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Deciphering the mechanisms and effects of hyperglycemia on skeletal muscle atrophy

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ABSTRACT

Hyperglycemia, a hallmark of diabetes mellitus, significantly contributes to skeletal muscle atrophy, characterized by progressive muscle mass and strength loss. This review summarizes the mechanisms of hyperglycemia-induced muscle atrophy, examines clinical evidence, and discusses preventive and therapeutic strategies. A systematic search of electronic databases, including PubMed, Scopus, and Web of Science, was conducted to identify relevant papers on hyperglycemic skeletal muscle atrophy. Key mechanisms include insulin resistance, chronic inflammation, oxidative stress, and mitochondrial dysfunction. Crucial molecular pathways involved are Phosphoinositide 3-kinase/Protein kinase B signaling, Forkhead box O transcription factors, the ubiquitin-proteasome system, and myostatin-mediated degradation. Hyperglycemia disrupts normal glucose and lipid metabolism, exacerbating muscle protein degradation and impairing synthesis. Clinical studies support the association between hyperglycemia and muscle atrophy, emphasizing the need for early diagnosis and intervention. Biomarkers, imaging techniques, and functional tests are vital for detecting and monitoring muscle atrophy in hyperglycemic patients. Management strategies focus on glycemic control, pharmacological interventions targeting specific molecular pathways, nutritional support, and tailored exercise regimens. Despite these advances, research gaps remain in understanding the long-term impact of hyperglycemia on muscle health and identifying novel therapeutic targets. The review aims to provide a comprehensive understanding of the mechanisms, clinical implications, and potential therapeutic strategies for addressing hyperglycemia-induced skeletal muscle atrophy.

1. Introduction

Diabetes, caused by insulin dysfunction, results in elevated blood sugar levels due to inadequate insulin production (Type 1) or insufficient insulin response (Type 2) [1]. Type 1 diabetes, affecting 5–10 % of all diabetic cases, requires lifelong insulin administration and routine blood glucose testing due to immune-mediated destruction of beta cells. Type 2 diabetes, affecting 90–95 % of diabetic patients, involves insulin resistance and often goes undiagnosed in early stages, increasing the risk of microvascular and macrovascular complications. Diabetic dermadromes, such as skin rashes, are also common [2,3].

Diabetes mellitus affects over 500 million people globally, with numbers expected to rise by 30 % by 2045. Many individuals are unaware of their condition, increasing susceptibility to complications. Despite differences in Type 1 and Type 2 diabetes, both share overlapping microvascular and macrovascular complications. In context to microvascular complications, Chronic hyperglycemia leads to nephropathy, neuropathy, and retinopathy through advanced glycation end-products (AGEs), pro-inflammatory environments, and oxidative stress. Diabetic nephropathy (DN) is the most common, initiated by the loss of podocyte integrity in the glomerular basement membrane, mediated by alpha-3-beta-1-Integrin. Chronic hyperglycemia-induced reactive oxygen species (ROS) production affects the renin-angiotensin system and TGF-beta signaling, causing inflammation and kidney hypertrophy. While in macrovascular complications, Hyperglycemia impairs vascular tissues via methylglyoxal (MGO) and other mediators, causing endothelial dysfunction and uncontrolled ROS production. This leads to vasoconstriction, lipid degradation, inflammation, and atherosclerosis, characterized by LDL deposition in blood vessels and increased

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Abbreviations

AGEs	Advance glycation end-products
DN	Diabetic nephropathy
MGO	Methylglyoxal
ROS	Reactive oxygen species
TIDM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
MOA	Monoamine oxidases
GC	Glucocorticoids
CRP	C reactive protein
IL-6	Interleukin 6
TNF	Tumour necrosis factor
SRF	Serum response factor
MEF2	Myocyte enhancer factor 2
BCAAs	Branched-chain amino acids
MSCs	Mesenchymal stem cells
IFN γ	Interferon gamma
miRs	MicroRNAs
FGF-21	Fibroblast Growth Factor-21
BMP-7	Bone Morphogenetic Protein-7
CML	N-(carboxymethyl)-lysine
S6K1	S6 kinase 1
ncRNAs	non-coding RNAs
MEF2	Myocyte enhancer factor 2
DPP-4	Dipeptidyl peptidase-4
ACE	Angiotensin-converting enzyme

endothelial permeability. High ROS levels suppress HDL's protective functions, promoting oxidation of phospholipids and sterols. Other macrovascular issues include calcification and plaque formation, contributing to serious vascular complications. Both microvascular and macrovascular complications significantly impact diabetes management and patient health, emphasizing the need for early diagnosis and intervention to mitigate these effects [4–6].

