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

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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

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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.

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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 of improving 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 II B/X fibers, as well as a decrease in type II A and II B/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 *Ins2*^{Akita+/-} 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 *Ins2*^{Akita+/-} 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 accu-

mulation 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 evident 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

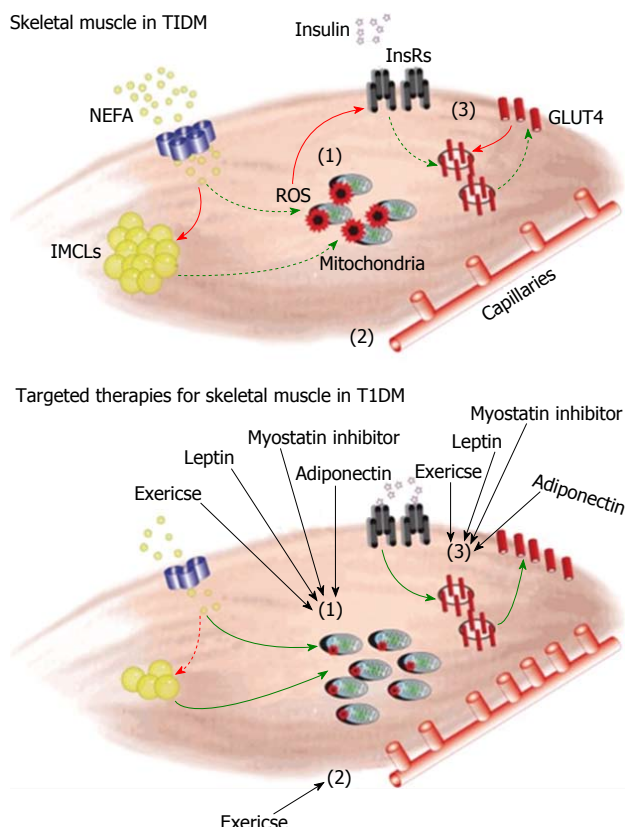


Figure 1 Schematic figure representing skeletal muscle dysfunction in type 1 diabetes mellitus and possible therapeutic approaches targeting skeletal muscle. (1) In T1DM, due to dyslipidemia and/or the reduced ability for muscle to uptake carbohydrates, an increased amount of non-esterified fatty acids (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; GLUT4: Glucose transporter type 4.

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 adaptations 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.*, interleukin 1B (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 of 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 nuclear factor κ B 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 5' AMP-activated protein kinase (AMPK)-PGC1 α -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 *et al.*^[138] have shown that a transplant of brown adipose tissue into STZ-diabetic mice resulted in normalization of glucose and attenuation of the diabetic state. This effect is thought to occur through recovery of subcutaneous white adipose tissue, resulting in the normalization of adipokines leptin, adiponectin and insulin-like growth factor-1 (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, Wang *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 *et al.*^[162] 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 acetyl-CoA carboxylase^[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 *et al.*^[191] 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. 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^[192] 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 .

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.

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Observational Study

Evaluation of the Finnish Diabetes Risk Score to predict type 2 diabetes mellitus in a Colombian population: A longitudinal observational study

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Abstract

AIM: To assess the performance of the Finnish Diabetes Risk Score (FINDRISC) questionnaire for detecting and predicting type 2 diabetes mellitus (DM2) in a Colombian population.

METHODS: This is a longitudinal observational study conducted in Floridablanca, Colombia. Adult subjects (age ≥ 35 years) without known diabetes, were included. A modified version of FINDRISC was completed, and the glycemia values from all the subjects were collected from the hospital's database. Firstly, a cross-sectional analysis was performed and then, the subsample of prediabetic participants was followed for diabetes incidence.

RESULTS: A total of 772 subjects were suitable for the study. The overall prevalence of undiagnosed DM2 was 2.59%, and the incidence of DM2 among the prediabetic participants was 7.5 per 100 person-years after a total of 265257 person-years follow-up. The FINDRISC at baseline was significantly associated with undiagnosed and incident DM2. The area under receiver operating characteristics curve of the FINDRISC score for detecting undiagnosed DM2 in both men and women was 0.7477 and 0.7175, respectively; and for predicting the incidence of DM2 among prediabetics was 71.99% in men and 67.74% in women.

