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Diabetic Skeletal Muscle Atrophy: Molecular Mechanism and Recent Treatment Approach – Review

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ABSTRACT:

Diabetic mellitus is a chronic metabolic disorders that change in protein and lipid metabolism. Chronic diabetic mellitus causes cardiomyopathy, retinopathy, nephropathy, and neuropathy. Compared to diabetic mellitus, skeletal muscle atrophy receives less attention and is an unrecognized side of diabetic complications, and not treating diabetic skeletal muscle atrophy leads to diabetic neuropathy. It affects normal day-to-day life activities because muscle strength and mass are reduced. This review discusses the skeletal muscle normal signaling (protein synthesis and protein degradation) mechanism, how diabetic mellitus affects the skeletal muscle signaling pathways what are the options to treat diabetic skeletal muscle atrophy at the molecular level. Anti-inflammatory and oxidative stress-reducing substances play an important role and insulin signaling changes are used in treating diabetic skeletal muscle atrophy. We discuss the ongoing research to treat skeletal muscle atrophy by using plant material and synthetic substances and how effective in treating this condition. In this review, understand the effective use of already available treatments and new treatments for diabetic skeletal muscle atrophy.

Keywords: diabetic skeletal muscle atrophy, Insulin resistance, Insulin deficiency, STZ, TNF-α

ABBREVIATION: T1DM -Type 1 Diabetic Mellitus, T2DM-Type 2 Diabetic Mellitus, MyHC-Myosin heavy chain, IKKβ-Inhibitor of nuclear factor Kappa-B Kinase subunit Beta, TWEAK- TweakR/Fn14, IFN-γ - Interferon-gamma, GLUT-4-Glucose Transporter Type 4, JNK-C-jun N-terminal kinases, MAPK-mitogen-activated protein kinase, SOCS3-Suppressor of cytokine signaling 3, PI3K-phosphatidylinositol 3-kinase. Akt-protein kinase B, NFκB- Nuclear factor kappa-light-chain-enhancer of activated B cells, MyoD-myoblast determination protein 1,LC3-Microtubule-associated protein 1A/1B-light chain 3, Mfn2- Mitofusin-2, Drp1-Dynamin-related protein 1, FIS1-Mitochondrial fission 1 protein, FGF-21- Fibroblast growth factor 21, c-AMP-cyclic adenosine monophosphate, BMP-7 –Bone morphogenetic protein 7, FOXO1-Forkhead box protein O1,GAP-43-Growth Associated Protein 43,KIF5B-Kinesin family member 5B

INTRODUCTION:

Diabetes mellitus is a prevalent chronic metabolic disorder characterized by elevated blood glucose levels (over 126 mg/dL), which can lead to changes in carbohydrate, protein, and lipid metabolism. Normal fasting values range from 60 to 99 mg/dL. There are two types of endocrine cells in pancreatic islets: B cells and A cells. Islet B cells produce insulin and islet A cells secrete glucagon. These cell types work together to regulate blood glucose levels in the body[(1)(2)]. Diabetes mellitus (DM) is classified into two types: Type 1 (T1DM) and Type 2 (T2DM)[(3)]. Type 1 diabetes is primarily caused by the autoimmune death of pancreatic beta cells, which results in insulin insufficiency. Obesity is a major risk factor for developing type 2 diabetes. Type 2 diabetes, enhanced glucotoxicity, lipotoxicity, endoplasmic reticulum- induced stress, and apoptosis all contribute to the gradual loss of beta cells[(4)]. Both types are linked to an increased risk of macrovascular (cardiomyopathy) and microvascular (retinopathy, nephropathy, and neuropathy) issues related to diabetes. Diabetes is linked to diabetic myopathy, which reduces the muscles and skeletal[(5)]. **Skeletal muscle** is the largest organ in the human body made up of around 600 parts and constitutes approximately 40% of body weight. This tissue provides structure, mobility, and protection for vital organs while regulating body temperature and metabolism[(6)(7)]. Skeletal muscles control mobility, gestures, and daily tasks, consisting of fiber bundles. skeletal muscle fibers are classified based on MyHC as slow- twitch (Type 1, oxidative) and fast-twitch (Type 2, glycolytic), differing in movement patterns, neural reactivity, and metabolism[(8)]. Furthermore, skeletal muscles serve as the primary tissue involved in energy metabolism and take a role in the absorption, use, and storage of substrates for energy metabolism, including lipids, glucose, and amino acids[(9)]. **Skeletal Muscle atrophy** is the loss of tissue caused by protein degradation exceeding synthesis[(10)]. Muscle atrophy is caused by immobility, aging, malnutrition, Systemic

