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Review

Diabetes-Associated Changes in Skeletal Muscle Function and Their Possible Links with Prediabetes: A Literature Review

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Abstract: The skeletal muscle plays a critical role in regulating systemic blood glucose homeostasis. Impaired skeletal muscle glucose homeostasis associated with type 2 diabetes mellitus (T2DM) has been observed to significantly affect the whole-body glucose homeostasis, thereby resulting in other diabetic complications. T2DM does not only affect skeletal muscle glucose homeostasis, but it also affects skeletal muscle structure and functional capacity. Given that T2DM is a global health burden, there is an urgent need to develop therapeutic medical therapies that will aid in the management of T2DM. Prediabetes is a prominent risk factor of T2DM that usually goes unnoticed in many individuals as it is an asymptomatic condition. Hence, research on prediabetes is essential because establishing diabetic biomarkers during the prediabetic state would aid in preventing the development of T2DM, as prediabetes is a reversible condition if it is detected in the early stages. Literature predominantly documents the changes in skeletal muscle during T2DM, but the changes in skeletal muscle during prediabetes remain unknown. In this review, we seek to review the existing literature on prediabetic and T2DM associated changes in skeletal muscle function.

Keywords: type 2 diabetes mellitus; prediabetes; skeletal muscle; satellite cells; myogenic regulatory factors; insulin resistance; muscle fibers; inflammation; oxidative stress

Introduction

The skeletal muscle is one of the most prominent insulin-sensitive tissue in the body and functions as the primary site for insulin-stimulated glucose uptake [1]. Skeletal muscle satellite cells are among the most paramount progenitor cells responsible for maintaining skeletal muscle health under physiological and pathophysiological conditions [2]. Satellite cells are proposed to play a critical role in muscle fiber maintenance, repair, and remodeling, ultimately maintaining skeletal muscle plasticity [3]. Alterations in skeletal muscle health can affect whole-body glucose homeostasis as it is the skeletal muscle that is chiefly involved in regulating glucose uptake and maintaining glucose homeostasis. Chronic metabolic diseases, such as diabetes mellitus have been observed to affect skeletal muscle health by negatively modulating satellite cell quantity or functionality [2].

Diabetes mellitus is a metabolic disorder characterized by chronically elevated blood glucose levels due to defective insulin release or function [2]. Approximately 422 million people have been diagnosed with diabetes mellitus globally, with the majority living in low and middle-income countries [4]. Type 2 diabetes mellitus (T2DM) is the most prevalent type, accounting for approximately 90% of global diabetes cases [2, 5]. T2DM is anticipated to affect almost 8% of the worldwide population by 2030 [6]. T2DM is characterized by insulin resistance, where the body cells cannot effectively respond to insulin action, which leads to hyperglycemia. Unhealthy lifestyle behaviors, such as sedentary lifestyle combined with chronic consumption of high caloric diets, result in the onset of impaired glucose tolerance and insulin resistance seen in T2DM (7). Prediabetes is characterized by blood glucose levels higher than those in the homeostatic range, but below the threshold for diabetes mellitus for a diagnosis of T2DM [8]. It is observed that both fasting glucose levels and glucose tolerance are impaired during the prediabetic state [8]. T2DM has been observed

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to considerably compromise skeletal muscle health, a phenomenon known as diabetic myopathy [2]. Diabetic myopathy is associated with reduced physical capacity, strength, and muscle mass [9-11]. Diabetic myopathy is one of the understudied complications of diabetes mellitus, and it is proposed to be directly involved in the rate of comorbidity development [2].

However, the onset of T2DM is often preceded by an asymptomatic condition known as prediabetes [8]. There are several studies that have suggested that the onset of complications associated with T2DM begin during the prediabetic state. Literature predominantly documents the changes in skeletal muscle during T2DM, but the changes in skeletal muscle during prediabetes remain unknown. In this review, we seek to review the existing literature on prediabetic and T2DM associated changes in skeletal muscle function.

Skeletal Muscle Progenitor Cells and Muscle Strength

Skeletal muscle can adapt to various stimuli via the modulation of muscle size, fiber-type distribution, and metabolism. This phenomenon is due to the skeletal muscle progenitor cells, particularly satellite cells, playing a role in skeletal muscle maintenance and plasticity [2]. The skeletal muscle is regarded as the principal regulator of systemic glucose homeostasis in the body [12]. Thus, dysregulation in skeletal muscle glucose homeostasis can affect whole-body glucose homeostasis [2]. Approximately 80% of postprandial glucose is delivered to the skeletal muscle via translocation of insulin-dependent glucose transporters such as glucose transporter 4 (GLUT4), which contributes to the maintenance of the individual's physical and metabolic well-being [13]. The following section describes the role of skeletal muscle satellite cells in skeletal muscle health maintenance and skeletal muscle strength.

