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Skeletal muscle atrophy and dysfunction in obesity and type-2 diabetes mellitus: Myocellular mechanisms involved

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Abstract
Obesity and type-2 diabetes mellitus (T2DM) are interrelated metabolic disorders primarily driven by overnutrition and physical inactivity, which oftentimes entails a transition from obesity to T2DM. Compromised musculoskeletal health consistently emerges as a common hallmark in the progression of these metabolic disorders. Skeletal muscle atrophy and dysfunction can further impair whole-body metabolism and reduce physical exercise capacity, thus instigating a vicious cycle that further deteriorates the underlying conditions. However, the myocellular repercussions of these metabolic disturbances remain to be completely clarified. Insulin signaling not only facilitates skeletal muscle glucose uptake but also plays a central role in skeletal muscle anabolism mainly due to suppression of catabolic pathways and facilitating an anabolic response to nutrient feeding. Chronic overnutrition may trigger different myocellular mechanisms proposed to contribute to insulin resistance and aggravate skeletal muscle atrophy and dysfunction. These mechanisms mainly include the inactivation of insulin signaling components through sustained activation of stress-related pathways, mitochondrial dysfunction, a shift to glycolytic skeletal muscle fibers, and hyperglycemia. In the present review, we aim to delve on these mechanisms, providing an overview of the myocellular processes involved in skeletal muscle atrophy and dysfunction under chronic overnutrition, and their contribution to the progression to T2DM.

Keywords Obesity · Type 2 diabetes mellitus · Skeletal muscle · Atrophy · Dysfunction · Mechanisms

1 Introduction

Obesity and type-2 diabetes mellitus (T2DM) are closely related clinical conditions that have reached pandemic proportions, significantly overlapping in several factors responsible for their etiology, pathogenesis, and treatment [1]. In 2022, the global age-standardized prevalence of diabetes assessed based on fasting glucose, glycated hemoglobin or use of hypoglycemic drugs or insulin was 13.9% for women and 14.3% for men, accounting for 828 million adults (T2DM accounts for 85–95% of diabetes cases in adults) [2]. This represents an increase of 630 million adults compared to 1990 data. Estimates of age-standardized diabetes prevalence are notably higher, even surpassing 25%, in low- and middle-income countries in Polynesia and Micronesia, Middle East and North of Africa compared to the lowest estimates of 2–4% reported in European countries such as France, Denmark, and Spain [2]. Similarly, the global age-standardized prevalence of obesity, defined as a body mass index (BMI) ≥ 30 (used as an index of adiposity due to practical considerations), increased from 8.8% to 18.5% in women, and from 4.8% to 14.0% in men during the same time period. This represents an estimated increase of 684 million adults [3]. Low- and middle-income countries in Polynesia and Micronesia, Middle East and North of Africa have experienced the largest increments in prevalence of obesity in adults, whereas some European countries (e.g., Spain and France) have seen flattened or decreased prevalence during the same time period [3]. These data reinforce comprehensive longitudinal evidence positioning obesity as a major risk factor in the onset of T2DM [4, 5]. A recent systematic analysis of 216 cohort studies involving 26 million individuals concluded that each 5-unit increase in BMI associates with a 72% higher risk of T2DM [6]. This risk intensifies with increased ectopic or visceral fat content at any BMI level [6, 7]. Consequently, coexistence of both conditions, oftentimes termed "diabesity"

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[8], is a reality for many individuals, and it typically entails a transition from obesity to T2DM. To prevent T2DM progression, the critical role of body composition management is nowadays well-recognized, which is typically achieved through lifestyle interventions including physical activity programs and nutritional strategies as well as adjunct pharmacotherapy and surgery when needed [1].

The skeletal muscle represents ≈40% of total body weight under physiological conditions and contains 50–75% of all body proteins [9]. It serves as the primary reservoir of glucose (stored as glycogen) [10], accounts for ≈80% glucose disposal under hyperinsulinemic-euglycemic conditions [11], and is responsible for 30% to over 90% of whole-body metabolic rate at rest and during intense physical exercise, respectively [12]. Further, the skeletal muscle is described as the largest secretory organ in the normal-weight human body, exerting autocrine, paracrine and endocrine effects implicated in metabolic homeostasis [13]. As such, a growing body of evidence focuses on impaired skeletal muscle plasticity – changes in muscle mass, and quality/function to meet metabolic requirements – as a key player in the onset and progression of metabolic disorders such as obesity and T2DM [14, 15].

Although not all obese individuals exhibit insulin resistance – a condition that some authors referred to as 'metabolically healthy obesity' [16] – and patients with T2DM are not invariably obese [17], compromised musculoskeletal health consistently emerges as a common hallmark in both conditions. T2DM patients display skeletal muscle atrophy denoted by greater loss of muscle mass compared to age-matched subjects without diabetes [18, 19]. Specifically, the decline in skeletal muscle mass associated with aging has been reported to occur at twice the rate in individuals with T2DM compared to non-diabetic older adults [18]. Compared to non-diabetic matched controls, T2DM patients also display reduced absolute skeletal muscle strength [20]. Individuals with diabetes have approximately 1.5 times the odds of developing sarcopenia, as determined by criteria that include both muscle mass and function parameters, compared to non-diabetic subjects [21]. Unlike diabetes, obesity per se is not typically associated with lower absolute skeletal muscle mass [22, 23]. In fact, increased adiposity has been observed to correlate with higher absolute measurements of muscle strength [24]. This phenomenon is frequently explained by the augmented mechanical loading stimulus that skeletal muscles experience due to higher body weight, especially those responsible for maintaining posture [25]. However, when normalized to total mass, subjects with obesity do exhibit impaired skeletal muscle function (i.e., lower strength measurements relative to muscle mass) [24, 26], thus indicating reduced muscle quality. Further, a shift from highly-vascularized oxidative type-I fibers to glycolytic type-IIx fibers has been reported in obese, and diabetic skeletal muscles [27–33], which might correlate with increased fatigability, albeit observations are not always consistent [34]. Along with macrovascular complications, T2DM associates with capillary rarefaction [35], altered microvascular network structure [36], and impaired endovascular function [35], altogether compromising blood flow to the skeletal muscle. Signs of impaired microvasculature have been also documented in patients with obesity, which are typically linked to the onset of insulin resistance [37, 38]. Further, lipid oversupply in obesity leads to fat redistribution to ectopic locations, including non-adipose tissues such as the skeletal muscle, where lipid droplets accumulate to the subsarcolemmal region or in-between myofibrils [39]. Co-existence of obesity and T2DM associates with presence of remarkably enlarged lipid droplets, which might locate preferentially to type-II myofibers [40]. While a similar phenomenon of increased intramyocellular lipid (IMCL) content is known to occur in endurance-trained athletes, the preferential distribution to type-I myofibers, and the lower lipid droplet size suggest that these may serve a physiological purpose of facilitating efficient energy supply through β-oxidation during long-duration exercise in metabolically healthy individuals [41]. On the other hand, IMCL accumulation in obesity and T2DM leads to a loss of muscle contractile properties, and deleterious metabolic effects termed "lipotoxicity" [42, 43]. These, compounded with other histological features of obese and diabetic muscles (e.g., expanded extracellular matrix (ECM) component [44, 45]), are thought to contribute to impaired skeletal muscle function and decreased exercise tolerance [46].