CONCLUSION: The FINDRISC questionnaire is a useful screening tool to identify cross-sectionally unknown DM2 and to predict the incidence of DM2 among prediabetics in the Colombian population.

Key words: Finnish diabetes risk score; Type 2 diabetes mellitus; Prediabetes; Screening; Colombia

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Core tip: The prevalence of type 2 diabetes mellitus (DM2) is rapidly increasing worldwide, and unfortunately its diagnosis is being made when vascular complications are already exhibited. Since laboratory-based diagnostic methods are costly, the International Diabetes Federation suggests to do an early detection of undiagnosed DM2 patients, and to identify individuals at risk for developing DM2 by simple risk-scoring questionnaires. The present study assesses the performance of the Finnish Diabetes Risk Score questionnaire in a Colombian population, and aims to establish the specific cutoff values for detecting subjects at increased risk of undiagnosed DM2 and for predicting the incidence of DM2 in prediabetic individuals.

Gomez-Arbelaes D, Alvarado-Jurado L, Ayala-Castillo M, Forero-Naranjo L, Camacho PA, Lopez-Jaramillo P. Evaluation of the Finnish Diabetes Risk Score to predict type 2 diabetes mellitus in a Colombian population: A longitudinal observational study. *World J Diabetes* 2015; 6(17): 1337-1344 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v6/i17/1337.htm> DOI: <http://dx.doi.org/10.4239/wjd.v6.i17.1337>

INTRODUCTION

The prevalence of type 2 diabetes mellitus (DM2) is

rapidly increasing worldwide^[1]. Recently, it has been estimated that the number of adults with DM2 will increase between 2010 and 2030 by 69% and 20% in developing and industrialized countries, respectively^[1]. In Colombia the overall prevalence of DM2 is 5.51%, however significant differences are observed and in some regions the prevalence rises to 8.2%^[2]. The increase in the prevalence of DM2 across the world has become an important public health concern given that it is a major risk factor for death and numerous nonfatal complications. Hence, this situation will form a large burden to the patients, their families, and the health care system^[3].

Several studies have demonstrated that DM2 could be prevented, and its complications can be limited when a timely and appropriate intervention is started^[4,5]. However, in the majority of cases detection is delayed and at the time of diagnosis many patients already exhibit signs of microvascular and macrovascular complications^[6]. Remarkably, there has been proposed that Latin American population has an increased vulnerability for developing macrovascular diseases at glycemia levels lower than the internationally established cut points for DM2^[7,8]. Thus, it is clinically important to do an early detection of undiagnosed DM2 patients, and to identify individuals at risk for developing DM2 to implement intensive preventive interventions.

The diagnosis of DM2 is obtained by increased values of fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) and/or glycated hemoglobin (HbA1C)^[9], but the determination of biochemical variables is costly, and this impairs its use as a large scale screening tool. Conversely, simple risk-scoring questionnaires are useful and constitute a more cost-effective DM2 screening approach^[10]. Hence, the international diabetes federation has recommended performing a blood test to detect possible diabetes when a high risk score has been obtained^[11].

A number of predictive risk-scoring models for DM2 are currently available for clinical use^[12-14]. But, most require specific blood test results and this limits its widespread use from a public health perspective. Meanwhile, the Finnish Diabetes Risk Score (FINDRISC)^[15] has demonstrated to be a simple, fast, inexpensive, noninvasive, and reliable tool to identify individuals at high risk for DM2. Therefore, the FINDRISC has been internationally assessed in several countries, including Colombia^[16-20]. However, in our country the ability of FINDRISC to predict the development of incident DM2 was not evaluated, and the specific risk scores for predicting undiagnosed and incident DM2 in our population were not established. Hence, this study aims to assess the performance of the FINDRISC score in detecting undiagnosed DM2 in the general population and to predict incident DM2 among prediabetics. Moreover, the study aims to establish the specific cutoff values for identifying increased risk of undiagnosed DM2 in the general population and incident DM2 among prediabetics in Colombia.