Role of Satellite Cells in Skeletal Muscle

Skeletal muscle satellite cells are vital for skeletal muscle fiber maintenance, repair, and remodeling [3]. The term "satellite cell" arose from the anatomical location of the satellite cells between the sarcolemma and basal lamina of their associated muscle fiber [3]. Satellite cells are generally latent in adult skeletal muscle and become only functional upon stimulation. Stimulation of satellite cells results in satellite cell activation, proliferation, and differentiation [3]. Myoblasts, the progeny of satellite cells, play a role in skeletal muscle growth and regeneration of satellite cells. Skeletal muscle growth mediated by myoblasts occurs by the combination of myoblasts to form new myofibers or combine with an existing muscle fiber and donate their nucleus during the fusion process. Satellite cell regeneration occurs when myoblasts return to a quiescent state which replenishes the resident pool of satellite cells [14].

Paired box transcription factor 7 (Pax7) and Myogenic regulatory factors (MRFs), such as MyoD, Myf5, MRF4, and myogenin, are observed to regulate the function of satellite cells during myogenesis [3]. Pax7 is mainly expressed in quiescent satellite cells, and plays a role in self-renewal and maintenance of basal satellite pool [15]. Studies illustrate that there is a functional overlap between the MRFs in establishing myogenesis. MyoD and Myf5 are proposed to induce myoblast activation and proliferation, whereas myogenin and MRF4 are proposed to induce terminal differentiation of satellite cells [16]. In a study of newborn mice lacking MyoD and Myf5, it was observed that the mice were devoid of myoblasts and myofibers [17]. Contrarily, mice with myogenin deficiency generated myoblasts but demonstrated insufficient skeletal muscle differentiation, with minimum and smaller myotubes [18, 19]. Hence the coordinated action of MRFs is vital for establishing myogenic lineage and terminal myogenic phenotype [20]. MRFs consist of a basic helix-loop-helix (bHLH) domain that enables them to recognize and bind to the E box sequence (CANNTG), known as the muscle enhancer factor-1 (MEF-1) site [21] (Figure 1). Heterodimerization of MRFs with Jun D, a ubiquitously expressed E-protein family of bHLH proteins (i.e., E12), orchestrates the binding of MRFs to MEF-1 (Figure 1).

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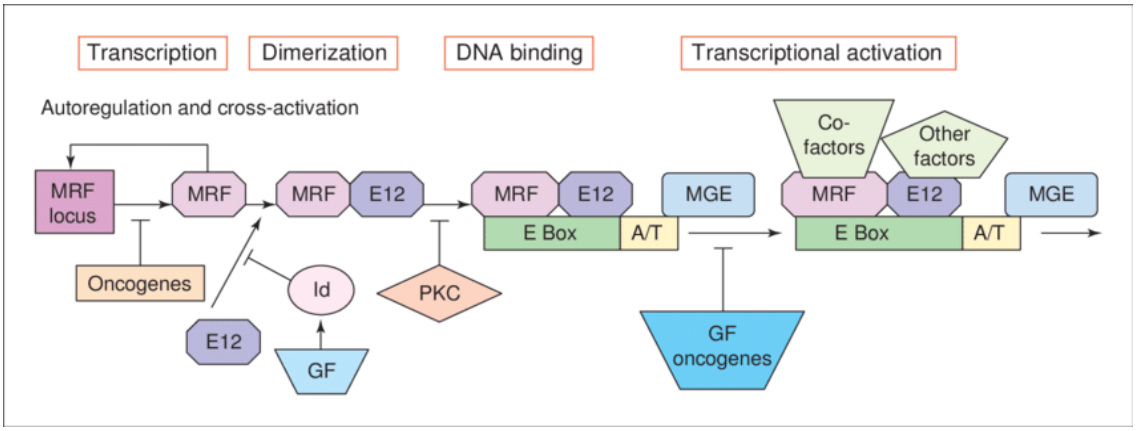

Figure 1. Schematic representation of myogenic regulatory factor (MRF) regulation of muscle-specific gene expression (MGE).