Hyperglycemia, a prominent diabetes condition, plays a significant role in skeletal muscle atrophy by activating pathogenic pathways that produce free radicals and cause oxidative stress. This oxidative stress is linked to numerous chronic hyperglycemic consequences, including cardiovascular disease, neuropathy, nephropathy, immune dysfunction, and pulmonary problems [7]. Hyperglycemia encourages ROS overproduction, leading to cell damage and irreversible tissue loss, known as muscular atrophy. Diabetic myopathy results from disrupted glucose, lipid, and protein metabolism, impacting the liver, adipose tissue, and skeletal muscle [8]. Insulin resistance in these tissues impairs glucose uptake, glycogen synthesis, and lipid oxidation, leading to triglyceride accumulation in myofibers. This disruption in nutrient handling causes decreased physical stamina, muscle power, and muscle mass, as well as impaired muscle growth and regeneration. The murine model of diabetes also shows reduced mitochondrial content and metabolic rigidity [9].

2. Skeletal muscle in diabetes mellitus

Skeletal muscle development and growth are significantly hindered in both type 1 and type 2 DM, leading to reduced muscle mass, smaller myofiber size, decreased metabolic activity, and a shift toward a glycolytic phenotype. In T1DM, studies have shown decreased skeletal muscle capillarization and angiogenesis, impairing the muscle's ability to repair damage [10]. Progenitor cells play a crucial role in diabetic conditions, serving as the primary therapeutic targets to enhance muscle health as the disease progresses. However, diabetes adversely impacts the quality and functionality of these progenitor cells (Fig. 1) [11].

Similarly, T2DM results in muscular atrophy and reduced capillary density in skeletal muscles. Muscle metabolism disturbances, common in T2DM, lead to abnormal lipid accumulation and reduced intermyofibrillar mitochondrial content. These changes make it difficult for muscles to switch between burning fat and carbohydrates, causing rigid metabolic responses to insulin. Consequently, both T1DM and T2DM severely affect skeletal muscle health, emphasizing the need for targeted therapeutic interventions to mitigate these detrimental effects and improve muscle function and repair in diabetic individuals (Fig. 1) [12].

3. Muscle atrophy (diabetic myopathy)

Diabetic myopathy, a prevalent yet often overlooked microvascular complication of diabetes, significantly impacts skeletal muscle, which is crucial for mobility and glucose homeostasis. This condition contributes

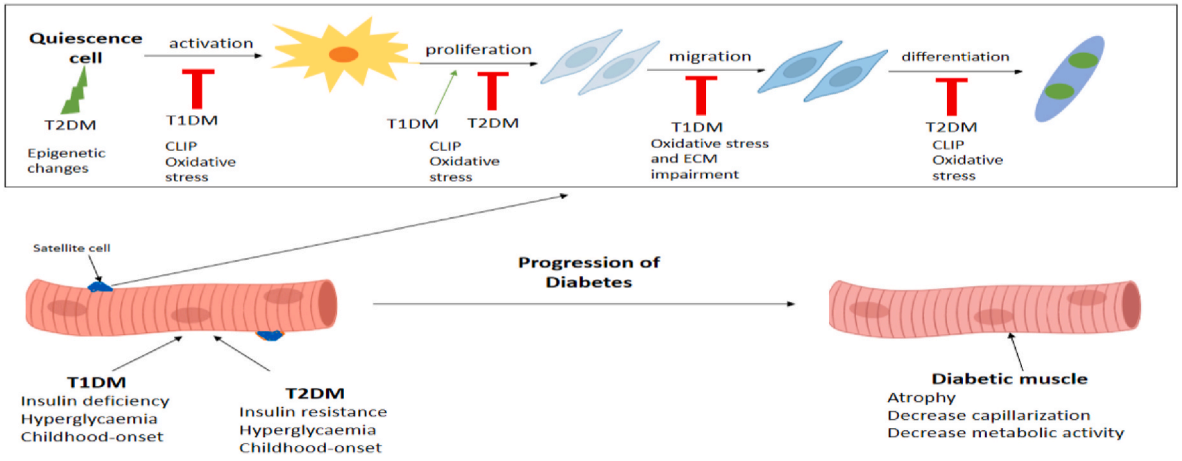

Fig. 1. Diabetes mellitus negatively impacts skeletal muscle health and progenitor cell populations, including satellite cells, in both T1DM and T2DM, despite their different etiologies and development courses. Diabetes affects satellite cells at various stages of adult myogenesis, which is crucial for muscle maintenance. Chronic low-grade inflammation, oxidative stress, and impaired extracellular matrix remodelling are key factors contributing to reduced satellite cell functionality and muscle health in diabetes.

to the persistence of secondary diabetic complications. Muscle atrophy in diabetic myopathy is driven by a reduction in muscle protein synthesis and an increase in the activity of calcium-triggered intramuscular proteases. These proteases lead to the production of ROS, ATP synthesis disruptions, and cellular death [10]. As muscle atrophy progresses, mitochondrial shrinkage occurs due to heightened ROS production and diminished oxidative capacity, evident in the transition from type 1 and type 2a fibers to type 2x fibers [13].

