcaletti S, Marcellin D, Bergling S, Brachat S, Persohn E, Pierrel E, Bombard F, Hatakeyama S, Trendelenburg AU, Morvan F, Richardson B, Glass DJ, Lach-Trifilieff E, Feige JN. Blockade of the activin receptor IIb activates functional brown adipogenesis and thermogenesis by inducing mitochondrial oxidative metabolism. *Mol Cell Biol* 2012; **32**: 2871-2879 [PMID: 22586266 DOI: 10.1128/MCB.06575-11]

134 **Braga M**, Reddy ST, Vergnes L, Pervin S, Grijalva V, Stout D, David J, Li X, Tomasian V, Reid CB, Norris KC, Devaskar SU, Reue K, Singh R. Follistatin promotes adipocyte differentiation, browning, and energy metabolism. *J Lipid Res* 2014; **55**: 375-384 [PMID: 24443561 DOI: 10.1194/jlr.M039719]

135 **Braga M**, Pervin S, Norris K, Bhasin S, Singh R. Inhibition of in vitro and in vivo brown fat differentiation program by myostatin. *Obesity* (Silver Spring) 2013; **21**: 1180-1188 [PMID: 23868854 DOI: 10.1002/oby.20117]

136 **Kim WK**, Choi HR, Park SG, Ko Y, Bae KH, Lee SC. Myostatin inhibits brown adipocyte differentiation via regulation of Smad3-mediated β-catenin stabilization. *Int J Biochem Cell Biol* 2012; **44**: 327-334 [PMID: 22094186 DOI: 10.1016/j.biocel.2011.11.004]

137 **Shan T**, Liang X, Bi P, Kuang S. Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1α-Fndc5 pathway in muscle. *FASEB J* 2013; **27**: 1981-1989 [PMID: 23362117 DOI: 10.1096/fj.12-225755]

138 **Gunawardana SC**, Piston DW. Reversal of type 1 diabetes in mice by brown adipose tissue transplant. *Diabetes* 2012; **61**: 674-682 [PMID: 22315305 DOI: 10.2337/db11-0510]

139 **Wang Q**, Guo T, Portas J, McPherron AC. A soluble activin receptor type IIB does not improve blood glucose in streptozotocin-treated mice. *Int J Biol Sci* 2015; **11**: 199-208 [PMID: 25561902 DOI: 10.7150/ijbs.10430]

140 **Ingalls AM**, Dickie MM, Snell GD. Obese, a new mutation in the house mouse. *J Hered* 1950; **41**: 317-318 [PMID: 14824537]

141 **Zhang Y**, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; **372**: 425-432 [PMID: 7984236]

142 **Blüher S**, Mantzoros CS. Leptin in reproduction. *Curr Opin Endocrinol Diabetes Obes* 2007; **14**: 458-464 [PMID: 17982352 DOI: 10.1097/MED.0b013e3282f1cfdc]

143 **Hamrick MW**. Leptin, bone mass, and the thrifty phenotype. *J Bone Miner Res* 2004; **19**: 1607-1611 [PMID: 15355554 DOI: 10.1359/JBMR.040712]

144 **Fantuzzi G**, Faggioni R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. *J Leukoc Biol* 2000; **68**: 437-446 [PMID: 11037963]

145 **Kershaw EE**, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004; **89**: 2548-2556 [PMID: 15181022 DOI: 10.1210/jc.2004-0395]

146 **Hanaki K**, Becker DJ, Arslanian SA. Leptin before and after insulin therapy in children with new-onset type 1 diabetes. *J Clin Endocrinol Metab* 1999; **84**: 1524-1526 [PMID: 10323373 DOI: 10.1210/jcem.84.5.5653]

147 **Kratzsch J**, Deimel A, Galler A, Kapellen T, Klinghammer A, Kiess W. Increased serum soluble leptin receptor levels in children and adolescents with type 1 diabetes mellitus. *Eur J Endocrinol* 2004; **151**: 475-481 [PMID: 15476448 DOI: 10.1530/eje.0.1510475]

148 **Havel PJ**, Uriu-Hare JY, Liu T, Stanhope KL, Stern JS, Keen CL, Ahrén B. Marked and rapid decreases of circulating leptin in streptozotocin diabetic rats: reversal by insulin. *Am J Physiol* 1998; **274**: R1482-R1491 [PMID: 9612417]