The presence of growth factors (GF) during skeletal muscle growth is observed to stimulate the proliferation of myoblasts, which lack the expression of differentiation markers such as myogenin. Growth factors are observed to induce the expression of inhibitor of differentiation (Id) protein which forms a dimerization with E12 and prevents the heterodimerization between MRF and Jun D, hence inhibiting MEF-1 DNA binding activity. Growth factors also lead to the activation of protein kinase C (PKC), which phosphorylates MRF and inhibits DNA-binding activity. Hence, inhibition of mitogenic factors decreases Id and promotes the formation of bHLH heterodimers, which bind to their DNA targets and induce muscle-specific gene transcription involved in myogenesis (Figure 1). Myoblasts can only differentiate when proliferating cells exhibit a low mitogen-containing environment [21].

Studies document that subpopulations of satellite cells can undergo asymmetric divisions to synthesize myogenic progenitors or symmetric divisions to increase satellite cell pool [22]. Moreover, satellite cells are observed to also commit to the myogenic lineage and proliferate to give rise to committed myogenic progenitors, which can asymmetrically divide or directly differentiate into myocytes that will fuse and form new myofibers [22] (Figure 2). The ability of satellite cells to be able to choose between performing asymmetric or symmetric divisions enables them to coordinate their activity with the needs of the regenerating muscle. The increased propensity of symmetric division during muscle regeneration would stimulate the expansion of the satellite cell pool [23]. In contrast, the asymmetric division would favor the generation of myogenic progenitors and maintenance of the stem cell pool (Figure 2). Thus, a dynamic balance must be established between the fluctuating symmetric and asymmetric divisions that occur during the different stages of muscle regeneration, as an imbalance would result in muscle regeneration impairment [22]. Hence MRFs can be used as a biomarker to assess satellite cell function in myogenesis.

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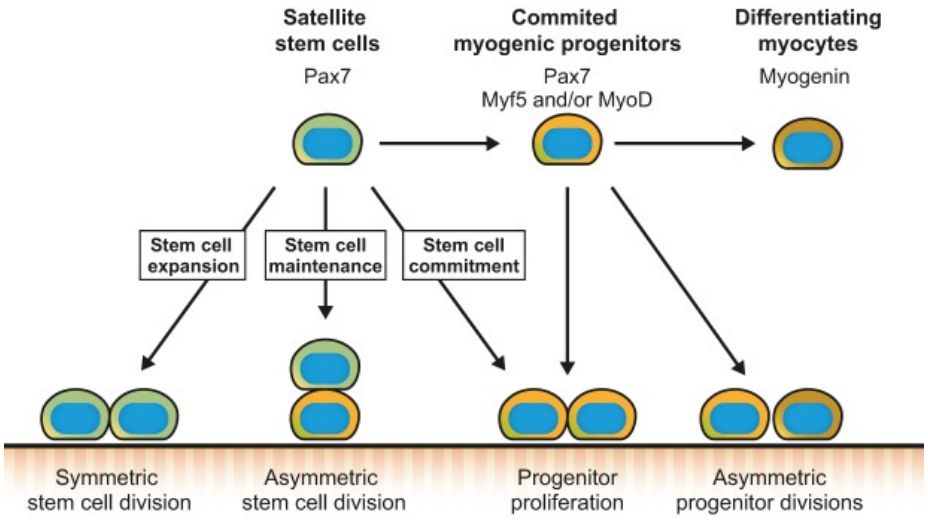

Figure 2. Schematic representation of symmetric and asymmetric satellite cell divisions.

Skeletal Muscle Strength

Skeletal muscle strength is determined by the number and size of muscle fibers present in the skeletal muscle tissue [21]. Skeletal muscle fibers are categorized into two fiber types, i.e., "slow-twitch" (type I) and "fast-twitch" (type II) muscle fibers. Skeletal muscle fiber types are observed to play a role in skeletal muscle strength [24]. Skeletal muscle fibers contain four major myosin heavy chain (MHC) isoforms: the "slow" MHC and three "fast" type (IIa, IIx, and IIb) MHCs; and three major myosin light-chain (MLC) isoforms, the "slow" MLC1s and the two "fast" MLC1f and MLC3f [25]. MHC IIb, MHC IIa, and MCH IIx account for 90% of MHC in adult muscles [26]. "Slow-twitch" muscle fibers are associated with contraction endurance with lesser strength and rely on oxidative metabolism for energy production. "Fast-twitch" muscle fibers supply short-lived bursts of energy to the muscle and depend on glycolytic metabolism for energy production [24]. Thus, "fast-twitch" muscle fibers are observed to have considerable muscle strength and contraction speed, but only for short bursts of anaerobic activity before the muscle fatigue [27]. Type IIa/IIx fibers comprise heterogeneous characteristics of type I and type IIb fibers. They have intermediate numbers of mitochondria and oxidative potential, promoting moderate strength and improved resistance to fatigue [27].