In the context of skeletal muscle atrophy, cellular factors involved in injury healing and disease progression are activated, impairing muscle function. Dormant satellite cells are stimulated by growth factors to form new myotubes, while inflammatory cells are mobilized to repair tissue damage and restore muscle function. However, the generation of numerous regulatory mediators during this immune response prevents complete tissue regeneration. Regulatory non-coding RNAs play a pivotal role in the imbalanced failure of muscle regeneration and serve as indicators of disease. Specifically, certain microRNAs (miRs), known as dystromiRs, are elevated in individuals with muscle atrophy. For instance, Becker muscular dystrophy, a milder form of Duchenne muscular dystrophy (DMD), is associated with higher levels of miR-206, miR-1, and miR-133, whereas DMD biopsies reveal increased levels of miR-1, miR-31, miR-133, and miR-206 proteins Specifically, certain microRNAs (miRs), like miR-23a, miR-29, miR-146a, miR-133, miR-206, miR-210 known as dystromiRs, are elevated in individuals with muscle atrophy [14].

3.1. Role of myokines and osteokines in diabetic muscle atrophy

Myokines and osteokines are critical signaling molecules released by muscle and bone cells that play essential roles in regulating physiological processes, including muscle metabolism, bone health, inflammation, and energy homeostasis. Their functions are interconnected, influencing both muscle and bone metabolism, particularly in the context of metabolic disorders such as diabetes. Myokines are peptides or proteins released by skeletal muscle cells in response to muscle contraction or stress. They act as signaling molecules that communicate with other tissues, including adipose tissue, liver, and bone. Meanwhile, osteokines are signaling molecules secreted by bone cells, such as osteoblasts and osteocytes. They play a crucial role in regulating bone remodelling and metabolic processes[15–17].

In diabetes, the dysregulation of myokines and osteokines contributes significantly to muscle atrophy. Myokines such as myostatin and interleukin-6 promote muscle degradation and inflammation, while reduced levels of beneficial myokines like irisin impair muscle regeneration. Osteokines, including osteocalcin, are involved in insulin sensitivity; their decreased levels exacerbate muscle wasting. The chronic inflammation characteristic of diabetes alters the secretion and action of both myokines and osteokines, disrupting the muscle-bone crosstalk [18,19]. This interplay leads to increased muscle protein breakdown and decreased muscle mass, ultimately resulting in significant muscle atrophy in diabetic individuals, as summarized in Table 1.

Table 1
Summary of myokine/osteokine in diabetic muscle atrophy.

Myokine/Osteokine	Role in Diabetic Muscle Atrophy
Myostatin	A negative regulator of muscle growth. elevated in diabetes, inhibits protein synthesis and promotes degradation, leading to muscle atrophy.
Irisin	Promotes muscle hypertrophy and fat browning. Levels are reduced in diabetes, which can lead to impaired muscle regeneration and increased atrophy.
Interleukin-6 (IL-6)	Acts as a pro-inflammatory myokine in excess. Chronic elevation in diabetes promotes muscle protein breakdown and exacerbates muscle atrophy through inflammatory pathways.
Fibroblast Growth Factor-21 (FGF-21)	Induced by metabolic stress, FGF-21 helps maintain metabolic balance. Its dysregulation in diabetes is linked to muscle wasting due to disrupted energy metabolism.
Osteonectin (SPARC)	An osteokine that supports muscle regeneration. Dysregulated in diabetes leads to impaired muscle repair and increased atrophy.
Osteocalcin	Enhances insulin sensitivity and muscle function. Decreased levels in diabetic patients contribute to insulin resistance and muscle atrophy.
Bone Morphogenetic Protein-7 (BMP-7)	Promotes muscle mass maintenance. Its reduction in diabetic states is associated with increased muscle loss.
RANKL	Stimulates bone resorption. Increased levels in diabetes may lead to bone loss and indirectly affect muscle function.