MATERIALS AND METHODS

A longitudinal observational study has been conducted. Between June 1, 2012 and October 31, 2012 adult subjects (age ≥ 35 years) who attended the general practitioner for any reason at the ambulatory service of the Ophthalmological Foundation of Santander - FOSCAL in Floridablanca, Colombia, were involved in the screening. People with known diabetes mellitus (type 1 or 2) were not recruited. Any acute illness, pregnancy in women, and currently use of metformin or other glucose-modifying prescription drugs, were also considered as exclusion criteria.

The subjects were asked to complete a modified version of the FINDRISC score^[15], which evaluates eight variables that are clearly correlated with the risk of DM2: Age, body mass index (BMI), waist circumference (WC), current antihypertensive medication, frequency of fruit and vegetable consumption, physical activity, personal history of high blood glucose, and family history of DM2. Variables are scored according to the risk that they may confer, resulting in a range of 0-26 total points. We adjusted the WC cutoffs points according to the previously described values that confer an increased cardio-metabolic risk in the Colombian population^[21]. As a result, the WC has been scored as follows: Men: < 90 cm, the score is 0; 90-98 cm, the score is 3; > 98 cm, the score is 4. Women: < 80 cm, the score is 0; 80-88 cm, the score is 3; > 88 cm, the score is 4.

General practitioners performed the anthropometric measurements. Weight and height were measured with light clothing and no shoes with calibrated scales and a wall-mounted stadiometers, respectively, while participants were asked to stand erect with their head positioned in the Frankfort horizontal plane. WC was measured midway between the lowest rib and the iliac crest using an anthropometric tape. BMI was calculated by dividing body weight by the square of height [BMI = weight (kg)/height (m)²].

Laboratory tests (FPG, OGTT and HbA1C) were collected directly from the hospital's database. Only those tests taken within the two months previous or after the survey were valid for the study. At least one of the tests: FPG, OGTT or HbA1c, should be present to consider the patient as suitable for the study. Classification of glucometabolic state was based on the American Diabetes Association (ADA) criteria^[9]. The diagnosis of DM2 was established when FPG ≥ 126 mg/dL, OGTT ≥ 200 mg/dL and/or HbA1c $\geq 6.5\%$. Prediabetes was diagnosed by the presence of impaired FPG (≥ 100 mg/dL to < 126 mg/dL), impaired OGTT (≥ 140 mg/dL to < 200 mg/dL) and/or impaired HbA1c ($\geq 5.7\%$ to $\leq 6.4\%$).

Thereafter, the subsample of baseline prediabetic participants was followed for diabetes incidence in real life settings. The updated glucometabolic tests (FPG, OGTT and HbA1C) were also collected from the hospital's database, and DM2 incident cases were diagnosed according to the ADA criteria^[9].

Ethics statement

The study protocol was in accordance with the Declaration of Helsinki, and the health research ethics board of the Ophthalmological Foundation of Santander - FOSCAL approved all study procedures. The subjects expressed their interest in participating in the study before they were included. As there were no interventions directly related to the study written informed consent was not required.

Statistical analysis

Descriptive statistics were computed for variables of interests, and included mean values and standard deviations of continuous variables and absolute and relative frequencies of categorical factors. Normality of distribution was checked for continuous variables using the Shapiro-Wilk test and by graphical methods. Wilcoxon Rank Sum test was used to investigate the differences in continuous variables. Testing for differences in categorical variables was accomplished using the Pearson's χ^2 test.

Moreover, we used unconditional multivariate logistic regression models to assess the associations between the FINDRISC score and undiagnosed and incident DM2. These analyses were adjusted for potential confounders, such as gender and age. We re-coded the FINDRISC into tertiles and compared the risk of DM2 in each tertile with the lowest category of risk (reference group).