Gene transcription of light and heavy myosin chain is regulated by MRFs, particularly MyoD, and MEF-1 DNA binding activity (26). Studies illustrate that MyoD is required for muscle fiber maintenance as it is observed to promote the development of slow and fast muscle fibers [28]. The myosin creatine kinase (MCK) gene is the most abundant nonmitochondrial mRNA expressed in all skeletal muscle fibers, which becomes activated when myoblasts commit to terminal differentiation into myocytes [29]. Thus, the MCK enzyme plays a pivotal role in differentiated skeletal muscle function (26). Myosin creatine kinase catalyzes the transfer of high-energy phosphate from ATP to creatine to promote energy storage in the form of phosphocreatine, thereby maintaining ATP homeostasis for the differentiated myocytes, ensuring optimum myocyte function [30]. The MEF-1 site has been observed in the enhancer region of MCK, which is considered to be prominent for MCK transcription [31]. The expression of MCK protein, as well as its enzymatic product, creatine phosphate, are observed to be considerably higher in fast-twitch muscles than in slow-twitch muscles [32]. The following section will outline the effect of T2D on satellite cell function and muscular strength.

Type 2 Diabetes Mellitus

Type 2 diabetes is one of the leading types of DM, accounting for approximately 90% of global DM cases [2]. T2DM is associated with peripheral insulin resistance, impaired regulation of hepatic

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glucose production, and decreased pancreatic β-cell function, eventually leading to β-cell failure [33]. An oral glucose tolerance test (OGTT), a fasting glucose test, a postprandial glucose test, or glycated haemoglobin (HbA1c) test can be used to diagnose T2DM [33]. Type 2 diabetes is established when fasting blood glucose (FBG) levels are ≥ 7mmol/L, postprandial glucose concentration ≥11.1mmol, and glycated haemoglobin concentrations ≥6,5% [34]. Other organs implicated in T2DM development, other than the pancreas, include the liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue [35]. T2DM results in micro and macrovascular complications such as nephropathy, neuropathy, cardiovascular diseases, and diabetic myopathy [2]. Diabetic myopathy is associated with reduced physical capacity, strength, and muscle mass [11]. Diabetic myopathy is proposed to be directly involved in the rate of comorbidity development; however, it is a relatively understudied diabetic complication [2].

Effects of T2DM on Skeletal Muscle Progenitor Cells and Muscle Strength

Type 2 diabetes mellitus is observed to affect skeletal muscle metabolism, structure, and function [2]. The skeletal muscle alterations observed in T2D include muscle atrophy [36, 37], fiber-type transition [38], impaired glucose uptake [39], glycogen synthesis [40, 41], and defective myokine secretion [42, 43], which eventually result to muscle weakness and compromised muscle functional capacity [44]. Diminished appendicular lean mass and decreased skeletal muscle strength are usually observed in T2D patients regardless of gender and ethnicity, and the incidence increases with aging [45, 46]. T2D is proposed to affect skeletal muscle progenitor cells, particularly the satellite cells, by altering progenitor cell quantity and function, thereby affecting overall skeletal muscle health [2]. This section will outline the effect of T2DM on skeletal muscle satellite cells and muscle strength.

Effects of T2DM on Skeletal Muscle Satellite Cells

T2DM has been observed to alter the function of satellite cells involved in muscle growth and regeneration [2]. Satellite cell function has been proposed to be considerably affected by hyperglycemic and lipotoxic conditions associated with type 2 diabetic states. For instance, a study discovered that three weeks of high-fat feeding (HFF) affected satellite cell content and functionality. The latter was characterized as the quantity of regenerating fibers present following injury [47]. Another study documented reduced muscle regeneration following eight months of HFF, which was proposed to be induced by delayed myofiber maturation [48]. A study conducted in the Obese Zuker Rat model for metabolic syndrome documented reduced satellite cell proliferative capacity; however, quiescent species remained unaltered [49]. A similar outcome was reported in another T2D study, whereby SC cell proliferation and activation were compromised, thereby affecting muscle regeneration [50].

Oxidative stress associated with T2DM is proposed to impair myogenesis [2]. Myogenesis is regulated by an integrated interaction between myogenic regulatory factors (MRFs), such as Myo, Jun D, and myogenin. These MRFs specifically bind to the muscle enhancer factor (MEF)-1 site, which regulates gene transcription of light and heavy chains of myosin and myosin creatine kinase (MCK) [51-53]. Disruption in the coordinated interaction between MRFs and the MEF-1 site can affect muscle protein synthesis and subsequent compromised skeletal muscle health [26]. Studies illustrate reduced myogenic factors (MyoD, myogenin, and Jun D) in STZ-diabetic and Zucker diabetic rodents. MEF-1 DNA binding activity is also observed to be altered in T2D rats [26]. Myosin creatine kinase and myosin expression are also observed to be impaired due to reduced MEF-1 DNA binding activity associated with T2DM [54]. The binding of the homo and heterodimers of MFRs to the MEF-1 site tightly regulates the development and differentiation of skeletal muscle progenitor cells into multinucleated myotubes [55].