4. Molecular mechanisms of hyperglycaemic skeletal muscle atrophy

4.1. AGEs

AGEs may play a harmful role in the diverse reactive oxygen species that are produced as a result of diabetes. AGEs are fluorescent; insoluble adducts that form on proteins and change physiological function. AGEs can build up in diabetic patients and animals' kidneys, lenses, and hearts, causing diabetic problems like retinopathy, nephropathy, and cardiovascular disease. The Maillard reaction, a non-enzymatic glycation mechanism, produces a group of heterogenous products known as AGEs. By reducing the carbonyl group of the reducing sugar, this reaction (also known as the Millard reaction) produces 1-amino-1-deoxy ketose. It starts with Schiff bases and the Amadori product (glucose). According to reports, N-(carboxymethyl)-lysine (CML), one of the AGEs, builds up in the myofibers of plantar diabetic rat muscle and undergoes fibre type change as a result (Fig. 3) [20,21].

ROS generation and removal must balance each other out to prevent oxidative stress, which can be brought on by either weaker antioxidant defences or higher ROS formation. Excessive ROS production, which also occurs in healthy cells, is a common component in the majority of diseases. Islet beta cells are particularly vulnerable to ROS, which harms the cells and causes death. Many physiological processes, such as the oxidation of cysteine residues in proteins, require ROS activation [22]. Most research revealed that monoamine oxidases (MAO) has recently been connected to musculoskeletal disorders, which are an important mitochondrial source of ROS. Oxidative stress causes muscle loss by preventing protein synthesis through the AKT-mTOR pathway and its downstream targets [23]. ROS is a key component in the pro-inflammatory signalling pathway's initiation. Additionally, ROS is produced by NOX, which is strongly supported by inflammatory cells as well as other cells like smooth, heart, and skeletal muscle. It is in the sarcolemma where NOX is found. According to reports, NOX plays a significant part as a source of ROS in the cardiac and skeletal muscles of mdx mice, where it was found to be more active and expressed [24].

Oxidative stress plays a central role in the development of diabetic myopathy by causing direct cellular damage, inducing inflammation, impairing muscle regeneration, disrupting insulin signaling, and causing mitochondrial dysfunction. Targeting oxidative stress and its downstream effects may offer therapeutic strategies for preventing and managing diabetic myopathy (Fig. 3) [25].

4.2. Hyperglycaemia

One of the most detrimental effects of hyperglycemia is protein glycation; a decrease in sugar causes protein chemical change, which ultimately results in advanced glycation [26]. The end result of these AGEs is clinically evident in the aging process, a complication of T1DM. In the presence of hyperglycemia, the amount of AGEs species has been observed to rise, which results in a reduction in actin-myosin motility [9]. In individuals with T1DM, numerous studies indicate that AGEs primarily accumulate in type 2 (fast-twitch) muscle fibers, leading to

degeneration and a loss of contractile function in these muscles [27]. Through the stimulation of the polyol pathway, hyperglycemia had a negative impact on skeletal muscle. This process results in a decrease in the protective response to oxidative stress, which damages tissue. Aldose reductase, a significant enzyme in the pathway, is activated by hyperglycemia, which accumulates sorbitol and other metabolites, causing osmotic stress, oxidative stress, and depletion of essential cofactors like NADPH. These changes contribute to cellular damage and the development of diabetic complications, including neuropathy, retinopathy, and nephropathy [8].

4.3. Glucocorticoid

Amino acids are primarily stored in skeletal muscles, and because glucocorticoids (GC) have a catabolic impact on these muscles, they prevent amino acids from being transported there, raising the levels of free amino acids in the blood [28]. The muscle-specific ubiquitin ligases are increased, and glucocorticoids activate the ubiquitin-proteasome pathway. Muscle atrophy is triggered by an increase in polyubiquitination-mediated protein mortification caused by MuRF-1 and atrogin-1 [29]. Additionally, GC has been linked to fast-twitch (Type II) muscle fiber degeneration, with a negligible impact on slow-twitch fibers (Type I). This may be because glycolytic muscles, such as the tibialis anterior, have more GC receptors than oxidative muscles (i.e., the soleus) GC limits the eIF4E-binding protein 1 (4E-BP1), and ribosomal protein S6 kinase 1 (S6K1) phosphorylation, which are crucial for protein synthesis, from being activated by insulin, IGF-1, and amino acid (Fig. 2) [30].