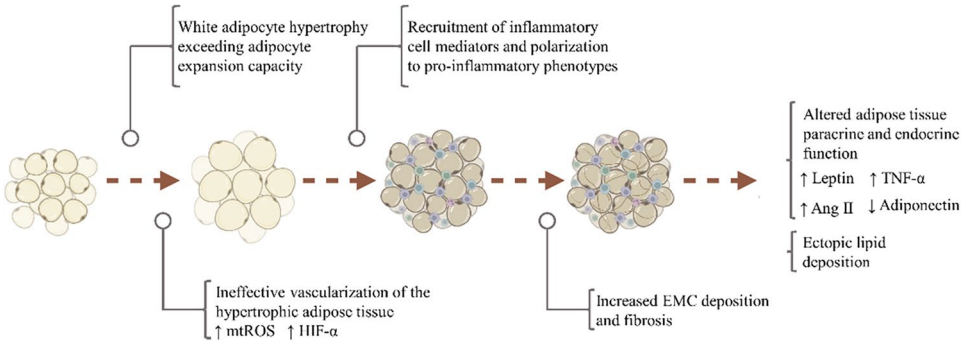
It is worth noting that differences in skeletal muscle biology have been also reported between metabolically healthy and unhealthy obese phenotypes [47], yet differences between these groups of study strongly rely on the criteria used to classify them. Besides metabolic syndrome components, BMI may be insufficient to match metabolically healthy and unhealthy obese subjects in analyses and different body composition parameters have been suggested to contribute to metabolic health. Particularly, metabolically unhealthy individuals have been reported to present similar percentage body fat adjusted by BMI and sex, but increased intra-abdominal adipose tissue and intra-hepatic triglyceride content than those classified as metabolically healthy [48]. Non-invasive body composition assessment techniques, such as magnetic resonance imaging (MRI) and spectroscopy (MRS) may support assessments of regional body fat distribution in these individuals and evaluate its potential impact on muscle health [49]. Metabolically healthy obesity remains a topic of scientific debate, and approaches to characterize these phenotypes have been reviewed elsewhere [50].

Abovementioned deleterious effects of obesity and T2DM on skeletal muscle have significant implications for its metabolic and anabolic properties. In turn, these impairments contribute to a loss of functionality and compromised ability to perform physical activity and exercise, thus representing a vicious cycle that reinforces the underlying metabolic

conditions [51]. However, the cellular and molecular mechanisms underlying the phenotypical changes of the skeletal muscle induced by these metabolic disarrangements remain unclear. The goal of the present narrative review is to provide an overview of the myocellular mechanisms involved in the loss of skeletal muscle mass and function associated with obesity and T2DM, deepening our understanding of skeletal muscle atrophy and dysfunction as both potential cause and consequence of these metabolic conditions.

2 Metabolic signatures of obesity and T2DM implicated in musculoskeletal health

Inflammation, impaired adipocyte endocrine function, and ectopic tissue lipotoxicity have all been proposed as causes of insulin resistance (IR), and consequently T2DM in obese individuals. However, efforts to pinpoint a cause-effect relationship, elucidate initializing factors, or clarify whether IR propagates from one initial tissue to others have been shown largely unsuccessful [52]. Notwithstanding, a growing body of evidence supports the notion of adipocyte hypertrophy (Box 1) as an early contributor to metabolic dysfunction and the onset of systemic IR [53, 54]. For instance, plasma levels of adiponectin – a potent anti-inflammatory adipokine with triglyceride- and glucose-lowering effects on skeletal muscle, whose production is dysregulated in hypertrophic/fibrotic adipocytes [55, 56] – indirectly correlate with IR [57]. Landmark preclinical research demonstrated that overexpression of tumor necrosis factor α (TNF-α) induced in obese adipose tissue impairs peripheral glucose uptake in response to insulin [58]. There is compelling evidence of exacerbated renin-angiotensin (RAS) components expression in visceral adipose tissue in obese individuals, which correlates with increased circulating angiotensin II levels and different metabolic complications, including IR [59]. Several different adipokines (i.e., leptin, interleukin-6 (IL-6), IL-1β, etc.) have been involved in mechanisms causative of IR; however, some authors have questioned whether local increases in adipose tissue translate to systemic concentrations that are sufficient to impair systemic insulin sensitivity [60]. Nonetheless, intermyocellular and perimuscular adipose tissues (IMAT and PMAT) might mediate paracrine effects on skeletal muscle [61], and nutrient overload resulting in extracellular (i.e., enhanced local pro-inflammatory cytokine production [62], enhanced angiotensin II activity [63], decreased adiponectin autocrine/paracrine effects [64]) and intracellular events (mitochondrial oxidative damage [65], free fatty acid accumulation [66]) may altogether contribute to impaired insulin sensitivity in adipose tissue, which in turn might further aggravate lipid spillover through defective insulin-mediated inhibition of lipolysis [67].



Box 1 Contributory role of adipocyte hypertrophy to metabolic dysregulation Overnutrition coupled with physical inactivity is causative of white adipocyte hypertrophy through triglyceride accumulation [68, 69], which may be considered an early event in the metabolic dysregulation associated to obesity. Hypertrophic adipocytes are dysfunctional, presenting ultrastructural abnormalities and limited hyperplastic expansion capacity [70, 71], which compromises their lipid storage function and may result in lipid overflow to non-adipose tissues [72]. Exacerbated adipose growth also challenges the vascularization of the growing tissue resulting in hypoxia [73], which triggers the production of mitochondria-derived reactive oxygen species (mtROS) [74], and mediates the overexpression of hypoxia-inducible factors (HIF) [75]. Accumulation of macrophages and lymphocytes along with polarization to pro-inflammatory phenotypes, fatty acid overload, and persistent inflammation may underlie EMC deposition and ensuing fibrosis, thus further compromising both storage and endocrine functions [76]. Changes in production of cytokines/adipokines derived from adipocytes and immune cells (i.e., leptin, adiponectin, tumor necrosis factor α (TNF-α), angiotensin II (Ang II), etc.) contribute to metabolic dysregulation and persistent low-grade inflammation in obese patients, which has been associated with compromised insulin signaling and protein turnover in skeletal muscle [77].

T2DM is characterized by insulin resistance in combination with β-cell dysfunction. While hyperinsulinemia has been typically regarded as a compensatory mechanism triggered in response to IR, enhanced β-cell proliferation and increased insulin

secretion, which characterize diabetogenic processes, have been reported to precede IR in obesity and under obesogenic conditions [78, 79]. Although the interplay between β-cell dysfunction and IR is intricate, overt T2DM associates with reduced β-cell mass due to enhanced protein degradation [80], leading to inability to compensate sustained insulin resistance, and hyperglycemia [81]. Excess glucose availability and increased insulin production promote hepatic *de novo* lipogenesis, which aggravates hepatic lipid accumulation, and consequently enhances gluconeogenesis, therefore contributing to systemic hyperglycemia and β-cell dysfunction [82]. Long-term elevation in glucose levels is considered the main culprit of β-cell demise and dysfunction due to impaired calcium handling and ROS/inflammation-mediated mechanisms, which combined with lipid accumulation and impaired lipid metabolism is termed "glucolipotoxicity" [83]. Particularly, β-cells are highly susceptible to oxidative damage due to their limited antioxidant capacity [84], being ROS generation and mitochondrial damage proposed as major mechanisms driving glucolipotoxicity-induced β-cell dysfunction [85].

Hyperglycemia represents a key mediator in the transition from obesity to T2DM through IR and β-cell dysfunction, and is positioned as a central factor in the pathogenesis of skeletal muscle atrophy in T2DM patients [86]. Non-controlled hyperglycemia promotes irreversible formation of advanced glycation end products (AGEs) through non-enzymatic processes, whose accumulation in musculoskeletal tissues compromises their biomechanical properties and promotes the interaction with cell membrane receptors (e.g., receptor for advance glycation end products (RAGE)), thus triggering intramyocellular events involved in processes of atrophy (e.g., inflammation and ROS generation, etc.) [87]. Not only hyperglycemia but also impaired nitric oxide (NO) production in skeletal muscle arterioles through endothelial nitric oxidate synthetase (eNOS)-dependent pathways is a critical consequence of peripheral IR [88]. Further, elevations in endothelium-derived entohelin-1 (ET-1) correlate with IR in humans and may directly impact the skeletal muscle through inhibited insulin-mediated glucose uptake [89], with recent evidence pointing to a potential direct impact of ET-1 on skeletal muscle atrophy through pro-inflammatory signaling pathways [90]. Decrements in NO levels combined with enhanced ET-1 activity operate to decrease blood flow to skeletal muscle tissue, and, consequently, compromise nutrient delivery, including amino acids needed for skeletal muscle protein turnover [91].