To assess performance of the FINDRISC score with respect to undiagnosed and incident DM2, receiver operating characteristics (ROC) curves, sensitivity, specificity, positive predictive values and negative predictive values (NPV) were calculated. The maximum values of the Youden's index^[22] were used as a criterion for selecting the optimum cut-off points. All statistical analysis was carried out by a biomedical statistician using Stata statistical software, release 12.0 (Stata Corporation, College Station, TX, United States). A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 772 subjects were suitable for the study, of which 544 (70.47%) were women. The overall mean age was 58.34 ± 12.07 years, the overall prevalence of undiagnosed DM2 was 2.59% (95%CI: 1.46-3.71), and the prevalence of prediabetes was 24.09% (95%CI: 21.06-27.11) (Table 1). Baseline demographic, anthropometric and metabolic characteristics of the study population are presented in Table 1, and the prevalences of FINDRISC questionnaire components are presented in Table 2.

The FINDRISC score was positively associated with undiagnosed DM2 (Table 3). The risk of DM2 increased with increasing tertiles of FINDRISC. Compared with participants in the lowest tertile, the risk of DM2 was 5.69 times higher for those in the highest tertile (OR = 5.69, 95%CI: 1.56-20.67).

Table 1 Baseline characteristics of the study population according to gender

Variables	Total (n = 772)	Men (n = 228)	Women (n = 544)
¹ Age, yr	58.34 (12.07)	58.63 (12.67)	58.22 (11.82)
¹ BMI, kg/m ²	27.36 (4.56)	27.08 (4.56)	27.47 (4.56)
¹ Waist circumference, cm	91.91 (10.47)	97.05 (10.88)	89.78 (9.52) ²
¹ Fasting plasma glucose, mg/dL	94.41 (12.60)	96.17 (13.94)	93.68 (11.94) ²
^{1,4} Oral glucose tolerance test, mg/dL	107.89 (32.82)	111.11 (36.55)	106.23 (30.75)
^{1,4} HbA1c, %	6.49 (1.27)	6.39 (1.24)	6.56 (1.31)
Undiagnosed DM2, n(%)	20 (2.59)	6 (2.63)	14 (2.57)
Prediabetes, n(%)	186 (24.09)	61 (26.75)	125 (22.98)
FINDRISC score	11.84 (4.80)	11.00 (4.71)	12.18 (4.80) ³

¹Data are presented as mean ± SD for continuous variables; ²Wilcoxon Rank Sum test $P < 0.05$;

³Wilcoxon Rank Sum test $P < 0.005$; ⁴Variable with missing values. BMI: Body mass index; DM2: Type 2 diabetes mellitus; FINDRISC: Finnish Diabetes Risk Score; HbA1c: Hemoglobin A1c.

Table 2 Prevalence of components of the Finnish Diabetes Risk Score according to gender n (%)

Variables	Total (n = 772)	Men (n = 228)	Women (n = 544)
Age (yr)			
< 45	106 (13.73)	35 (15.35)	71 (13.05)
45-54	207 (26.81)	59 (25.88)	148 (27.21)
55-64	203 (26.30)	51 (22.37)	152 (27.94)
> 64	256 (33.16)	83 (36.40)	173 (31.80)
BMI (kg/m ²)			
< 25	250 (32.38)	75 (32.89)	175 (32.17)
25-30	331 (42.88)	105 (46.05)	226 (41.54)
> 30	191 (24.74)	48 (21.05)	143 (26.29)
WC (cm)			
M: < 90; W: < 80	121 (15.67)	50 (21.93)	71 (13.05) ²
M: 90-98; W: 80-88	272 (35.23)	84 (36.84)	188 (34.56)
M: > 98; W: > 88	379 (49.09)	94 (41.23)	285 (52.39)
PA (30 min/d)			
Yes	362 (46.95)	112 (49.12)	250 (46.04)
No	409 (53.05)	116 (50.88)	293 (53.96)
Vegetables - fruits			
Daily	433 (56.09)	112 (49.12)	321 (59.01) ¹
No daily	339 (43.91)	116 (50.88)	223 (40.99)
Hypertension			
Without medication	442 (57.25)	136 (59.65)	306 (56.25)
With medication	330 (42.75)	92 (40.35)	238 (43.75)
Hyperglycemia antecedent			
No	634 (82.12)	199 (87.28)	435 (79.96) ¹
Yes	138 (17.88)	29 (12.72)	109 (20.04)
Familiar antecedents DM2			
No	473 (61.27)	147 (64.47)	326 (59.93)
Grandparents	72 (9.33)	26 (11.40)	46 (8.46)
Parents	227 (29.40)	55 (24.12)	172 (31.62)

¹Pearson's χ^2 test (χ^2) $P < 0.05$; ²Pearson's χ^2 test (χ^2) $P < 0.005$. DM2: Type 2 diabetes mellitus; BMI: Body mass index; WC: Waist circumference; PA: Physical activity; M: Male; F: Female.