4.4. Inflammation

ROS, lipotoxicity, glucotoxicity, oxidative stress, and mitochondrial dysfunction are some of the factors that cause the development of insulin resistance, which causes T2DM by activating inflammatory pathways. Several inflammatory mediators, including circulating C reactive protein (CRP) and pro-inflammatory cytokines like interleukin 6 (IL-6) and tumour necrosis factor (TNF), are seen in T2DM individuals [31]. Chronic illnesses, aging, and obesity speed up the atrophy of muscles, which triggers the release of inflammatory cytokines (TNF-a, IL-6, and IL-1b) that obstruct the routes for protein synthesis and proteolysis. The pathways that these mediators further stimulate include NF-kB and p38-MAPK. The signalling pathway NF kB is primarily responsible for triggering muscle atrophy because it encourages the production of inflammatory factors. Both monomeric and heterodimeric (p50/p65) forms of NF-kB are found. When NF kB's p50/p65 complex is present, the target gene is transcripted. Even so, pro-inflammatory factor receptor binding that results in target gene transcription (TNF-alpha, IL-1), UPS stimulation, and eventually proteolysis and skeletal muscle atrophy also causes NF-kB activation [32]. PGC-1 plays a crucial role in reducing NF-kB phosphorylation, suppressing the pathway, inhibiting the expression of the target gene, and producing pro-inflammatory cytokines [33].

JAK/STAT pathway, which is activated by type I interferon (IFNα, -β, and –ω), type II IFNs, IL-2, and IL-6, also controls inflammatory reactions. IL-6 receptor alpha and gp130 exert IL-6's metabolic effects [34]. Tyrosine acids and STAT phosphorylation are stimulated by IL-6's binding to p80, which results in the formation of the complex protein gp130 and homodimerization. STAT phosphorylation causes muscle loss via a number of different pathways [35].

4.5. Molecular biomarkers

Biomarkers are used to assess how therapeutic interventions, pathogenic interventions, and indicators of normal biologic activity respond. The three major categories of circulating biomarkers that are found in blood are proteins and metabolites, DNA, and RNA. Various methods are employed based on the characteristics of the biomarkers. Diagnostic biomarkers are used to pinpoint the disease or condition of concern in an individual. Prognostic biomarkers may identify disease progression, disease recurrence, and clinical symptoms. These kinds of biomarkers offer the advantage of early patient clinical symptom identification. Currently, biomarkers are used to track disease development in muscular dystrophies. Pharmacodynamic/response biomarkers are used to assess how the patient is responding to therapeutic action. For muscle dystrophies, circulating biomarkers have been developed to track the progression of the condition and how well it responds to treatment [36].

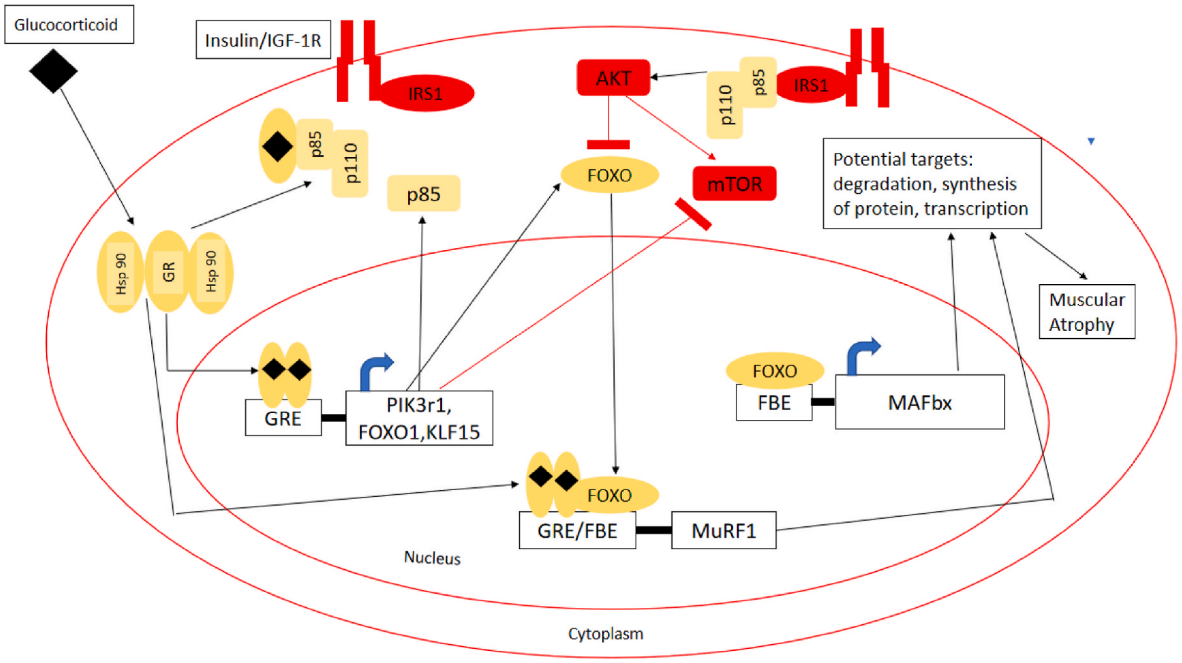

Fig. 2. The glucocorticoid-induced skeletal muscle atrophy process is depicted schematically.