diseases (such as diabetes, obesity, inflammation, and cancer), bad lifestyle choices (such as obesity, high-fat diets (HFD), and long-term medication use (such as glucocorticoids) affecting the nervous or musculoskeletal system[11]. Primary sarcopenia is the term used when it is age-related. Sarcopenia caused by chronic disease or lack of mobility is referred to as secondary sarcopenia. sarcopenia is listed in the International Classification of Diseases (ICD code M62.8) and acknowledged as a disease by the World Health Organization[12]. There are two types of skeletal muscle atrophy: physiological and pathological While pathological atrophy is brought on by fasting, nerve damage, stroke, and numerous other illnesses like cachexia, diabetes mellitus, and chronic obstructive pulmonary disease (COPD), physiological atrophy mostly happens in less active people, such as athletes who have stopped training, people who are sedentary, and astronauts who are under less gravitational load[13]. Recent attention has shifted towards a novel complication associated with diabetes muscle atrophy, which is characterized by a reduction in muscle mass, strength, and function. A cross-sectional study conducted on 6,381 adults aged over 50 years revealed that individuals with type 2 diabetes exhibited a prevalence of 28% for muscle atrophy, compared to only 16% in those without diabetes[14].

Protein synthesis in skeletal muscle is a dynamic process that plays a crucial role in muscle growth, repair, and maintenance. Skeletal muscle is an endocrine organ that synthesizes bioactive molecules like inflammatory cytokines, growth factors, adipokines, carnitine, and hydrogen sulfide (H_2S)[15]. The basic molecular mechanisms involved in skeletal muscle atrophy include the ubiquitin-proteasome system (UPS), autophagy, inflammation, the insulin- like growth factor 1 (IGF-1)/PI3K/Akt signaling pathway, and the myostatin pathway. UPS is believed to be responsible for the degradation of contractile proteins in skeletal muscle[16].

Molecular Mechanisms of Skeletal Muscle Atrophy:

In skeletal muscle, oxidative stress is one of the reasons for skeletal muscle atrophy by increasing ROS.ROS increases muscle protein degradation through the upregulating of MuRF- 1 and Atrogin-1 which are involved in the muscle degradation. Low oxidative stress prevents muscle atrophy and it's a promising target for preserving muscle mass and function[17].

In the immune, inflammation, and muscle wasting settings NFκB acts through induction of TNFα followed by activation of IKKβ resulting in IκB degradation and translocation to the nucleus. MuRF1 kinase-negative IKKβ overexpression and blockade of function prevents muscle loss due to denervation by inhibition of MK2. Hindlimb unloading atrophy is blunted in p105/p50 NFκB and iNOS knockout mice. TNFα suppresses IGF1-Akt activation promoting muscle wasting, whereas deletion of IKKβ in mice reduces atrophy despite hyperphosphorylation with; BRB (−) TNFα rescued myotube development features mediated by NFκB and Akt crosstalk. TNFα also increases myogenin, MuRF1 and atrogin-1 but this response is ameliorated by GβGi2 signaling. TWEAK ligand activates NFκB in denervated muscle and binds Fn14, leading to atrophy through a subsequent increase in MuRF1. TWEAK-deficient mice have increased resistance to neuronal degeneration-induced atrophic phenotypes and reduced expression of key genes including NFκB. However not all atrophy conditions induce high Fn14 expression, e. g after dexamethasone stimulation there is no significant increase in levels of this receptor. TRAF6 activation leads to fasting-induced expression of Fn14 and Phospho-FoxO3-mediated catabolic regulation by triggering both autophagy-lysosome pathways through AMPK activation. Overall, more intricate and context-dependent crosstalk between NFκB pathway with Akt and FoxO3 signaling pathways related to muscle atrophy- autophagy connection[18].