Table 3 Odds ratios of undiagnosed type 2 diabetes mellitus according to Finnish Diabetes Risk Score tertiles at baseline

	Undiagnosed DM2 (FPG \geq 126 mg/dL and/or OGTT \geq 200 mg/dL and/or HbA1c \geq 6.5%)								
	1 st tertile			2 nd tertile			3 rd tertile		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Unadjusted	1.0	-	-	2.45	0.60-9.92	0.207	5.69	1.56-20.67	0.008
Gender-adjusted	1.0	-	-	2.49	0.61-10.10	0.199	5.88	1.60-21.54	0.007
Age- and gender-adjusted	1.0	-	-	2.28	0.55-9.35	0.252	4.93	1.28-18.92	0.020

1st tertile: \leq 10; 2nd tertile: 11-14; 3rd tertile: \geq 15. OR: Odds ratio; DM2: Type 2 diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; OGTT: Oral glucose tolerance test.

Table 4 Hazard ratios of incident type 2 diabetes mellitus according to Finnish Diabetes Risk Score tertiles at baseline, during follow-up and among the subsample of prediabetic patients

	Incident DM2 (FPG \geq 126 mg/dL and/or OGTT \geq 200 mg/dL and/or HbA1c \geq 6.5%)								
	1 st tertile			2 nd tertile			3 rd tertile		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
Unadjusted	1.00	-	-	3.67	0.77-17.36	0.101	5.31	1.15-24.43	0.032
Gender-adjusted	1.00	-	-	3.93	0.81-18.89	0.087	5.75	1.22-27.03	0.027
Age- and gender-adjusted	1.00	-	-	3.52	0.70-17.53	0.124	4.81	0.93-24.85	0.061

1st tertile: \leq 12; 2nd tertile: 13-16; 3rd tertile: \geq 17. HR: Hazard ratio; DM2: Type 2 diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; OGTT: Oral glucose tolerance test.

Table 5 Finnish Diabetes Risk Score to identify undiagnosed type 2 diabetes mellitus by gender

FINDRISC score	Undiagnosed DM2 (FPG \geq 126 mg/dL and/or OGTT \geq 200 mg/dL and/or HbA1c \geq 6.5%)				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index
Cutoff value \geq 11					
Men	83.3	49.1	4.2	99.1	0.324
Women	85.7	37.2	3.5	99.0	0.228
Cutoff value \geq 12					
Men	66.7	56.8	4.0	98.4	0.234
Women	85.7	44.9	3.9	99.2	0.306
Cutoff value \geq 13					
Men	66.7	66.2	5.1	98.7	0.328
Women	78.6	54.3	4.4	99.0	0.329
Cutoff value \geq 14					
Men	66.7	75.2	6.8	98.8	0.419
Women	71.4	62.6	4.8	98.8	0.340
Cutoff value \geq 15					
Men	50.0	81.1	6.7	98.4	0.310
Women	57.1	70.7	4.9	98.4	0.278
Cutoff value \geq 16					
Men	33.3	86.0	6.1	98.0	0.193
Women	50.0	76.2	5.3	98.3	0.262
Cutoff value \geq 17					
Men	33.3	88.3	7.1	98.0	0.216
Women	50.0	81.9	6.8	98.4	0.318

DM2: Type 2 diabetes mellitus; FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test; HbA1c: Hemoglobin A1c; PPV: Positive predictive value; NPV: Negative predictive value; FINDRISC: Finnish Diabetes Risk Score.