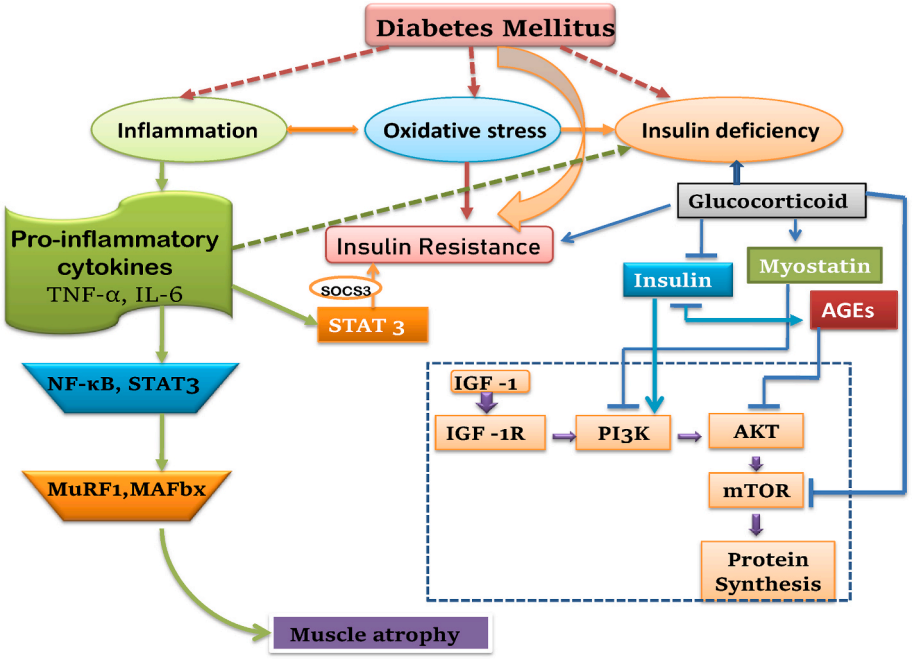

Fig. 3. Major pathway involved in skeletal muscle atrophy.

5. Potential biomarker for skeletal muscle atrophy

5.1. MicroRNA

MicroRNAs (miRNAs) are 17–22 tiny single-stranded non-coding RNAs (ncRNAs) that are expressed in different ways depending on the tissue. They are divided into two groups based on whether they are found in muscle or tissue, namely miRNAs (non-muscular tissue) and myomiRs (muscle tissue). Both have a substantial impact on the growth and differentiation of muscle cells. MiRNAs regulate gene expression at the posttranscriptional level by promoting the translation of their target mRNAs or inhibiting their decay. MyomiRs primarily control muscle balance and myogenesis. MiR-1, miR-133 (which is found in the heart and skeletal muscle), and miR206 are the main MyomiRs engaged in the process (skeletal muscle) [37]. Serum response factor (SRF), myogenic regulatory factor (myoD, Myf5, MRF4, and myogenin), and myocyte enhancer factor 2 (MEF2) all control the expression of these miRNAs. To transversely induce the expression of three pairs of muscle-specific miRNA in skeletal muscle, namely miR-1-1 and miR-133a-2, miR-1-2 and miR-133a-1, and miR-206 and miR-133b, SRF and MEF2 link with myoD and myogenin (Table 2) [38].