Lastly, shifts in the composition of the gut microbiota observed with obesity and T2DM are considered to contribute to low-grade inflammation [92]. Whereas core sets of microorganisms defining "healthy" or "unhealthy" gut microbiota profiles are far from delineated, enhanced

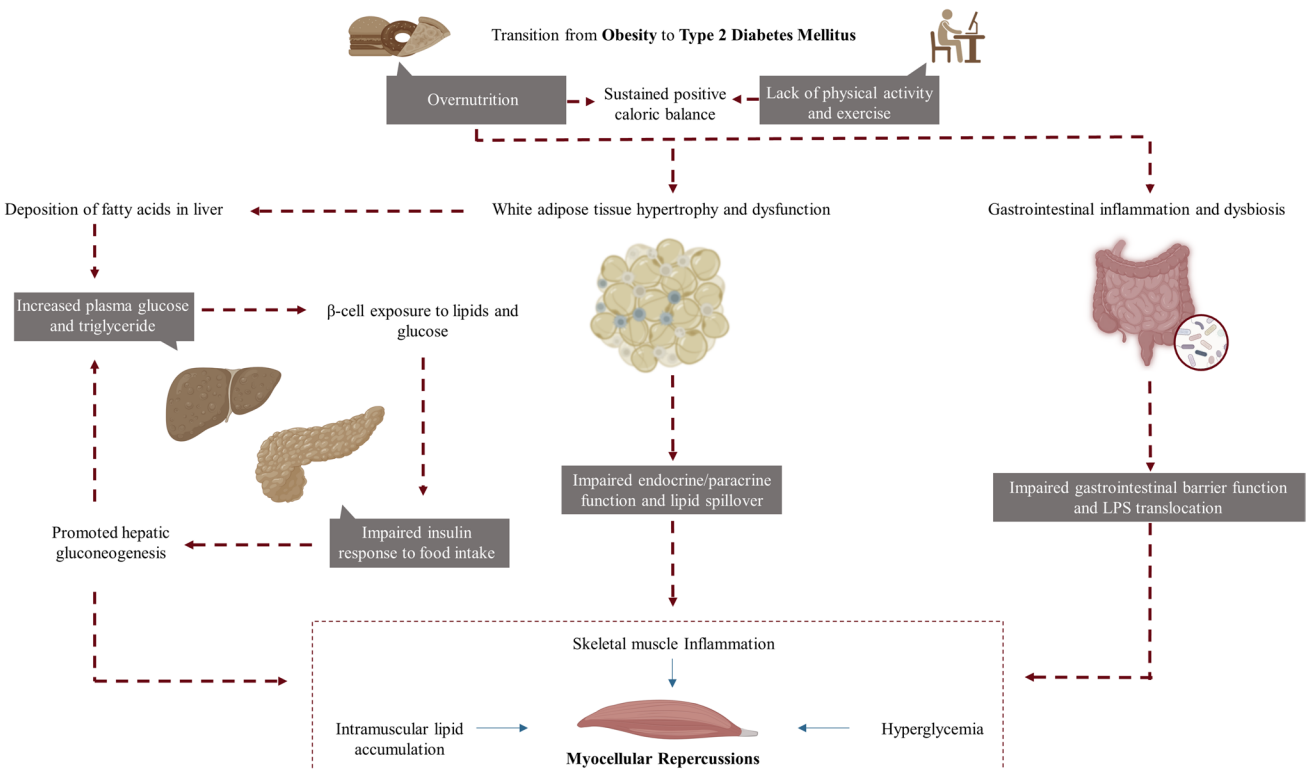


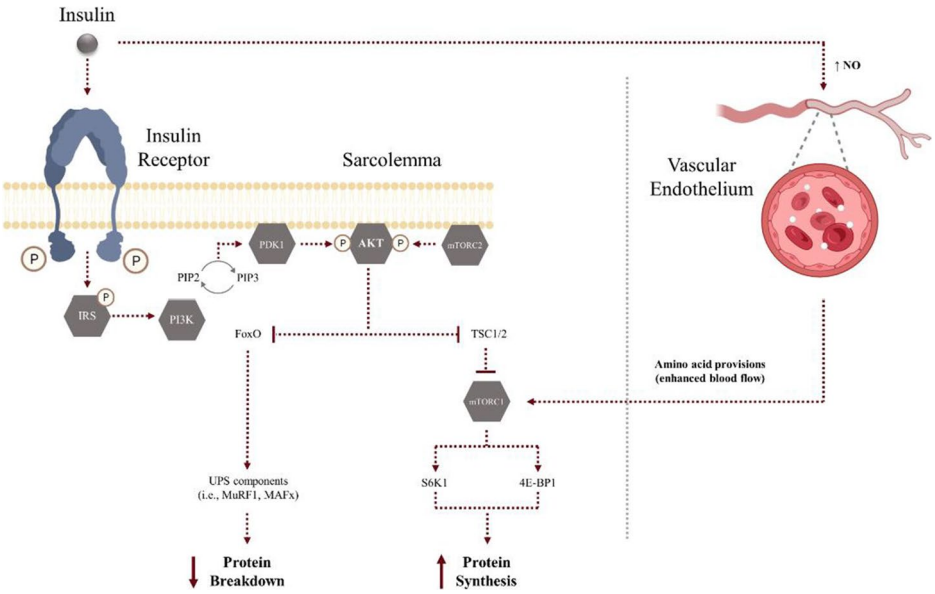
Fig. 1 Main metabolic signatures of obesity and type 2 diabetes mellitus involved in musculoskeletal health

intestinal permeability is consistently documented both in obesity and T2DM [93, 94], which is linked to lipopolysaccharide (LPS) endotoxemia [95]. LPS is a potent proinflammatory mediator contained in gram-negative bacteria outer membrane, and capable of inducing pro-catabolic state in skeletal muscle [96]. In addition, gut dysbiosis is associated with differences in metabolomic profiles of gut bacterial byproducts with documented systemic effects in insulin signaling and muscle metabolism [97]. Some of these metabolites, most notably short-chain fatty acids (SCFAs), are also implicated in the remodeling and maintenance of the gut barrier [98]. However, the intricate interplay between gut bacteria metabolites and the skeletal muscle – oftentimes referred to as "the gut-muscle axis" – in the context of metabolic disorders, such as obesity and T2DM, remains an emerging topic of research, and further studies are needed to delineate mechanisms at play. A schematic representation of the main metabolic signatures of obesity and T2DM involved in musculoskeletal health is presented in Fig. 1.

3 Myocellular repercussions of obesity and T2DM

Skeletal muscle atrophy and dysfunction are typically discussed in terms of decrements in mass and quality. While skeletal muscle mass refers collectively to all body's skeletal muscle tissue, muscle quality is a multi-dimensional aspect of skeletal muscle, and is typically measured as strength relative to muscle mass [99]. Different dimensions have been proposed to integrate muscle quality including skeletal muscle composition, architecture, and ultrastructure [99]. However, metabolic, thermoregulatory, autocrine, paracrine, and endocrine domains may be also considered within this framework [100]; therefore, skeletal muscle quality should be evaluated from a broader viewpoint extending beyond relative strength.