149 **Sivitz WI**, Walsh S, Morgan D, Donohoue P, Haynes W, Leibel RL. Plasma leptin in diabetic and insulin-treated diabetic and normal rats. *Metabolism* 1998; **47**: 584-591 [PMID: 9591751 DOI: 10.1016/S0026-0495(98)90244-X]

150 **Ueno N**, Inui A, Kalra PS, Kalra SP. Leptin transgene expression in the hypothalamus enforces euglycemia in diabetic, insulin-deficient nonobese Akita mice and leptin-deficient obese ob/ob mice. *Peptides* 2006; **27**: 2332-2342 [PMID: 16621153 DOI: 10.1016/j.peptides.2006.03.006]

151 **Kojima S**, Asakawa A, Amitani H, Sakoguchi T, Ueno N, Inui A, Kalra SP. Central leptin gene therapy, a substitute for insulin therapy to ameliorate hyperglycemia and hyperphagia, and promote survival in insulin-deficient diabetic mice. *Peptides* 2009; **30**: 962-966 [PMID: 19428774 DOI: 10.1016/j.peptides.2009.01.007]

152 **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 USA* 2010; **107**: 4813-4819 [PMID: 20194735 DOI: 10.1073/pnas.0909422107]

153 **Kruger AJ**, Yang C, Lipson KL, Pino SC, Leif JH, Hogan CM, Whalen BJ, Guberski DL, Lee Y, Unger RH, Greiner DL, Rossini AA, Bortell R. Leptin treatment confers clinical benefit at multiple stages of virally induced type 1 diabetes in BB rats. *Autoimmunity* 2011; **44**: 137-148 [PMID: 20695765 DOI: 10.3109/08916934.2010.482116]

154 **Sindelar DK**, Havel PJ, Seeley RJ, Wilkinson CW, Woods SC, Schwartz MW. Low plasma leptin levels contribute to diabetic hyperphagia in rats. *Diabetes* 1999; **48**: 1275-1280 [PMID: 10342816 DOI: 10.2337/diabetes.48.6.1275]

155 **Fujikawa T**, Chuang JC, Sakata I, Ramadori G, Coppari R. Leptin therapy improves insulin-deficient type 1 diabetes by CNS-dependent mechanisms in mice. *Proc Natl Acad Sci USA* 2010; **107**: 17391-17396 [PMID: 20855609 DOI: 10.1073/pnas.1008025107]

156 **Lee Y**, Berglund ED, Wang MY, Fu X, Yu X, Charron MJ, Burgess SC, Unger RH. Metabolic manifestations of insulin deficiency do not occur without glucagon action. *Proc Natl Acad Sci USA* 2012; **109**: 14972-14976 [PMID: 22891336 DOI: 10.1073/pnas.1205983109]

157 **Lee Y**, Berglund ED, Yu X, Wang MY, Evans MR, Scherer PE, Holland WL, Charron MJ, Roth MG, Unger RH. Hyperglycemia in rodent models of type 2 diabetes requires insulin-resistant alpha cells. *Proc Natl Acad Sci USA* 2014; **111**: 13217-13222 [PMID: 25157166 DOI: 10.1073/pnas.1409638111]

158 **Wang MY**, Yan H, Shi Z, Evans MR, Yu X, Lee Y, Chen S, Williams A, Philippe J, Roth MG, Unger RH. Glucagon receptor antibody completely suppresses type 1 diabetes phenotype without insulin by disrupting a novel diabetogenic pathway. *Proc Natl Acad Sci USA* 2015; **112**: 2503-2508 [PMID: 25675519 DOI: 10.1073/pnas.1424934112]

159 **Cusin I**, Zakrzewska KE, Boss O, Muzzin P, Giacobino JP, Ricquier D, Jeanrenaud B, Rohner-Jeanrenaud F. Chronic central leptin infusion enhances insulin-stimulated glucose metabolism and favors the expression of uncoupling proteins. *Diabetes* 1998; **47**: 1014-1019 [PMID: 9648822 DOI: 10.2337/diabetes.47.7.1014]