6. Therapeutic interventions

6.1. Pharmacological therapeutic intervention

Therapeutic interventions focus on reducing muscle atrophy and improving muscle function through pharmacological and non-pharmacological strategies. Pharmacologically, insulin sensitizers like metformin and thiazolidinediones are commonly used to enhance insulin sensitivity and reduce hyperglycemia-induced damage. Antioxidants, such as alpha-lipoic acid and vitamin E, help combat oxidative stress, a significant contributor to muscle atrophy in diabetes [46]. SGLT2 Inhibitors, like Dapagliflozin, lowers blood glucose levels by promoting glucose excretion in urine, indirectly preventing muscle atrophy [47]. Anti-inflammatory drugs such as NSAIDs and COX2 inhibitors reduce chronic inflammation, slowing muscle degradation [48]. GLP-1 receptor agonists (Liraglutide, Semaglutide) work by enhancing insulin sensitivity and lowering glucose levels; GLP-1 receptor agonists help preserve muscle mass. They also reduce inflammation and improve mitochondrial function, which is crucial in preventing muscle atrophy [49]. DPP-4 inhibitors (Sitagliptin and Linagliptin) show action by modulating glucose levels and improving metabolic control; they prevent muscle breakdown caused by chronic hyperglycemia. Incretins also have direct anabolic effects on skeletal muscle by improving nutrient uptake and reducing proteolysis [49]. ACE Inhibitors and ARBs (Lisinopril, Losartan) showed improved blood flow enhances nutrient delivery to muscles, while the reduction in inflammation prevents muscle breakdown. These drugs have been shown to have protective effects on muscle mass in diabetic patients, reducing the rate of atrophy mTOR Modulators (Rapamycin, Sirolimus), Although still under investigation, mTOR modulation may provide benefits in maintaining muscle mass by optimizing protein synthesis and preventing catabolic processes [50, 51]. Anabolic Steroids (Oxandrolone) can help temporarily reverse muscle loss by enhancing protein synthesis and counteracting catabolic signals [52].

6.2. Non-pharmacological therapeutic intervention

Non-pharmacological interventions for hyperglycemia-induced skeletal muscle atrophy focus on lifestyle changes that improve glucose control and muscle preservation. Exercise, particularly resistance and aerobic training, is crucial. Resistance training stimulates muscle protein synthesis and enhances insulin sensitivity, while aerobic exercise improves glucose metabolism and cardiovascular health, helping prevent muscle loss [53]. Dietary management with a balanced intake of proteins and low-glycemic index carbohydrates supports muscle regeneration and stabilizes blood sugar levels. Protein and amino acid supplements further aid muscle repair. Physical therapy helps maintain muscle function and strength, especially in those already experiencing muscle loss, while stress management techniques like yoga and meditation help reduce the impact of chronic stress, which can worsen hyperglycemia and muscle atrophy. Promoting overall healthy lifestyle habits, including adequate sleep, hydration, and regular activity, supports both muscle health and metabolic control. Education on glucose monitoring, diet, and physical activity empowers individuals to take charge of their condition and slow the progression of muscle atrophy associated with hyperglycemia [54].

Table 2
Summary of skeletal muscle MyomiRs target genes and functions.

Sr. No.	MyomiRs	Targets in skeletal muscle	Expression Pattern	Function in skeletal muscle	References
1	miR-1	PAX3/7, POLA1, CCDN1/2, YY1, CX43, HDAC4, MEOX2, RARB, BAF47, BAF60A, FZD7, CNN3, SFRP1, NOTCH3, HAND2, DII-1, HES1, FRS2, myocardin	Skeletal muscle and heart	Fostering myoblast differentiation, regeneration, angiogenesis regulation, pro-apoptotic, oxidative stress control, anti-migration	Sugiyama Y. et al.,2020 [39] Koutsoulidou A et al.,2020 [40]
2	miR-133a	FGFR1, PP2AC, CCN1, RUNX2, BAF60B, PRDM16, SRF, nPTB, IGF-1R, UCP2, FOXL2, FGFR1, PP2AC, ESFR, SNAI1, cyclin D2, SP1	Skeletal muscle and heart	Fostering myoblast proliferation, differentiation and fusion, regeneration, alternative splicing regulation, chromatin remodelling, cell fate regulation, pro-apoptotic, mitochondrial metabolism control, muscle fibre shift	Szigyarto C. A. et al.,2018 [76 Freitas P.A.C. et al., 2017 [41]
3	miR-133b	FAIM, FGFR1, MAML1, PP2AC, PRDM16, PTBP2, SP1	Skeletal muscle and heart	development of myoblast differentiation and fusion, regeneration, alternative splicing regulation, chromatin remodelling, cell fate regulation, pro-apoptotic	Freitas P.A.C. et al., 2017 [41] Al-Mshhdani BA. et al., 2021 [42]
4	miR-206	PAX3/7, POLA1, CCDN1/2, YY1, CX43, HDAC4, MEOX2, RARB, BAF47, BAF60A, FZD7, UTM, FSTL1, nPTB	Skeletal muscle (Type 1fibre)	Promotion of myoblast differentiation, regeneration, regeneration of neuromuscular synapses, chromatin remodelling, anti-angiogenic, pro-apoptotic, oxidative stress control, anti-migration	Ehtewish H. et al.,2022 [43]
5	miR-208b	SOX6, MYH6	Skeletal muscle (type I fibres), heart (low expression)	Muscle fibre shift, promotion of muscle growth	Brown, L.A. et al., 2020 [44] Al-Mshhdani BA. et al., 2021 [42]
6	miR-486	PAX7, PTEN, FOXO1A	Skeletal muscle Heart	Promotion of myoblast differentiation and fusion, alternative splicing regulation, anti-apoptotic, pro- migration	Chen R et al., 2020 [45]
7	miR-499	SOX6, MEF2C	Skeletal muscle (type I fibres), Heart	Muscle fibre shift, promotion of muscle growth	Sugiyama Y. et al.,2020 [39] Chen R et al., 2020 [45]