Effect of T2DM on Skeletal Muscle Strength

Studies document that T2D individuals have reduced type I muscle fibers and elevated type IIx muscle fiber proportions, potentially accounting for the reduced functional capacity observed in T2D

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individuals (56, 57). Type I levels directly correlate with insulin sensitivity hence the insulin resistance associated with T2D considerably affects the expression of Type I fibers (58). In another study, biopsies from T2DM patients illustrated a reduced oxidative metabolism program, along with increased type 2x fibers (59). MCK synthesis is observed to be reduced in T2D rats, which is proposed to possibly result from the loss of MEF-1 binding activity observed in T2D conditions (26). Furthermore, MHC IIb synthesis is reduced in the gastrocnemius muscle of T2D rats. MLC1 and MLC3 isoforms are also observed to be decreased in T2D rats (26). The reduction in skeletal muscle fiber MHC and MLC isoforms results in diminished muscle fiber number and size, thereby affecting skeletal mass and muscle strength (21).

T2D skeletal muscles portray diminished contractile force in humans and mice [60]. Studies document that the hands are a target for several diabetes-induced complications. Hence, low handgrip strength is observed to be related to hand disability in T2DM [61]. Previous studies on the relationship between handgrip strength and T2DM have been conflicting [62]. Some studies document a significant inverse association between handgrip strength and T2DM [63-66], and some studies observed no significant association between handgrip strength and T2DM [67, 68]. Studies illustrate that handgrip strength differs between ethnic groups, possibly accounting for the conflicting findings [66]. Low grip strength associated with T2DM is observed to be substantially higher in the South Asian population than in the Western population [66]. The inflammation associated with T2DM is also proposed to be related to low muscular strength [69]. In another study, high tumor necrosis factor-alpha (TNF-α) levels induced a decline in muscle strength [70]. The loss of skeletal muscle mass and strength caused by T2DM results in decreased surface area for glucose transport, further exacerbating insulin resistance [71]. Studies propose that fat accumulation in skeletal muscle observed under T2D conditions, combined with low mitochondrial oxidative capacity, is associated with low muscle strength [72].

Prediabetes

Prediabetes is an asymptomatic condition that usually precedes the onset of type 2 diabetes [8]. A large proportion of the global population is predisposed to prediabetes. The global prevalence rate of prediabetes in 2017 was estimated to be 352,1 million (7.3%) of the adult population, and it is anticipated to increase to 587 million (8.3%) individuals by 2045 [73]. Prediabetes is characterized by higher than normal blood glucose levels but not high enough to establish a T2DM diagnosis and presents as a risk for the onset of T2DM [8]. According to the World Health Organisation (WHO), the prediabetes diagnostic criteria include individuals presenting with one or both of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). IFG is characterized by fasting plasma glucose (FPG) concentration ≥6.1 mmol/L and <7 mmol/L and IGT is characterized by FPG concentration <6.1 mmol/L and a 2-hour post-load plasma glucose concentration between ≥7.8 mmol/L and <11.1 mmol/L measured during the oral glucose tolerance test (OGTT) [74]. The glycated hemoglobin A1c (HbA1c) levels between 5.7 and 6.4% is also used for prediabetes diagnosis [75]. Several factors such as genetic predisposition, insulin resistance, glucotoxicity, lipotoxicity, and β-cell dysfunction result in prediabetes development [8].

Studies document prediabetes to be related to early forms of micro and macrovascular diabetic complications such as nephropathy, chronic kidney disease, small fiber neuropathy, diabetic retinopathy, and heightened risk of macrovascular disease [76]. Studies have observed an increased risk of coronary disease during the prediabetic state [77, 78]. Considering that the onset of T2DM complications occurs during the prediabetic state, prediabetic conditions need to be well elucidated as this would aid in preventing some of the overlapping prediabetic and T2D complications.