160 **Chinookoswong N**, Wang JL, Shi ZQ. Leptin restores euglycemia and normalizes glucose turnover in insulin-deficient diabetes in the rat. *Diabetes* 1999; **48**: 1487-1492 [PMID: 10389859 DOI: 10.2337/diabetes.48.7.1487]

161 **Toda C**, Shiuchi T, Kageyama H, Okamoto S, Coutinho EA, Sato T, Okamatsu-Ogura Y, Yokota S, Takagi K, Tang L, Saito K, Shioda S, Minokoshi Y. Extracellular signal-regulated kinase in the ventromedial hypothalamus mediates leptin-induced glucose uptake in red-type skeletal muscle. *Diabetes* 2013; **62**: 2295-2307 [PMID: 23530005 DOI: 10.2337/db12-1629]

162 **Yu X**, Park BH, Wang MY, Wang ZV, Unger RH. Making insulin-deficient type 1 diabetic rodents thrive without insulin. *Proc Natl Acad Sci USA* 2008; **105**: 14070-14075 [PMID: 18779578 DOI: 10.1073/pnas.0806993105]

163 **Ceddia RB**, William WN, Curi R. Comparing effects of leptin and insulin on glucose metabolism in skeletal muscle: evidence for an effect of leptin on glucose uptake and decarboxylation. *Int J Obes Relat Metab Disord* 1999; **23**: 75-82 [PMID: 10094581 DOI: 10.1038/sj.ijo.0800762]

164 **Hidaka S**, Yoshimatsu H, Kondou S, Tsuruta Y, Oka K, Noguchi H, Okamoto K, Sakino H, Teshima Y, Okeda T, Sakata T. Chronic central leptin infusion restores hyperglycemia independent of food intake and insulin level in streptozotocin-induced diabetic rats. *FASEB J* 2002; **16**: 509-518 [PMID: 11919153 DOI: 10.1096/fj.01-0164com]

165 **Muoio DM**, Dohm GL, Fiedorek FT, Tapscott EB, Coleman RA. Leptin directly alters lipid partitioning in skeletal muscle. *Diabetes* 1997; **46**: 1360-1363 [PMID: 9231663 DOI: 10.2337/diab.46.8.1360]

166 **Steinberg GR**, Parolin ML, Heigenhauser GJ, Dyck DJ. Leptin increases FA oxidation in lean but not obese human skeletal muscle: evidence of peripheral leptin resistance. *Am J Physiol Endocrinol Metab* 2002; **283**: E187-E192 [PMID: 12067860 DOI: 10.1152/ajpendo.00542.2001]

167 **Minokoshi Y**, Kim YB, Peroni OD, Fryer LG, Müller C, Carling D, Kahn BB. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 2002; **415**: 339-343 [PMID: 11797013 DOI: 10.1038/415339a]

168 **German JP**, Wisse BE, Thaler JP, Oh-I S, Sarruf DA, Ogimoto K, Kaiyala KJ, Fischer JD, Matsen ME, Taborsky GJ, Schwartz MW, Morton GJ. Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. *Diabetes* 2010; **59**: 1626-1634 [PMID: 20424233 DOI: 10.2337/db09-1918]

169 **Kusakabe T**, Tanioka H, Ebihara K, Hirata M, Miyamoto L, Miyanaga F, Hige H, Aotani D, Fujisawa T, Masuzaki H, Hosoda K, Nakao K. Beneficial effects of leptin on glycaemic and lipid control in a mouse model of type 2 diabetes with increased adiposity induced by streptozotocin and a high-fat diet. *Diabetologia* 2009; **52**: 675-683 [PMID: 19169663 DOI: 10.1007/s00125-009-1258-2]

170 **Lin CY**, Higginbotham DA, Judd RL, White BD. Central leptin increases insulin sensitivity in streptozotocin-induced diabetic rats. *Am J Physiol Endocrinol Metab* 2002; **282**: E1084-E1091 [PMID: 11934674 DOI: 10.1152/ajpendo.00489.2001]

171 **Kraus D**, Herman MA, Kahn BB. Leveraging leptin for type I diabetes? *Proc Natl Acad Sci USA* 2010; **107**: 4793-4794 [PMID: 20212134 DOI: 10.1073/pnas.1000736107]