Emerging therapies include gene and cell-based approaches, such as the use of mesenchymal stem cells (MSCs) to promote muscle regeneration and repair damaged tissues. Also, targeting the AGE-RAGE pathway with specific inhibitors can reduce inflammation and oxidative stress, potentially alleviating muscle damage associated with diabetes. Combining these therapeutic strategies provides a comprehensive approach to managing diabetic myopathy and improving patients' quality of life [55].

7. Future research Directions

Future research on diabetic skeletal muscle atrophy should focus on elucidating the precise molecular mechanisms, including the roles of oxidative stress, inflammation, and mitochondrial dysfunction. Investigating genetic and epigenetic factors, such as gene expression and epigenetic modifications, is crucial for understanding the disease's progression. Developing reliable diagnostic and prognostic biomarkers will enable early detection and monitoring. Novel therapeutic targets, including drug discovery and gene therapy, hold promise for preventing or reversing muscle atrophy. Nutritional interventions and exercise regimens tailored for diabetic patients need thorough exploration to optimize muscle health. Stem cell therapy and tissue engineering offer the potential for muscle regeneration. Conducting randomized controlled trials and long-term studies will evaluate the efficacy and safety of new treatments. Technological innovations like advanced imaging techniques and wearable devices can enhance muscle health assessment. Translational research should improve animal models and ensure effective clinical application. This multifaceted approach aims to mitigate the impact of diabetic myopathy and enhance the quality of life for diabetic patients by translating laboratory findings into effective patient care.

8. Conclusion

Diabetes mellitus, characterized by chronic hyperglycemia, significantly impacts skeletal muscle health, leading to a condition known as diabetic myopathy. Both Type 1 and Type 2 diabetes contribute to skeletal muscle atrophy, which is marked by a reduction in muscle mass, strength, and metabolic function. Hyperglycemia disrupts normal glucose and lipid metabolism, exacerbating muscle protein degradation and impairing synthesis. The mechanisms underlying hyperglycemia-induced muscle atrophy involve insulin resistance, chronic inflammation, oxidative stress, and mitochondrial dysfunction. Key molecular pathways implicated include PI3K/Akt signaling, FOXO transcription factors, the ubiquitin-proteasome system, and myostatin-mediated degradation. AGEs accumulate in tissues, including skeletal muscle, under hyperglycemic conditions, leading to structural and functional impairments. Oxidative stress, driven by excessive ROS production,

further damages muscle cells and contributes to inflammation and mitochondrial dysfunction. This oxidative stress impedes protein synthesis via the AKT-mTOR pathway, exacerbating muscle atrophy. Glucocorticoids also play a role by activating the ubiquitin-proteasome pathway, leading to muscle protein degradation [56].

Therapeutic strategies to mitigate muscle atrophy in diabetes focus on glycemic control, pharmacological interventions, nutritional support, and exercise regimens. Insulin sensitizers, antioxidants, and anti-inflammatory agents are commonly used to target specific molecular pathways and reduce hyperglycemia-induced damage. Nutritional interventions, including a balanced diet rich in proteins and essential nutrients, support muscle repair and growth, while exercise, particularly resistance training, promotes muscle hypertrophy and improves mitochondrial function. Emerging therapies, such as MSC treatments and inhibitors targeting the AGE-RAGE pathway, hold promise for muscle regeneration and reducing inflammation and oxidative stress [21].

Future research should delve into the molecular mechanisms of diabetic muscle atrophy, focusing on genetic and epigenetic factors, and develop reliable biomarkers for early detection and monitoring. Investigating novel therapeutic targets, optimizing nutritional and exercise interventions, and exploring stem cell therapy and tissue engineering are essential. A comprehensive approach combining these strategies aims to mitigate diabetic myopathy and improve the quality of life for diabetic patients.

CRediT authorship contribution statement

Khushboo Gaur: Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Conceptualization. **Lucy Mohapatra:** Writing – review & editing, Supervision. **Pranay Wal:** Writing – review & editing, Supervision. **Amana Parveen:** Writing – review & editing, Writing – original draft, Resources. **Shivam Kumar:** Writing – review & editing. **Vaishali Gupta:** Writing – review & editing, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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