A total of 20 incident cases of DM2 (10.75%, 7 men and 13 women) among baseline prediabetic individuals occurred during 265.257 (82.234 men and 182.923 women) person-years of follow-up. The overall incidence of subsequent DM2 development was 7.5 (95%CI: 4.9-11.7) per 100 person-years. The incidence rates were slightly higher in men (8.5, 95%CI: 4.0-17.8, per 100 person-years) than in women (7.1, 95%CI: 4.1-12.2, per 100 person-years), but the difference was not statistically significant. Likewise, compared with participants in the lowest tertile of FINDRISC score at baseline, the risk of incident DM2 was 5.31 times higher for those in the highest tertile (HR = 5.31, 95%CI: 1.15-24.43) (Table 4).

The area under ROC curve (AUROC) of the FINDRISC score for detecting undiagnosed DM2 in both men and women was 0.7477 (95%CI: 0.5722-0.9232) and 0.7175 (95%CI: 0.5868-0.8481), respectively (Figure 1). The performance assessment of the FINDRISC score for identifying individuals at risk of undiagnosed DM2 is shown in Table 5. At the cutoff value of 14 in both

men (sensitivity = 66.7%; NPV = 98.8%) and women (sensitivity = 71.4%; NPV = 98.8%), the Youden's index was the highest for undiagnosed DM2 (0.419 in men and 0.340 in women).

The ROC curve for the incidence of DM2 among the prediabetic subsample by FINDRISC is shown in Figure 2. The AUROC curve were 0.7199 (95%CI: 0.5355-0.9043) in men and 0.6774 (95%CI: 0.5401-0.8146) in women. Given a Youden's index of 0.383 in men and 0.305 in women, FINDRISC cutoff values for incident DM2 were calculated to be 13 (sensitivity = 85.7%; NPV = 95.2%) in men and 16 (sensitivity = 69.2%; NPV = 93.4%) in women (Table 6).

DISCUSSION

Key findings

The current study assessed the performance of the FINDRISC questionnaire, and demonstrates that this can work reasonably well as screening tool, detecting cross-sectionally undiagnosed DM2 in the general population,

Table 6 Finnish Diabetes Risk Score to predict incident type 2 diabetes mellitus by gender, during follow-up and among the subsample of prediabetic patients

FINDRISC score	Incident DM2 (FPG \geq 126 mg/dL and/or OGTT \geq 200 mg/dL and/or HbA1c \geq 6.5%)				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index
Cutoff value \geq 12					
Men	85.7	44.7	22.2	94.4	0.304
Women	92.3	28.0	15.2	96.3	0.202
Cutoff value \geq 13					
Men	85.7	52.6	25.0	95.2	0.383
Women	92.3	34.4	16.4	97.0	0.267
Cutoff value \geq 14					
Men	71.4	60.5	25.0	92.0	0.319
Women	84.6	39.8	16.4	94.9	0.244
Cutoff value \geq 15					
Men	57.1	65.8	23.5	89.3	0.229
Women	76.9	49.5	17.5	93.9	0.263
Cutoff value \geq 16					
Men	42.9	68.4	20.0	86.7	0.112
Women	69.2	61.3	20.0	93.4	0.305
Cutoff value \geq 17					
Men	42.9	73.7	23.0	87.5	0.165
Women	53.9	66.7	18.4	91.2	0.205
Cutoff value \geq 18					
Men	42.9	79.0	27.3	88.2	0.218
Women	46.2	76.3	21.4	91.0	0.224

DM2: Type 2 diabetes mellitus; FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test; HbA1c: Hemoglobin A1c; PPV: Positive predictive value; NPV: Negative predictive value; FINDRISC: Finnish Diabetes Risk Score.

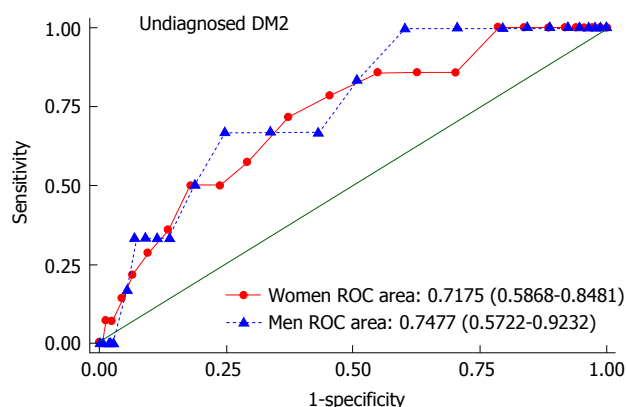


Figure 1 Receiver operating characteristics curves for the prevalence of undiagnosed type 2 diabetes mellitus by gender and Finnish Diabetes Risk Scores. DM2: Type 2 diabetes mellitus; ROC: Receiver operating characteristics.