Effects of Prediabetes on Skeletal Muscle Glucose Homeostasis

The insulin resistance associated with prediabetes is proposed to contribute to endothelial dysfunction [79] (Figure 3). Insulin is vital for endothelial function and glucose metabolism [80]. Studies document that insulin induces vasodilation in resistant arterioles, increases compliance of large arteries, promotes capillary recruitment, and maintains capillary permeability to support

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nutrient delivery [81, 82]. The effects of insulin require coordinated downstream events to keep the vascular tone in the basal state while the vasodilatory response to insulin is elevated in the postprandial state. The skeletal muscle microvasculature, therefore, links insulin's vascular and metabolic functions by increasing the surface area for tissue perfusion. Considering that the skeletal muscle is the principal tissue for insulin-stimulated glucose disposal, these insulin actions represent the role of the endothelium in regulating glucose homeostasis [80].

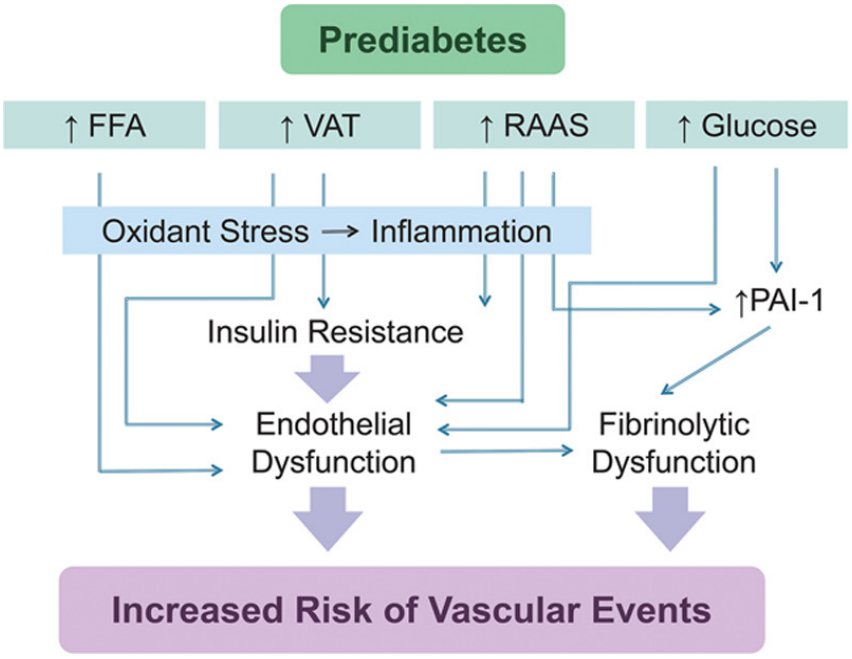

Figure 3. Endothelial insulin resistance, hyperglycemia, and increased free fatty acids (FFAs) give rise to oxidative stress, inflammation, endothelial dysfunction, and fibrinolytic dysfunction in prediabetes. PAI-1 indicates plasminogen activator inhibitor-1; RAAS renin–angiotensin–aldosterone system; and VAT, visceral adipose tissue.

Increased FFAs induce insulin resistance and endothelial dysfunction in obese patients with prediabetes [79]. A high-fat diet triggers endothelial dysfunction in mice [85], and eating a meal high in fat reduces brachial artery reactivity in humans [86]. FFAs decrease tyrosine phosphorylation of IRS-1/2 and inhibit the PI3K/Akt pathway, resulting in reduced glucose transport and reduced phosphorylation of eNOS [87-89] (Figure 4). FFAs activate NADPH oxidase via protein kinase C (PKC) to generate reactive oxygen species (ROS) [90]. Activated PKC contributes to endothelial permeability [91] and extracellular matrix (ECM) expansion [92].

Elevated oxidative stress is associated with the activation of several serine/threonine kinases and the activation of transcription factors NF-kB and activator protein (AP-1), which result in insulin resistance [93]. The activation of serine/threonine kinases c-Jun NH_2-terminal kinase (JNK), PKCs, and IkB kinase complex β (IKKβ) leads to serine phosphorylation of IRS-1, which disrupts its ability to bind and activate PI 3-kinase. Thus, there is reduced activation of downstream kinases Akt and PKC-ζ, which reduces the translocation of GLUT4 and glucose transport [94-96] (Figure 4). Current literature mainly focuses on microvascular and macrovascular prediabetic complications such as endothelial dysfunction and cardiovascular disease. The skeletal muscle plays a substantial role in glucose homeostasis [93]. Hence, more studies must be conducted to contribute to the current understanding of prediabetic complications, within the context of skeletal muscle.