It is important to mention that most mechanisms involved in changes of muscle properties associated with obesity and T2DM are centralized through insulin signaling, a key player in the transition from obesity to T2DM, due to its profound impact on skeletal muscle anabolism/catabolism, and metabolism [51] (Box 2). The question herein is how impaired insulin signaling translates to compromised skeletal muscle mass. Current consensus supports that insulin has a permissive effect on skeletal muscle anabolism when amino acids are sufficiently available [101]. In fact, IR is proposed to contribute to an age-related decline in muscle protein synthesis (MPS) in response to anabolic stimuli, particularly amino acid feeding, a phenomenon termed "age-related anabolic resistance" [102, 103]. Studies using stable isotope tracer methodologies have indicated that insulin anabolic effects on skeletal muscle are largely mediated through endothelial-dependent vasodilation, involving modulation of endothelial-derived signaling molecules namely NO and ET-1 [91]. Consequently, insulin stimulates nutrient delivery to the skeletal muscle, including amino acids that promote MPS through mTORC1 signaling [91]. Perhaps more important is the role of insulin in attenuating skeletal muscle catabolism. As mentioned, insulin controls the expression of atrogenes (i.e., UPS E3 ligases, autophagy) involved in muscle protein breakdown (MPB), mainly through Akt signaling. Together with the contributory role of Akt-independent activation of MPB through MAPK pro-inflammatory signaling, IR may induce skeletal muscle atrophy in insulin resistant obese individuals, and T2DM patients through unbalanced muscle protein turnover denoted by exacerbated MPB, and potentially impaired MPS response to nutritional anabolic stimuli. Lastly, it is worth noting that skeletal muscle atrophy may result in the selective loss of proteins with potential effects on muscle functionality, which has been scarcely explored. For example, aquaporins (e.g., aquaporin 4 (AQP4)), have been implicated not only in water transport but also in metabolism and fatigue resistance [104], and are markedly targeted for degradation under muscle atrophy [105].



Box 2 Insulin signaling in skeletal muscle anabolism and catabolism Insulin exerts a wide range of effects not only on skeletal muscle metabolism but also anabolism and catabolism through modulation of the insulin receptor-Akt signaling pathway. Briefly, the binding of insulin to its surface receptor triggers the recruitment and phosphorylation of insulin receptor substrates (IRS) mainly IRS1 and IRS2. Phosphorylation of IRS1 proteins creates binding sites for the regulatory subunit of phosphatidylinositol 3-kinase (PI3K). The second messenger phosphatidylinositol-3,4,5-triphosphate (PIP3) docks pleckstrin homology (PH) domains of Akt and phosphoinositide-dependent kinase 1 (PDK1), thus facilitating their activation and migration to the cell membrane [106]. Following membrane relocation, Akt is partially activated by PDK1 and, subsequently, activates the mechanistic target of rapamycin (mTOR) complex 2 (mTORC2) to facilitate a further Akt phosphorylation, leading to full activation [107]. Akt plays a central role in modulating distant insulin signaling effects at different levels, being the most representative process insulin-stimulated glucose uptake. Specifically, Akt is both necessary and sufficient to facilitate insulin-mediated translocation of the skeletal muscle glucose receptor GLUT4 and fusion with the plasma membrane, thus enabling muscle glucose uptake [108]. Other major metabolic pathways include those involved in fatty acid uptake and glycogen synthesis (reviewed in ref. [109]). In the context of skeletal muscle atrophy, the role of Akt in regulating skeletal muscle protein turnover is critical. Phosphorylation of tuberous sclerosis complex 2 (TSC2) by Akt facilitates mTORC1 activation at the lysosome. Activation of mTORC1, in turn, leads to phosphorylation of different substrates and downstream targets (e.g., translational initiation promotor ribosomal protein s6 kinase-1 (S6K1) and eukaryotic initiation factor (4E-BPI)) known to positively regulate translational machinery to trigger protein synthesis, cell growth, and proliferation [110]. Not only is mTORC1 considered a master regulator of protein synthesis but is also known to suppress cell catabolism through inhibition of multiple autophagy-related proteins (reviewed in ref. [110]). However, disrupted Akt signaling appears to be more relevant than mTORC1-mediated control of autophagy in settings of skeletal muscle atrophy [111]. Akt is demonstrated to negatively phosphorylate forkhead box class O (FoxO) transcription elements, particularly the skeletal muscle predominant isoforms FoxO1 and FoxO3, which facilitates their relocation to the cytoplasm and represses the expression of targeted downstream genes involved in the activation of ubiquitin-proteasome system (UPS) E3 ubiquitin ligases, mainly muscle RING finger 1 (MuRF1) and Atrogin-1/muscle atrophy F-box (MAFbx) [112], as well as different genes involved in autophagy/lysosomal pathways. The UPS involves the coordinated action of three enzymes (E1, E2, and E3) that operate to target short-lived/damaged proteins through ubiquitination in order to facilitate their degradation by the 26S proteasome complex, being MAFbx and MuRF1, two critical skeletal muscle-specific E3 ubiquitin ligases consistently described to be upregulated under atrophic conditions [113]. While FoxOs are thought to be primarily modulated by Akt, positive phosphorylation of FoxOs by mitogen-activated protein kinases (MAPKs) in Akt-independent manner has been described, which might also contribute to enhanced protein degradation in response to cellular stress (discussed in later sections) [114, 115].

3.1 Intramyocellular lipid accumulation

As mentioned before, ectopic lipid accumulation, particularly to skeletal muscles, may be a key contributor to IR under chronic overnutrition. SCFAs and most medium-chain fatty acids (MCFAs) readily cross cellular and mitochondrial membranes. In contrast, long-chain fatty acids (LCFAs) require fatty-acid binding proteins for cellular uptake, intracellular transport, and metabolism [116]. Upregulation of the skeletal muscle transmembrane fatty acid translocase FAT/CD36 has been reported in obese and T2DM individuals [117, 118]. Other putative sarcolemmal fatty acid transporters include the plasma membrane-associated fatty acid binding protein (FABPpm) and fatty acid transporters 1 and 4 (FATP1,4) [119]. Sarcolemmal translocation of all these transport proteins has been shown to be modulated by insulin [120], and several research lines suggest an impact of diabetogenic conditions on their translocation and expression in skeletal muscle [121, 122], albeit the individual contribution of each transporter remains ill-defined. Fatty acids are subsequently trapped within the muscle cell through conversion to fatty acyl-CoA esters mediated by acyl-CoA synthetases as well as through binding to the cytosolic binding protein FABPc [123], and mobilize to metabolic sites. Early studies observed a reduction in enzymatic oxidative pathways in mitochondria of T2DM patients [124] while more recent observations suggest that decreased mitochondrial content and impaired dynamics may underlie mitochondrial dysfunction and compromised fatty acid oxidation in obesity and diabetes (discussed in later sections) [125]. Promoted fatty acid cellular uptake coupled with mitochondrial dysfunction (impaired disposal) contribute to IMCL accumulation in skeletal muscle.

Among IMCLs, intramuscular triacylglycerides (IMTGs) were originally thought to the main culprit of IR resulting from lipid oversupply. However, accumulation of IMTGs may be considered to play a protective role aimed to prevent increases in different lipotoxic metabolites, most notably diacylglycerols (DAGs) and ceramides. DAGs are lipidic compounds that originate from multiple sources including breakdown and *de novo* synthesis of triglycerides [126]. Particularly, sn-1,2-DAGs stereoisomers have been extensively implicated in the onset of IR through recruitment/activation of atypical protein kinase-c (PKC) isoforms, particularly PKCε and PKCθ [127], yet associations of intramuscular DAGs and IR are not always consistent and might depend on length and saturation of DAG fatty acid chains, and divergent subcellular locations [128]. In this sense, recent research suggested that sn-1,2-DAGs contained in the skeletal muscle cell membrane might mediate IR [129], which consequently phosphorylate the insulin receptor substrate-1 (IRS-1) thus blocking downstream Akt activation, a key node in the insulin signaling cascade, and attenuating insulin signaling [130]. In support of these findings, overexpression of diacylglycerol kinase δ (DKG-δ), an isoform highly expressed in skeletal muscle of the enzyme that catalyzes the conversion of DAG to phosphatidic acid, has been shown to protect against high-fat diet-induced glucose intolerance in skeletal muscle [131, 132].