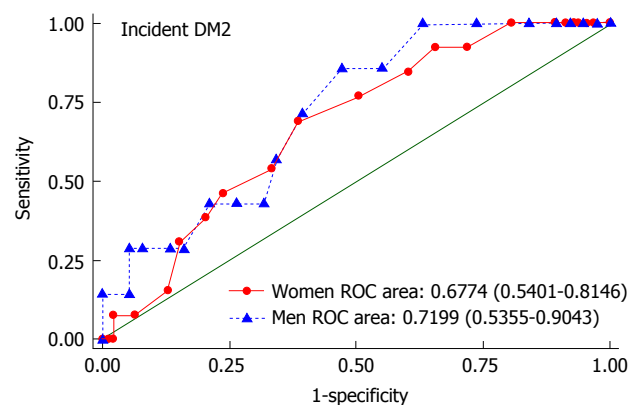


Figure 2 Receiver operating characteristics curves for the incidence of type 2 diabetes mellitus by gender and Finnish Diabetes Risk Scores, during follow-up and among the subsample of prediabetic patients. DM2: Type 2 diabetes mellitus; ROC: Receiver operating characteristics.

and longitudinally incident DM2 among individuals with prediabetes in Colombia. Our findings show a positive association between the FINDRISC score, undiagnosed DM2 in the general population and incident DM2 among prediabetic subjects. Moreover, in our population the FINDRISC score had an AUROC of 0.7477 in men and 0.7175 in women for identifying individuals at increased risk of undiagnosed DM2, and an AUROC of 0.7199 in men and 0.6774 in women for predicting incident DM2, which is comparable to that obtained in other similar studies^[18,19]. Using an optimal cutoff value of greater or equal to 14 both in men and women, this screening tool had good performance in identifying undiagnosed DM2. Meanwhile, FINDRISC cutoff values of 13 in men and 16 in women at baseline were defined as optimal to predict

DM2 in the subsample of prediabetic individuals.

DM2 is a strong, independent risk factor for cardiovascular disease and death^[3,23], and many epidemiologic analyses have identified a progressive relationship between prediabetes and these outcomes^[24,25]. Therefore, identifying individuals with undiagnosed DM2 and detecting individuals at risk for developing DM2 is essential to lead this target population the preventive actions, minimizing human and economic costs of diabetic complications^[9,11]. However, there are almost no symptoms of prediabetes or DM2 and as a consequence its detection is often delayed and at the time of diagnosis advanced complications are frequently present. It is estimated that approximately one-third of all people

with DM2 may be undiagnosed^[1,2]. Hence, using a simple and valid questionnaire, such as the FINDRISC score, as a preliminary screening method followed with more invasive and accurate diagnosis in primary care constitute a cost-effective and practical method with a potentially high national impact in terms of public health.

The efficiency of risk scores may vary between populations, and therefore, these should be validated in each population before use. The FINDRISC questionnaire was developed in Finland^[15], and has been validated in other populations studied so far^[16-20], demonstrating to be a simple and inexpensive tool that can identify those at high risk of having abnormalities in the glucose metabolism. Certainly, a previous study had already demonstrated the usefulness of FINDRISC to identify cross-sectionally people with glucose metabolism disorders in Colombia^[20], however in that study the cutoff level to identify patients at risk was chosen arbitrary. In that study, people with 13 or more FINDRISC points were screened with an OGTT, and they found this cutoff point to be useful to identify people with glucose metabolism disorders. Furthermore, this previous study did not assess the ability of FINDRISC in predicting incident DM2.