Intramuscular lipids affect the skeletal muscle and mitochondrial function which is involved in energy, and mitochondrial dynamics including biogenesis, and fission processes. mitochondrial dysfunction leads to ROS accumulation and myofibril, and motor neuron functions are changed. In the previous study, obese mice had an increase the mitochondrial function in skeletal muscle, which led to abnormal mitochondrial dynamics. mitochondrial biogenesis and mitochondrial DNA content is reduced and the result of fatty acid oxidation problems are caused by mitochondrial malfunction in skeletal muscles[19].

Skeletal muscle atrophy in T1DM for insulin deficiency:

In previous studies, muscle mass loss was measured through noninvasive methods for chronic diabetic patients, and muscle fiber size was reduced in new diabetic diagnostic patients before insulin treatment. recent time the diabetic diagnostic patient (T1DM range 1 to 28 weeks) was affected by fiber atrophy, for the disruption of Z-lines, mitochondria abnormalities, and without the morphological signs of neuropathy. The skeletal muscles are sensitive to T1DM related to the indication before the neuropathic complications lead to stress early diagnosis is important. In diabetic adult skeletal muscle fiber size loss, increased active percentage of glycolytic/fast-twitch muscle fibers and glycolytic enzymes are observed[20] as the important reason for this condition due to the Loss of insulin secretion and the autoimmune destruction of beta cells leads to loss of insulin production and secretion, resulting in impaired glucose homeostasis. Normal beta cells have a remarkable capacity to upregulate or downregulate insulin secretion in response to blood glucose levels. In T1D, this ability to tightly regulate insulin release is damaged early in pathogenesis due to beta cell stresses that disrupt secretory function. Pro-inflammatory cytokines like IL-1β, TNF-α, and IFN-γ secreted by infiltrating immune cells in islets are toxic to beta cells. They perturb cellular signaling pathways controlling glucose-stimulated insulin secretion. Beta cells initially compensate by increasing insulin output per cell and expanding beta cell mass. Eventually, the secretory

function cannot offset the degree of beta cell death, leading to insufficient basal and post-prandial insulin secretion. The resulting insulin deficiency prevents the regulation of hepatic glucose production and peripheral glucose uptake, causing hyperglycemia and classical diabetes symptoms[21].

Skeletal muscle atrophy in T2DM for insulin resistance:

Insulin resistance is an early sign of the development of T2DM and skeletal muscle atrophy. Skeletal muscle insulin resistance is linked to skeletal muscle atrophy and diabetic condition. In T2DM more than 90% of patients have a complication of unresponsiveness on skeletal muscle cells to insulin resistance[22]. The decreased sensitivity of target tissues, like skeletal muscle to insulin, is known as insulin resistance. Muscle insulin resistance is a critical abnormality that contributes significantly to metabolic dysfunction and manifests decades before β-cell loss. Normal β-cell in the insulin resistance condition increase the plasma insulin level. Prolonged physiologic increase in the plasma insulin concentration leads to the reduction of skeletal muscle insulin sensitivity. Increasing insulin concentration aggravates the underlying skeletal muscle insulin resistance[23]. Insulin resistance is linked to inflammatory indicators (other disorders connected). TNF α inhibits insulin receptor function and plays an important role in insulin resistance by downregulating GLUT-4. IL-6 either directly influences insulin sensitivity by blocking the insulin transcription factor or indirectly by increasing hepatic CRP production[24].