Another family of compounds argued to contribute to IR in skeletal muscle consists of ceramides, particularly C18 species [133]. Ceramides are synthetized via different pathways, including *de novo* synthesis in endoplasmic reticulum (ER) from serine and an acyl-CoA, preferentially palmitate, though the rate-limiting step enzyme serine palmitoyltransferase (SPT), to later undergo reduction, and an acetylation step responsible for their fatty acid chain composition [134]. Further reactions lead to different members of the family [134]. In settings of saturated FA oversupply, ceramide transporter (CERT) activity is attenuated, which compromises ceramide transport from ER to Golgi apparatus and promotes its accumulation [135]. Notably, ceramides are demonstrated to inhibit Akt in skeletal muscle by activating PKCζ and protein phosphatase 2A (PP2A) resulting in impaired insulin signaling [136, 137]. Of note, long-term exposure to ceramides may involve inhibition of IRS-1 though activation of the double-stranded RNA-activated protein kinase (PRK)/ cJun-N-terminal kinase (JNK) pro-inflammatory pathway [138]. Overall, compelling evidence supports a role of certain intramuscular toxic lipid species in the disruption of skeletal muscle insulin signaling in obesity, in turn compromising skeletal muscle mass and metabolism.

3.2 Skeletal muscle inflammation

Besides lipotoxicity induced by intramyocellular accumulation of above-mentioned lipid species, a solid body of evidence suggests that excess fatty acid supply might also mediate IR through pro-inflammatory mechanisms. Particularly, expanded IMAT and PMAT are considered major sources of pro-inflammatory factors in skeletal muscle though paracrine modulation [61, 139]. In line with visceral adipose tissue, polarized M1-like macrophages and T-cells, particularly Th1 cells, accumulate preferentially to IMAT and PMAT and promote the production of proinflammatory cytokines resulting in myocyte inflammation associated with IR [61]. On the other hand, local production of cytokines in the skeletal muscle (myokines) is closely linked to the acute effect of exercise, and myokines are typically attributed many of the beneficial effects of exercise on metabolism, including glucose homeostasis [140]. While a potential contributory role of persistent autocrine inflammation in skeletal muscle may not be discarded [141], an immune cell origin of pro-inflammatory mediators from adjacent adipose tissue appears to play a protagonist role in skeletal muscle inflammation.

Several pro-inflammatory factors have been proposed to compromise insulin signaling in obese skeletal muscle. Among them, TNF-α is probably the most extensively studied cytokine demonstrated to induce IR through activation of the TNF receptor 1 (TNFR1) [58, 142]. Thereinafter, several intracellular steps involving the formation of protein complexes, interaction with scaffolding kinases, and generation of ubiquitin chains take place to facilitate the interaction with the downstream MAPKs JNK, p38, and extracellular signal-regulated kinase (ERK) (a known IRS-1 kinase [143]) as well as the activation of the inhibitor of nuclear factor κB (IKK)/NF-κB pathway [144] – IKK promotes the degradation of the NF-κB inhibitor IκB in TNF-α-dependent manner [145] – thereby mediating disruption of IRS-1 in skeletal muscle [146, 147]. Other pro-inflammatory factors interact with MAPKs/NF-κB and might mediate IR in skeletal muscle. For instance, chemokines such as the leukotriene B4 (LTB4), have been shown to promote IR in myocytes through JNK-dependent mechanisms [148]. IL-1β is also demonstrated to interact with MAPK and NF-κB [149], and has been documented to mediate IR in different tissues [150–152]. Not only immune cell-derived cytokines but also circulating LPS can mediate interaction with MAPK and NF-κB through recognition/agonism of TLR4. Besides abovementioned effects of toxic lipid species, such as DAG and ceramides, on insulin signaling, saturated FAs (e.g., lauric acid and palmitic acid) are demonstrated to activate innate immune responses through interaction with TLR4 and TLR2 [153–155]. Interaction with TLRs can, in turn, contribute to IR through above-cited pro-inflammatory pathways.

IL-1β has gained great attention in recent years due to the potential role of the NLRP3 inflammasome, a protein complex responsible for the activation of pro-inflammatory IL-1β, in mediating insulin resistance in skeletal muscle. NLRP3 activation induced by diet has been consistently shown to interfere with insulin signaling in different tissues [156], including skeletal muscle [157, 158], and mechanisms involved in NLRP3-mediated IR remain an interesting field of research. Notably, NLRP3 is triggered through activation of TLR4, and stimulation of TLR4 by physiological levels of bacterial LPS in myocytes has been shown to promote mitochondrial dysfunction and mtROS production [159], which denotes the complex interaction between inflammatory and oxidative components, and supports a potential role of other circulating pro-inflammatory mediators in skeletal muscle IR.

Interferon γ (IFN- γ) produced by pro-inflammatory Th1 cells infiltrating to IMAT and PMAT is another potential contributor to skeletal muscle IR [61, 160]. Upon binding to the interferon receptor (IFN-γR1/2), Janus kinases JAK1 and JAK2 are stimulated, which induce phosphorylation and activation of signal transducer and activator of transcription (STAT) elements, primarily STAT1. Subsequently, STAT1 relocates to the nucleus and mediates transcription of genes involved in immune and inflammatory responses such as suppressor of cytokine signaling (SOCS) molecules [161]. Further, IL-6, a cytokine generally considered pro-inflammatory under obesogenic conditions, was demonstrated to activate STAT3 in myocytes and promote ubiquitination and degradation of IRS1 resulting in IR [162]. In alignment, chronic activation of the IL-6-JAK-STAT3 pathway in skeletal muscle has been shown to promote mtROS production, which in turn further enhanced STAT3 signaling and resulted in mitochondrial dysfunction and cellular oxidative stress [163].

Lastly, as noted above, inflammation related pathways may contribute to skeletal muscle atrophy in obesity and T2DM through insulin-independent mechanisms, involving activation of MAFbx and MuRF1 E3 ubiquitin ligases. NF-κB transcription factors p50 and Blc-3 were shown to be required for disuse-induced atrophy, and associated with enhanced expression of MuRF1 and MAFbx [164]. Further, increased expression of MuRF1, but not MAFbx, along with signs of muscle atrophy have been observed with induction of NF-κB in rodent models [165]. Induction of MAFbx in skeletal muscle by TNF-α exposure was shown to be mediated by p38 MAPK, but not JNK and ERK1/2 [166]. In same fashion, IL-6-mediated activation of STAT3 was shown sufficient to induce skeletal muscle atrophy *in vitro* and *in vivo* together with elevated expression of SOCS3 and MAFbx [167]. Moreover, STAT3 was observed to enhance expression of myostatin, a well-documented negative regulator of muscle growth, through activation of the transcription factor C/EBPδ in skeletal muscle [168]. Overall, skeletal muscle inflammation not only associates with IR but also with a promoted activation of protein degradation systems, which might contribute to unbalanced protein turnover and atrophy.

3.3 Mitochondrial dysfunction and oxidative stress

Decrements in skeletal muscle mitochondrial content have been observed in individuals with obesity, and in T2DM patients [169]. Lower mitochondrial content in these populations has been shown to associate with a reduction in the expression of genes involved in mitochondrial biogenesis, particularly the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) [170, 171], which is markedly expressed in oxidative (I and IIa) compared to glycolytic fibers (IIx) [172]. Saturated fatty acid feeding is documented to induce PGC-1α expression in lean subjects, but sustained overfeeding might exhaust PGC-1α signaling in obese individuals [173]. In alignment, lipid infusion has been reported to decrease skeletal muscle PGC-1α expression [174]. Among different upstream regulators, PGC-1α is activated by AMP-activated protein kinase (AMPK), a

central fuel-sensing enzyme that is activated in cellular situations of elevated AMP:ATP ratio, which results in the transcription of different nuclear factors known to promote mitochondrial biogenesis processes [175]. Overnutrition shuts down AMPK signaling leading to impaired PGC-1α, which may partially underlie decrements in mitochondrial content.