It is worth highlighting that there are several methodological differences between the several studies that have validated the FINDRISC questionnaire; modified or shortened versions have been used, in some studies the plasmatic glycemia tests have been only performed in subjects with a particular score, and in other cases prediabetes or metabolic syndrome has been also considered as an outcome. Therefore, the present study should be compared to these previously conducted studies with caution.

An important aspect of the present study is the assessment of the capacity of FINDRISC in the short-term prediction of incident DM2 among prediabetic individuals. To our knowledge, this is the first longitudinal validation of the FINDRISC questionnaire conducted in Latin America, while just other one study of similar characteristics was conducted in Europe. Soriguer *et al.*^[19] reported that in Spanish subjects with prediabetes the best prediction of risk of incident DM2 was found in those subjects with a FINDRISC score ≥ 9 . It should be noted that gender-specific cutoff values were not estimated in this previous study making thus comparisons difficult with our study.

Strengths and weaknesses of the study

There are some study limitations that warrant consideration. First, the participants were drawn from a unique healthcare center in Floridablanca and, thus, the results may not be applicable to the rest of Colombia. Second, the number of participants was relatively small, although the results were similar to those of other studies in different populations and larger cohorts^[16-20], which supports the validity of our present findings. Third, in most cases the diagnosis of DM2 was based on only one plasmatic value (FPG, OGTT or HbA1c

when performed), not two as recommended, and this may cause a serious bias in respect the definition of the main outcome event underestimating the true prevalence/incidence of DM2. However, diagnosis based on a single test result is accepted in epidemiological studies. In addition, it is noteworthy that this study was conducted in real life conditions, and the Colombian health system restricts the use of OGTT and HbA1c in patients with FPG < 100 mg/dL. Fourth, in our study most respondents were women, and this situation may partly be explained by behavioral habits, women are more likely to participate in completing questionnaires, they visit their physician more often, and usually pay more attention to their health.

This study has also considerable strengths. First, the diagnosis of DM2 was not self-reported. Second, all the analyzed subjects have available at least one plasmatic glycemia value. Third, the age distribution of the participants was wide and included the vast majority of the high-risk population.

In conclusion, the present study has assessed the performance of the FINDRISC questionnaire, demonstrating this as a useful screening tool to identify unknown DM2 in a cross-section of the Colombian population, and to predict incident DM2 among prediabetics. Moreover, we have demonstrated that a cutoff value greater or equal to 14 is the more appropriate detecting any previously undiagnosed DM2 in our population, both in men and women. Meanwhile, the optimal cutoff values for predict incident DM2 in prediabetic individuals were 13 in men and 16 in women.

COMMENTS

Background

The prevalence of type 2 diabetes mellitus (DM2) is increasing worldwide, but unfortunately its diagnosis is being made, in a high percentage, when vascular complications are already present. Therefore, the International Diabetes Federation recommends identification of persons at risk using simple risk-scoring questionnaires. Thus, this study aims to assess the performance of the Finnish Diabetes Risk Score (FINDRISC) questionnaire for detecting and predicting DM2 in a Colombian population.

Research frontiers

The FINDRISC questionnaire has been assessed and validated in several countries, including Colombia. However, in the authors' country the ability of FINDRISC to predict the development of incident DM2 has not been evaluated.

Innovations and breakthroughs

In the present study, the FINDRISC score demonstrated to be a useful screening tool to identify unknown DM2 in a cross-section of the Colombian population, and to predict incident DM2 among prediabetics.

Applications

Using a simple and valid questionnaire, such as the FINDRISC score, as a preliminary screening method for DM2 followed by more invasive and accurate diagnostic exams in primary care, constitute a cost-effective and practical method with a potentially high national impact in terms of public health.

Terminology

The FINDRISC is a simple, fast, inexpensive, noninvasive, and reliable tool to identify individuals at high risk for DM2.

Peer-review

This is a good observational study. Authors assessed the performance of the FINDRISC questionnaire in a Colombian population to detect undiagnosed DM2 in the general population and to predict incident DM2 among prediabetics. The study design is clear and the results are well to present. It demonstrated that the modified FINDRISC questionnaire is a good tool to detect undiagnosed DM2 and to predict incident DM2 in Colombian population.

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