172 **Miyanaga F**, Ogawa Y, Ebihara K, Hidaka S, Tanaka T, Hayashi S, Masuzaki H, Nakao K. Leptin as an adjunct of insulin therapy in insulin-deficient diabetes. *Diabetologia* 2003; **46**: 1329-1337 [PMID: 12928770 DOI: 10.1007/s00125-003-1193-6]

173 **Scherer PE**, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995; **270**: 26746-26749 [PMID: 7592907 DOI: 10.1074/jbc.270.45.26746]

174 **Berg AH**, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001; **7**: 947-953 [PMID: 11479628 DOI: 10.1038/90992]

175 **Fruebis J**, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 2001; **98**: 2005-2010 [PMID: 11172066 DOI: 10.1073/pnas.98.4.2005]

176 **Hotta K**, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 2001; **50**: 1126-1133 [PMID: 11334417 DOI: 10.2337/diabetes.50.5.1126]

177 **Yamauchi T**, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007; **13**: 332-339 [PMID: 17268472 DOI: 10.1038/nm1557]

178 **Arita Y**, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; **257**: 79-83 [PMID: 10092513]

179 **Weyer C**, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001; **86**: 1930-1935 [PMID: 11344187 DOI: 10.1210/jcem.86.5.7463]

180 **Yamauchi T**, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; **7**: 941-946 [PMID: 11479627 DOI: 10.1038/90984]

181 **Liu Y**, Chewchuk S, Lavigne C, Brûlé S, Pilon G, Houde V, Xu A, Marette A, Sweeney G. Functional significance of skeletal muscle adiponectin production, changes in animal models of obesity and diabetes, and regulation by rosiglitazone treatment. *Am J Physiol Endocrinol Metab* 2009; **297**: E657-E664 [PMID: 19531641 DOI: 10.1152/ajpendo.00186.2009]

182 **Imagawa A**, Funahashi T, Nakamura T, Moriwaki M, Tanaka S, Nishizawa H, Sayama K, Uno S, Iwahashi H, Yamagata K, Miyagawa J, Matsuzawa Y. Elevated serum concentration of adipose-derived factor, adiponectin, in patients with type 1 diabetes. *Diabetes Care* 2002; **25**: 1665-1666 [PMID: 12196453 DOI: 10.2337/diacare.25.9.1665]

183 **Abi Khalil C**, Mohammedi K, Aubert R, Travert F, Hadjadj S, Roussel R, Fumeron F, Marre M. Intensifying glycaemic control with insulin reduces adiponectin and its HMW isoform moderately in type 2, but not in type 1, diabetes. *Diabetes Metab* 2011; **37**: 259-261 [PMID: 21306933 DOI: 10.1016/j.diabet.2010.12.001]

184 **Pereira RI**, Snell-Bergeon JK, Erickson C, Schauer IE, Bergman BC, Rewers M, Maahs DM. Adiponectin dysregulation and insulin resistance in type 1 diabetes. *J Clin Endocrinol Metab* 2012; **97**: E642-E647 [PMID: 22278421 DOI: 10.1210/jc.2011-2542]

185 **Stadler M**, Storka A, Theuer EA, Krebs M, Vojtassakova E, Nowotny P, Pacini G, Kästenbauer T, Luger A, Prager R, Wolzt M, Anderwald C. Adipokines in type 1 diabetes after successful pancreas transplantation: normal visfatin and retinol-binding-protein-4, but increased total adiponectin fasting concentrations. *Clin Endocrinol* (Oxf) 2010; **72**: 763-769 [PMID: 19769621 DOI: 10.1111/j.1365-2265.2009.03709.x]

186 **Timar R**, Timar B, Degeratu D, Serafinceanu C, Oancea C. Metabolic syndrome, adiponectin and proinflammatory status in patients with type 1 diabetes mellitus. *J Int Med Res* 2014; **42**: 1131-1138 [PMID: 25053801 DOI: 10.1177/0300060514541829]

187 **Wijesekara N**, Krishnamurthy M, Bhattacharjee A, Suhail A, Sweeney G, Wheeler MB. Adiponectin-induced ERK and Akt phosphorylation protects against pancreatic beta cell apoptosis and increases insulin gene expression and secretion. *J Biol Chem* 2010; **285**: 33623-33631 [PMID: 20709750 DOI: 10.1074/jbc.M109.085084]