Balance between mitochondrial fusion and fission processes is critical to ensure adequate mitochondrial quality control. However, an increasing number of studies have reported fragmented mitochondrial networks and disrupted mitochondrial rhythm (i.e., circadian changes in mitochondrial dynamics and oxidative capacity [176, 177]) in skeletal muscle tissue in obesity and T2DM [178–180]. Promoted skeletal muscle expression of fission-related proteins (fission protein 1 (Fis1) and dynamin-related protein-1 (Drp-1)) occurs with palmitate treatment and high-fat diet consumption [181, 182], and associates with decreased insulin-mediated glucose uptake [182]. Overexpression of Drp-1, specifically, has been consistently shown to associate with mitochondrial fragmentation in obesity and T2DM [183]. In alignment, loss of Drp-1 in myocytes from obese insulin-resistant subjects was demonstrated to enhance insulin action and improve mitochondrial network morphology [184]. Further, lipid infusion has been documented to promote activation of Drp-1 and accumulation of PTEN-induced putative kinase-1 (PINK1), a protein involved in mitochondrial removal (mitophagy), in skeletal muscle of sedentary healthy subjects, which was also linked to increased mitochondrial fragmentation and impaired peripheral glucose disposal [185]. It is worth noting that ceramide accumulation has also been reported to promote mitochondrial fission via increased expression of Drp-1 [186, 187]. Mitochondrial accumulation of ceramides might be particularly detrimental for mitochondrial function since ceramides are reported to induce depletion of several electron transport chain complexes, and may be incorporated to mitochondrial membranes thus facilitating proton leakage [188, 189]. Based on these observations and supported by evidence from other knock-out/knock-down experiments, the pharmacological inhibition of Drp-1 has recently garnered attention as a therapeutic tool for obesity and T2DM [190].

Decreased expression of mitochondrial fusion elements might contribute to pro-fission phenotypes in skeletal muscles. Mitofusin 1 and 2 (MFN1 and MFN2) are transmembrane proteins responsible for the tethering of mitochondrial outer layers, thus playing a crucial role in mitochondrial fusion [191]. Particularly, MFN2 is highly expressed in skeletal muscle, and its expression has been shown to decrease in obese rodents and human subjects with obesity, and T2DM [181, 192, 193]. Interestingly, some authors have suggested that promotion of Drp-1 might precede altered expression of fusion-related proteins [194]. Nonetheless, some evidence suggests that compensatory mechanisms involving secretion of myokines (e.g., fibroblast growth factor 21 (FGF-21) with insulin-sensitizing properties might occur with Drp-1 deficiency due to endoplasmic reticulum (ER) stress, which highlights the complex interplay between mitochondrial dynamics and cell homeostasis [195, 196]. The removal of fragmented mitochondrial networks resulting from pro-fission phenotypes is key to facilitate quality control, and limited research suggests that enhanced mitophagy mechanisms might compensate promoted mitochondrial fragmentation in settings of cellular fuel oversupply [197]. However, science on the effects of obesity and diabetes on skeletal muscle mitophagy is in its infancy and further research is needed [125]. Overall, smaller and less abundant mitochondria in skeletal muscle of obese and T2DM individuals appear to be at least partially driven by compromised biogenesis, increased fragmentation of mitochondrial networks and, potentially, impairments in defective mitochondria removal mechanisms.

Sustained oxidative stress is considered as a key consequence of mitochondrial dysfunction. Nutrient overload in settings of low ATP demands puts an important strain on the electron transport chain (ETC) and promotes chronic production of mtROS such as peroxide (H_2O_2). ROS production may, in turn, potentially exceed the capacity of antioxidant mechanisms, and lead to increased generation of partially oxidized lipid intermediates [198]. Mitochondrial fragmentation has been documented to increase mtROS [199], and enhanced H_2O_2 may also may reciprocally contribute to mitochondrial fragmentation [200]. Importantly, mtROS production is a common factor in different IR models, and findings from different studies have supported a causative role of mtROS, particularly H_2O_2 [201, 202], in triggering IR [65, 203]. Further, overexpression of antioxidant enzymes has been shown to exert a protective effect against diet-induced IR mediated by mtROS in skeletal muscle [202, 204, 205].

Mechanisms underlying mtROS-mediated deleterious effects on skeletal muscle insulin actions are complex and involve the activation of several cellular metabolic stress sensors, most notably the extensively studied MAPK pro-inflammatory pathways. Probably, the most well-documented MPAK involved in ROS-mediated effects on insulin signaling is JNK. In settings of sustained oxidative stress, JNK1/2 isoforms are chronically activated, and activation of JNK1/2 leads to phosphorylation of IRS-1 and IRS-2, thus negatively regulating insulin actions [206, 207]. Mitochondrial ROS also favor the activation of p38 MAPK, and, although controversial, some evidence supports a potential role of p38 MAPK on mtROS-mediated impairment of insulin-induced glucose uptake [208, 209]. Besides, other redox-sensitive components with potential implications in insulin signaling include NF-κB, a pleiotropic transcription factor that upregulates cytokine and chemokine production

and may be involved in several processes of muscle atrophy, as well as activation of the NLRP3 inflammasome [157]. It should be noted that ROS produced from non-mitochondrial sources might also participate from activation of cited pro-inflammatory cascades. Particularly, an increasing body of evidence supports a role of angiotensin II in mediating phosphorylation of IRS-1 in skeletal muscle through a NADP-ROS-NF-κB -dependent pathway [210, 211]. Sustained oxidative stress associates with oxidative damage, and results in generation of oxidated molecules (e.g., lipid peroxides) and by-products. Particularly, the lipid peroxidation by-product 4-hydroxy-2-nonenal (4-HNE) has been shown to impair insulin sensitivity in skeletal muscle cells, which may be mediated by formation of adducts on IRS-1 and Akt, or acting as second messenger in MAPK-related pathways [212, 213]. Altogether, several lines of research support a contributory role of mitochondrial dysfunction in the onset of skeletal muscle IR in obesity and T2DM progression through the sustained generation of mitochondrial ROS. Further, a potential loss of mitochondrial plasticity in obesity and diabetes might compromise skeletal muscle metabolic flexibility in these individuals [214], with consequent implications in muscle functionality. A brief summary of how cellular stress signaling pathways and insulin resistance operate to compromise balance in skeletal muscle protein turnover in the context of chronic overnutrition is depicted in Fig. 2.

3.4 Skeletal muscle fiber shift

The study of skeletal muscle fiber phenotypes is complex due to different challenges including the existence of intermediate/hybrid human fiber types featuring different proportions of myosin heavy chain (MHC) isoforms, differences between human and rodent skeletal muscle fibers used in experimental models, differences in factors involved in developmental versus adult transition/reprogramming processes, and limitations of the methodological approaches used to characterize them [215]. Nevertheless, slow-twitch type I fibers have been documented to possess increased GLUT-4 protein content, promoted expression of various components of the insulin signaling cascade, and higher insulin sensitivity compared to fast-twitch fibers [29, 216–218]. They also have higher mitochondrial content, rely on mitochondrial oxidation as their main energy source [219], making them better equipped to handle excess fat supply, and are more resistant to atrophic conditions [219]. Therefore, the slow-to-fast shift in muscle