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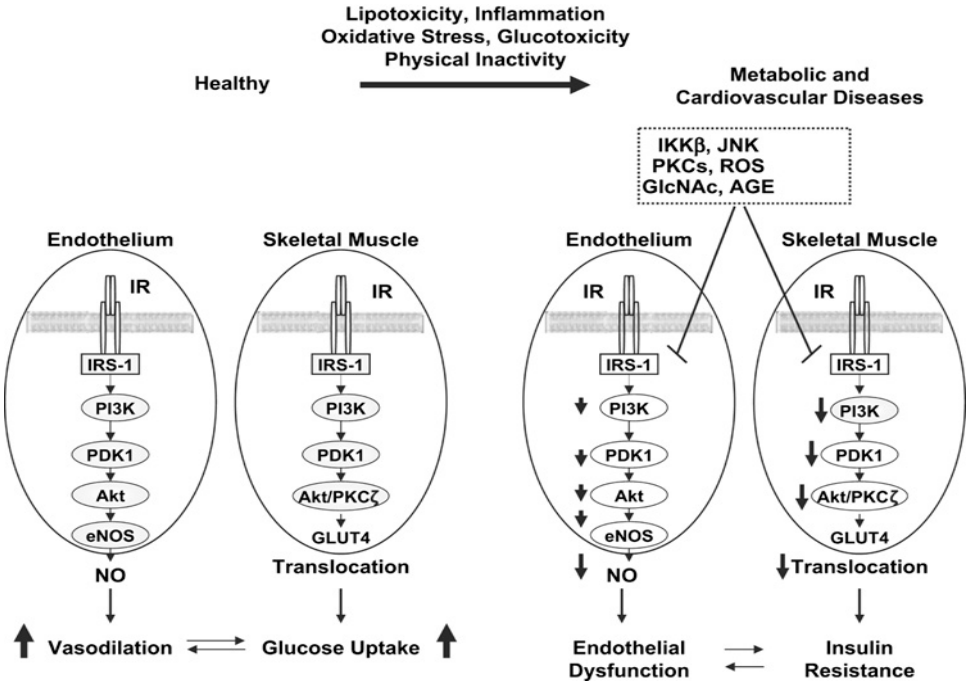

Figure 4. The physiology and pathophysiology of the vascular and metabolic actions of insulin.

Effects of Prediabetes on Skeletal Muscle Structure

The proinflammatory prediabetic state promotes increased skeletal muscle collagens and other ECM proteins [97] , including fibronectin, proteoglycans, and connective tissue growth factors, and ECM remodelling [98]. The glycosaminoglycans hyaluronan is elevated in tissues of prediabetic animals [99, 100]. Hyaluronan is a prominent component of the glycocalyx of capillary lumens, which may affect insulin access to tissues [79]. Reduced hyaluronan using PEGylated hyaluronidase in high-fat-fed mice ameliorates insulin action [99]. Expansion of the muscle ECM and decreased muscle capillary are proposed to contribute to muscle insulin resistance [101].

The chronic systematic inflammation associated with a high-fat diet [102, 103] is suggested to heighten ECM protein synthesis and decrease ECM degradation, leading to increased deposition and ECM remodelling [104, 105] (Figure 5). The increased protein expression within the ECM is hypothesised to induce a physical barrier, impeding normal insulin action and glucose diffusion across the sarcolemma [99, 106] (Figure 5).

The increased protein expression is suggested to be associated with collagen, fibronectin and proteoglycan proteins, which accumulate in the interstial space, resulting in increased diffusion distance and prevention of substrate and hormonal delivery [98, 106]. In support of this hypothesis, Kang et al. [99] illustrated that hyaluronan (a significant ECM component) in skeletal muscle was remarkably increased in insulin-resistant diet-induced obesity (DIO) mice when compared to normal chow-fed mice. Interestingly, the same authors also demonstrated that treatment with long-acting pegylated human recombinant PH20 hyaluronidase (PEGPH20) induced a dose-dependent decrease in muscle hyaluronan content and improved skeletal muscle insulin resistance in DIO mice [99]. These results suggest that depletion of ECM polysaccharide promotes muscle insulin sensitivity in obese mice, and contrarily, ECM protein accumulation seems to aggravate muscle insulin resistance [99].