188 **Fasshauer M**, Klein J, Neumann S, Eszlinger M, Paschke R. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 2002; **290**: 1084-1089 [PMID: 11798186 DOI: 10.1006/bbrc.2001.6307]

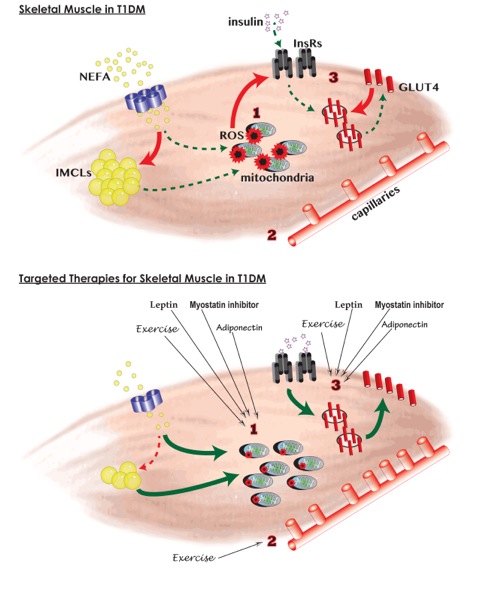
189 **Ebeling P**, Essén-Gustavsson B, Tuominen JA, Koivisto VA. Intramuscular triglyceride content is increased in IDDM. *Diabetologia* 1998; **41**: 111-115 [PMID: 9498639 DOI: 10.1007/s001250050875]

190 **Ling AH**, Donaghue KC, Howard NJ, Arrowsmith FE, Ward JA, Baur LA, Thompson CH. Intramyocellular lipid, adiposity, and muscle oxygen supply in prepubertal type 1 diabetes. *Pediatr Diabetes* 2003; **4**: 126-131 [PMID: 14655270 DOI: 10.1034/j.1399-5448.2003.00021.x]

191 **Krause MP**, Liu Y, Vu V, Chan L, Xu A, Riddell MC, Sweeney G, Hawke TJ. Adiponectin is expressed by skeletal muscle fibers and influences muscle phenotype and function. *Am J Physiol Cell Physiol* 2008; **295**: C203-C212 [PMID: 18463233 DOI: 10.1152/ajpcell.00030.2008]

192 **Behre CJ**. Adiponectin: saving the starved and the overfed. *Med Hypotheses* 2007; **69**: 1290-1292 [PMID: 17509773 DOI: 10.1016/j.mehy.2007.02.044]

**P-Reviewer:** Gorgey AS, Grau JM **S-Editor:** Ji FF **L-Editor: E-Editor:**

****

**Figure 1 Schematic figure representing skeletal muscle dysfunction in type 1 diabetes mellitus and possible therapeutic approaches targeting skeletal muscle**. (1) In T1DM, due to dyslipidemia and/or the reduced ability for muscle to uptake carbohydrates, an increased amount of non-esterified fatty acids (NEFA) are shuttled into the skeletal muscle. The majority of this excess fat is deposited in the form of intramyocellular lipid droplets (IMCLs) as there is a reduced ability to efficiently oxidize lipids due to impairments to oxidative capacity. An increased amount of metabolic stress and reactive oxygen species (ROS) production within the mitochondria is observed in T1DM and appears to be a causative factor; (2) T1DM also induces dysfunction with regard to the vasculature network. There is a thickening of the basement membrane and downregulation of angiogenesis resulting in a decreased capillary-to-fiber ratio. Impairments to microvasculature have also been linked with generation of macrovascular complications (*e.g*., atherosclerosis), a serious long-term diabetic complication; and (3) Insulin resistance results in disruptions to the insulin signalling pathway. Improper insulin signalling prevents excess glucose in the blood from being taken up by the muscle *via* decreased translocation of the GLUT4 glucose transporter. Our proposed treatments of exercise, myostatin inhibition, leptin and adiponectin target the specific pathways mentioned above in skeletal muscle. We hypothesize that if diabetic myopathy is attenuated it will allow muscle to contribute a greater amount towards reducing hyperglycemia. Since muscle is an important large metabolic organ, if skeletal muscle health was improved there would be resultant decreases in oxidative stress, improvements to glycemic control and a reduction in the need for exogenous insulin. T1DM: Type 1 diabetes mellitus.