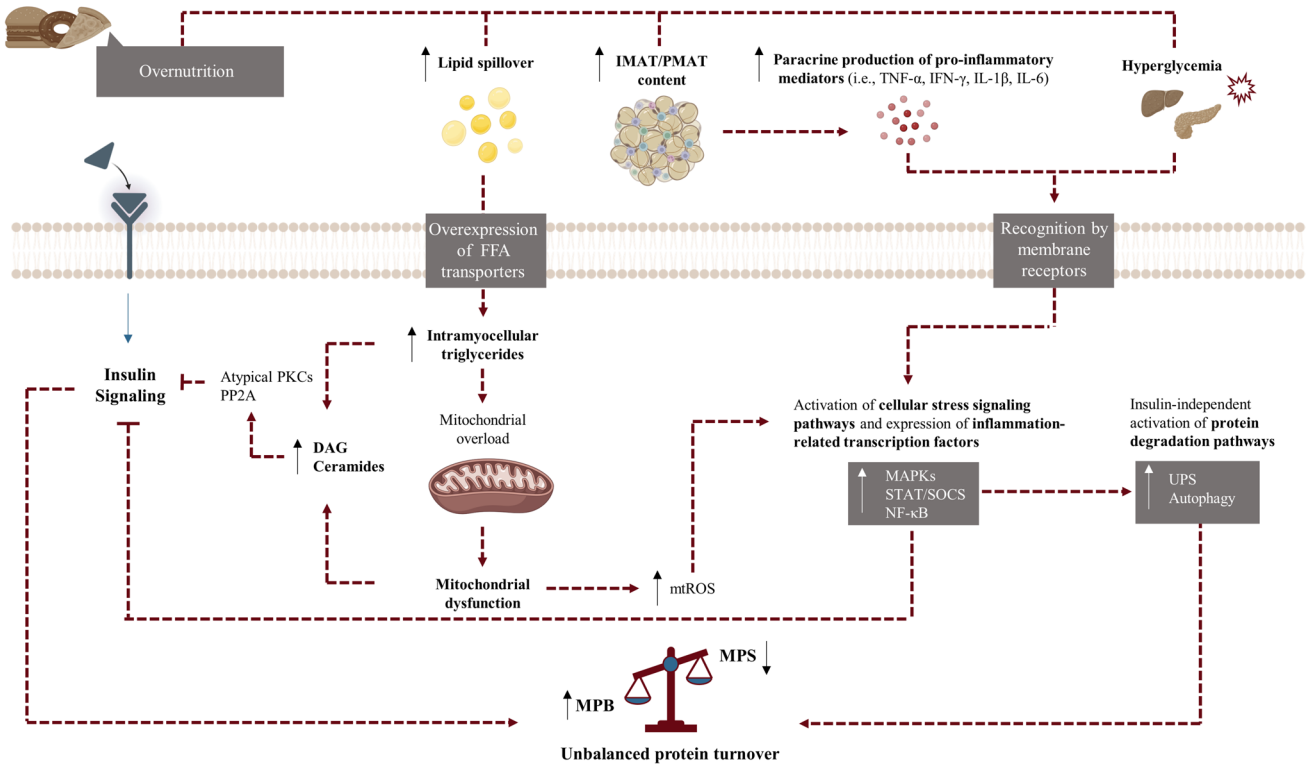


Fig. 2 Interplay between cellular stress signaling pathways, insulin resistance and skeletal muscle protein turnover. DAG, diacylglycerol; FFA, free fatty acids; IFN- γ, interferon γ; IL, interleukin; IMAT/PMAT, intermuscular/perimuscular adipose tissue; MAPK, mitogen activated protein kinases; MPB, muscle protein breakdown; MPS, muscle protein synthesis; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor κB; PKC, protein kinase C; PP2A, protein phosphatase 2A; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor α; UPS, ubiquitin proteasome system

fibers seen in obese [220] and diabetic individuals [27–30] is considered to negatively contribute to the progression of these metabolic conditions, and might be linked to the onset of IR in obese patients [217].

Signaling components involved in skeletal muscle fiber transition have been subject to extensive research. Overall, compelling evidence suggests that compromised content of skeletal muscle oxidative fibers may be partially attributed to impaired AMPK-PGC-1α signaling. As commented, overnutrition in absence of exercise leads to inhibition of AMPK-PGC-1α signaling. PGC-1α has been reported to directly activate several myocyte enhancer factor-2 (Mef2) proteins (particularly Mef2C and Mef2D), which are transcription factors known to promote the transition to oxidative fibers [221, 222]. Further, PGC-1α activates peroxisome proliferator-activated receptor β (PPARβ) (formerly PPARδ), which has been demonstrated to promote oxidative fiber shift [223, 224]. Adiponectin levels are decreased in obesity and T2DM, and activation of the skeletal muscle adiponectin receptor adipoR1 is known to upregulate PGC-1α through AMPK [225]. In the same vein, palmitate has been shown to stimulate folliculin interacting protein 1 (FNIP1) expression in skeletal muscle which is known to bind and repress AMPK activity, thus inhibiting fiber oxidative phenotypes [226]. In light of the evidence, targeting upstream AMPK regulators (i.e., Sirtuin 1 (SIRT1), adipoR1) through nutritional interventions aimed to reverse obesity- and T2DM-mediated conversion to type-II muscle fibers is increasingly pursued [227, 228].

Calcium signaling is critical for skeletal muscle fiber transition, particularly in response to exercise. Briefly, sustained muscle contraction elevates Ca^{+2} levels in muscle fibers, which are sensed by components of two signaling pathways involved in Mef2 activation, namely calmodulin-calcineurin complex and calcium/calmodulin-dependent protein kinase (CaMK). Binding of Ca^{+2} to the calmodulin-calcineurin complex activates the phosphorylation and translocation to the nucleus of nuclear factor of activated T cells (NFAT), particularly NFATc, which promotes Mef2 transcription [229]. Further, mentioned Ca^{+2}-dependent mechanism are documented to interact with PGC-1α signaling through coordinated changes in PGC-1α and PPARβ expression. Importantly, some evidence suggests that skeletal muscle Ca^{+2} handling might be impaired in obesity and T2DM through mechanisms involving ROS-mediated ryanodine receptor (RyR) inhibition, and mitochondrial dysfunction/impaired mitochondrial Ca^{+2} regulation [230], which might also partially underlie compromised muscle contraction capacity in these populations. It is also worth mention that type-I oxidative fiber are less-fatigable, but generate less force than type-II glycolytic fibers, which should theoretically imply higher skeletal muscle power output in obese individuals without signs of skeletal muscle mass loss [231]. Nonetheless, impaired calcium handling coupled with the potential deleterious effects of IMCL species on myosin binding protein-C (cMyBP-C) contractile properties have been proposed to partially explain impaired contractile function in obese subjects [232].

3.5 Impact of hyperglycemia on skeletal muscle

When increased insulin secretion in obese individuals fails to regulate glucose levels, hyperglycemia occurs, which is closely linked to aggravated IR and compromised β-cell function, thus being considered a major factor in the transition to T2DM. Sustained hyperglycemia in T2DM contributes to the formation of endogenous advanced glycation end products (AGEs), which consist of a diverse group of compounds generated through non-enzymatical reactions between carbonyl groups of reducing sugars and free amino acid groups of different body molecules [233]. Some early glucose-derived AGEs include well-described markers of glucose homeostasis such as glycated hemoglobin (Hb1AC) and fructosamine [233]. Further rearrangements facilitate the conversion of early AGEs into irreversible molecules, which are reported to accumulate in T2DM patients and associate with T2DM complications [234]. While AGEs encompass a highly heterogenous set of compounds – generally classified based on their chemical structure and ability to emit fluorescence – Nε-carboxymethyllysine (CML) (the dominant circulating AGE), Nε-carboxyethyllysine (CEL), and pentosidine are among the most frequently studied in the context of diabetes [235].

AGEs may play important roles in processes of skeletal muscle atrophy and dysfunction. AGE-induced modifications of skeletal muscle proteins, such as myosin and actin, might impair their contractile properties leading to loss of muscle strength [236]. Long-lived EMC proteins, particularly collagen, might be especially susceptible to AGE glycation and cross-linking, which in turn may result in structural disarrangements, disrupted binding affinity, and stiffness [237]. However, not only structural damage but also binding to cell receptors is reported to mediate AGE-induced impairments in skeletal muscle mass and quality. The receptor for advanced glycation end products (RAGE) is a multiligand receptor capable of recognizing several AGEs, s100 proteins, and high mobility group B1 (HMGB1) as well as pathogen associated molecular patterns, such as LPS [238]. Previously thought to be absent in healthy adult skeletal muscle tissue [238], recent research demonstrated RAGE expression in muscle of young healthy subjects [239]. Further, RAGE overexpression has been documented in skeletal muscle of obese subjects [239] and streptozotocin (STZ)-induced diabetic mice [240]. Upon ligand biding, the cytoplasmic domain of RAGE interacts with several adaptor proteins (e.g., mammalian diaphanous 1 (mdia1/Diaph1) and TIR

domain containing adaptor protein (TIRAP)) that connect RAGE with different pathways involved in cell stress signaling including JAK-STAT3, MAPKs (ERK1/2, p38, and JNK), IKK-NF-Kb, and AMPK-Akt [238]. Some of these pathways might result from RAGE-induced cytosolic ROS formation through activation of NADPH oxidases [241], which in turn might also promote mtROS generation (e.g., H_2O_2) [242].