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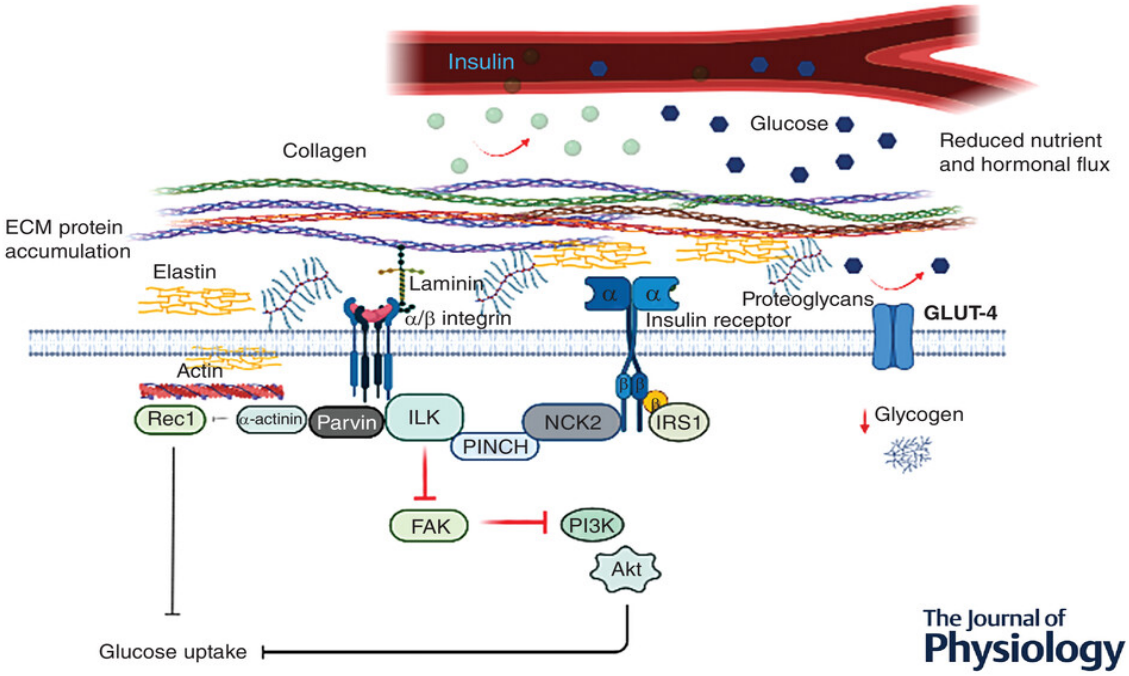

Figure 5. Potential pathway linking integrins and their associated proteins in the regulation of glucose metabolism in skeletal muscle.

Another hypothesised factor that is suggested to be linked to the underlying mechanism of ECM-associated insulin resistance in DIO, is that the muscle ECM may expand to disrupt vascular function and neovascular growth, provided the close contact between the ECM and endothelium [106]. Nutrient delivery to the contracting muscle requires functional blood flow to establish sufficient glucose (during exercise) and insulin (post-exercise) availability to facilitate glucose uptake and glycogen resynthesis, respectively [105]. Hence, ECM vascular dysfunction and capillary rarefaction have been associated with insulin resistance and T2D [106, 107]. Studies show that 40% of insulin-stimulated glucose uptake is attributed to augmented muscle perfusion; however, in the insulin-resistant state, this hemodynamic response is observed to be absent [108-110]. Insulin-resistant models and humans are documented to present with capillary rarefaction, thereby highlighting the importance of sufficient muscle capillarization for insulin-mediated disposal [108, 111].

Knockout mice lacking vascular endothelial growth factor (*m*vegf$^{-/-}$) are proposed to have reduced insulin-mediated glucose disposal [108]. Importantly, Bonner et al. discovered that the reduction in skeletal muscle insulin-mediated glucose uptake was not associated with a dysregulation in intracellular insulin signalling (IRS-1, p85 and phosphorylated total (p/t) Akt), proposing that reduced insulin-stimulated muscle glucose uptake was caused by inadequate muscle perfusion [108]. Consequently, it has been suggested that it is challenging to elucidate insulin signalling in skeletal muscle as it is possible that integrin-associated signalling could have been implicated in *m*vegf$^{-/-}$ rodent model [108]. The studies above suggest that ECM remodelling contributes to skeletal muscle insulin resistance via endothelial dysfunction and capillary rarefaction [106].

Conclusions

The research discussed in this review suggests that the skeletal muscle plays a substantial role in glucose homeostasis and illustrates the mechanisms involved in the onset of insulin resistance in the prediabetic and T2D states. Prediabetes is suggested to be related to early forms of T2D complications such as diabetic myopathy. A plethora of factors influence skeletal muscle function, among which are the satellite cells of skeletal muscles. Skeletal muscle satellite cells are proposed to maintain skeletal muscle health in physiological and pathophysiological conditions. Hence, the

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mechanisms involved in regulating skeletal muscle satellite cells' effective functioning need to be well elucidated in the prediabetic state, as literature mainly documents that satellite cell function is potentially impacted during the T2D state. Understanding the modifications that occur in the skeletal muscle during the prediabetic state can allow us to be able to target and prevent the processes that contribute toward the development of diabetic myopathy in the prediabetic state.

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