Emerging evidence directly links AGE-RAGE signaling with skeletal muscle atrophy. Specifically, preclinical studies have linked AGE-RAGE signaling to AMPK-mediated downregulation of Akt, and subsequent MAFbx activation and atrophy in diabetic skeletal muscle [240]. Long-term administration of an AGE-rich diet to mice was shown to deteriorate skeletal muscle mass and performance, and suppress phosphorylation of mTORC1 downstream targets (S6K1) without impacting MHC isoforms [236]. In alignment, AGE treatment was reported to attenuate muscle load-induced hypertrophy and compromise muscle function in mice, which was accompanied by lower mTOR and S6K1 phosphorylation [243]. Other recent preclinical studies have observed that AGE treatment induces skeletal muscle atrophy and IR, leading to enhance Foxo1-MAFbx activity which was proposed to occur through ROS-induced ER stress [244]. Interestingly, circulating soluble isoforms of RAGE lacking domains needed for intracellular transduction might act as decoys for RAGE signaling, and reduced expression of these receptors has been reported in obesity and impaired glucose tolerance, which might contribute to the development of T2DM [245]. Altogether, glycated stress denoted by increased glucose-derived AGE levels might contribute to the loss of skeletal muscle mass and function shown in T2DM patients. Lastly, hyperglycemia might participate in skeletal muscle atrophy through different mechanisms. Particularly, hyperglycemia has been documented to exert direct catabolic effects on skeletal muscle through attenuated expression of the novel E3 ubiquitin ligase WWP1, which in turn prevents the degradation of zinc-finger transcription factor Krüppel-like factor 15 (KLF15), a transcription factor proposed to contribute to skeletal muscle atrophy potentially through FoxOs and atrogen [86, 246].

4 Reciprocal impact of skeletal muscle atrophy and dysfunction on metabolic health

Skeletal muscle atrophy has negative effects in whole-body metabolism. For instance, impaired muscle mass results in decreased ability to store water, glycogen, and amino acids needed to regulate water and energy balance [14, 247]. In the context of metabolic disorders, impaired skeletal muscle plasticity can compromise functional capacity and the ability to conduct exercise. This is important since, together with healthy nutrition, sustained lifestyle interventions consisting of physical exercise programs are fundamental for treating obesity, preventing T2DM progression, and can potentially facilitate T2DM remission [248]. Most updated guidelines issued by expert organizations recommend aerobic exercise training programs supplemented with resistance training to delay or prevent the progression to T2DM, improve glycemic control, facilitate weight loss, and prevent cardiovascular complications [249, 250]. Particularly, the American College of Sports Medicine (ACSM) recommends adults with T2DM to engage in moderate (40–59% VO_2 reserve (VO_2R)) or intense (60–89% VO_2R) aerobic exercise at least 3 days per week, with no more than 2 consecutive days between exercise bouts. This translates to 150–300 min/week of moderate aerobic activity or 75–150 min/week of vigorous exercise. Additionally, moderate (50–69% 1-repetition maximum (1RM)) or vigorous (70–85% 1RM) resistance training consisting of 10–15 repetitions per set and 1–3 repetitions per type of exercise is recommended 2–3 days per week, without consecutive days [250]. T2DM patients with comorbidities and older adults should attempt to conduct as much aerobic activity as possible, and maintain fitness and balance [250]. Naturally, these programs must be accompanied by sustainable eating plans based on current dietary guidelines for healthy diets [251], and tailored to the specific needs of the training program. Details on diabetes-focused nutritional guidance in the context of skeletal muscle atrophy and dysfunction have been previously reviewed elsewhere [51].

During exercise, increased energy demands of contracting muscles coupled with production of myokines and metabolic intermediates (e.g., lactate) are responsible for mediating interorgan communication, leading to beneficial metabolic adaptations including improved insulin sensitivity, which is critical to prevent the onset of T2DM (reviewed in ref. [252]). Regarding myocyte adaptations, mechanical loading due to muscle movement has profound myocellular repercussions that contribute to attenuate the loss of muscle mass and function associated with metabolic diseases through wide-ranging mechanisms. While a complete picture of all signaling events involved is not clear, exercise training potently activates AMPK, and increases cytoplasmic Ca^{+2} levels, thus modulating calcium-dependent signaling, mainly CaMKII, and downstream regulation of transcriptional activators and transcription factors (e.g., PGC-1α, PPAR-β, HDACs, MEF-2, etc.) [253]. Mechanotranducers and other stress-related signaling molecules (e.g., HIF-1α, MAPKs, ROS) are thought to participate in processes of skeletal muscle adaptation in response to different types of exercises [254]. For example, p38 MAPK can activate PGC-1 and Mef2 in response to aerobic exercise while ERK1/2 and JNK are involved in muscle hypertrophy through mTORC1 signaling

and potential inhibition of myostatin resulting from resistance training [254]. However, contrary to sustained elevations seen in metabolic diseases, exercise elicits transient and pulsatile activation of these event cascades which associates to physiological effects leading to beneficial adaptations [253].

Overall, exercise induces adaptations that help counteract above-described deleterious effects of obesity and T2DM, being particularly important the effect of exercise on inducing GLUT4 expression in skeletal muscle (up to 100-fold compared to resting conditions) [255], which drives insulin-independent glucose uptake and attenuates increments in plasma glucose levels. Other key adaptations include promoted glycolytic-to-oxidative fiber type reprogramming, improved blood flow to the muscle, enhanced mitochondrial biogenesis, upregulated mitochondrial dynamics, and increased mitophagy flux particularly following endurance training [256, 257]. Resistance training, on the other hand, is the most powerful trigger of MPS through mTORC1 signaling, thus generating muscle mass when sufficient amino acid provisions are available [258]. Pulsatile release of myokines such as IL-6, particularly after aerobic exercise, regulates manifold processes in autocrine manner, including hypertrophy, lipolysis, and glucose disposal, among others [259]. Of note, while cross-communication between of muscle contraction to the gut microbiota is an expanding field of research, physical exercise modulates gastrointestinal transit times, this contributing to shaping the gut microbiota [260]. Impaired metabolism and decreased exercise tolerance resulting from skeletal muscle atrophy and dysfunction instigate a vice cycle in obese and T2DM patients which further aggravates the underlying metabolic conditions through the mechanisms herein discussed.

5 Conclusion

Preventing or mitigating skeletal muscle atrophy and dysfunction has become a pivotal objective in combating obesity and curbing the progression to type 2 diabetes (T2DM). Chronic overnutrition, coupled with physical inactivity, precipitates a cascade of metabolic disturbances that undermine musculoskeletal plasticity, with hypertrophy of white adipose tissue emerging as a potential early indicator. Consequently, intramuscular lipid accumulation, skeletal muscle inflammation, mitochondrial dysfunction, oxidative stress, skeletal muscle fiber reprogramming, and hyperglycemia may contribute to muscle atrophy and dysfunction, with insulin resistance playing a central role due to its anticatabolic and permissive anabolic effects. Hyperglycemia is a major factor involved in the transition from obesity and T2DM, and sustained elevations of glucose levels in overt T2DM can further deteriorate skeletal muscle mass and quality in these patients through the production of advanced glycation end-products, leading to structural damage and activation of cellular receptors. Resulting muscle atrophy and dysfunction compromise the metabolic properties of the skeletal muscle, hinder the maintenance of healthy physical activity habits, and impede participation in exercise programs, thereby perpetuating a vicious cycle that exacerbates the underlying metabolic conditions.

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Declarations

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