The biochemical mechanism involved in diabetic and skeletal muscle atrophy: Hormonal changes in diabetic skeletal muscle atrophy:

Some hormone concentrations and their metabolic roles are changed in diabetic conditions like T1DM. Cortisol, a hormone increases in the diabetic condition (compared to children high in adults with T1DM). cortisol is not high in resting young T1DM, but they do stressors like exercise which will increase the level[25]. Plasminogen activator inhibitor (PAI)-1 is a hormone that increases the level to inhibit skeletal muscle regeneration and leads to diabetic myopathy or skeletal muscle atrophy[20].

Role of Pro-Inflammatory Cytokines in Insulin Resistance in Skeletal Muscle

TNFα and IL-6 are two pro-inflammatory cytokines that are elevated in diabetes mellitus (T1DM and T2DM) and contribute to insulin resistance in skeletal muscle. TNFα binds to TNFR1 and TNFR2 both receptors are present in skeletal muscle. TNFα involves three pathways apoptosis, JNK/MAPK activation, and NF-κB activation[26]. In skeletal muscle TNFα decreases IKB levels, which activates NF-κB and JNK pathways, which inhibit IRS-1 and impair insulin signaling; still, TNFα blockade has not significantly improved glycemic control, indicating that its role is not independent; IL-6 has both pro-inflammatory and anti- inflammatory effects and increases in diabetic conditions activates the JAK/STAT3 pathway, which inhibits IRS-1 and reduces insulin-mediated absorption of glucose via SOCS3; some suggest that IL-6 to impaired insulin sensitivity, while others suggest it improves glucose uptake via AMPK stimulation; these discrepancies highlight the tissue-specific and secondary inflammatory effects of IL-6[20][26][27]. IL 15 also expressed in skeletal muscle acts as an anabolic factor, and induces hypertrophy of skeletal myotubes. IL 15 affects the TNFα signaling leading to reduced muscle fiber apoptosis and stimulating glucose transport[28].

Role of IGF-1/Akt Pathway in diabetic skeletal muscle atrophy:

In skeletal muscle, IGF1-Akt pathways are important to control protein synthesis and protein degradation[29]. the genetic activation of Insulin-like growth factor 1 (IGF-1) stimulates the anabolic signaling pathway, which in turn stimulates muscle hypertrophy by stimulating the PI3K/Akt pathway, regulating protein synthesis and degradation through the UPS and autophagy[16] and PDK1 activates the Akt/mTOR/S6K pathway to enhance protein synthesis, while also suppressing protein degradation by inhibiting FOXO1, a transcription factor that controls muscle-specific ubiquitin ligases, MuRF1, and Atrogin-1[30].

Role of glucocorticoids in diabetic skeletal muscle atrophy:

Amino acids are stored in skeletal muscle. In this muscle, the glucocorticoids (GC) have a catabolic activity because it's preventing the amino acid transported from muscle and blood increasing the level of free amino acid. Glucocorticoids are involved in fast-twitch (Type II) muscle fiber degeneration and insufficient action on slow-twitch fibers (Type I). GC receptors are higher in glycolytic muscles like the tibialis anterior than in oxidative muscles like the soleus. Glucocorticoids control the IF4E-binding protein 1 and ribosomal protein S6 kinase 1 (S6K1) phosphorylation these are important in protein synthesis, and it's activated through insulin, IGF-1, and amino acid[31].

Role of Inflammation-Mediated Muscle Atrophy in Diabetes:

In diabetes, the gastrocnemius muscle has a lower muscle-to-body mass ratio, tissue- specific NF-κB responses, decreased NF-κB

activation in diabetic RG but not in other muscles, and predominant p50 homodimers in all muscles[32]. Proinflammatory cytokines in muscle stimulate the NF-κB signaling pathway[11], increasing muscle atrophy by upregulating ubiquitin-proteasome proteins and inflammation-related molecules. This disrupts myogenic differentiation, resulting in muscle wasting and delayed regeneration[16]. Inflammation activates pro-inflammatory signaling pathways including NF-κB, disrupting protein synthesis and degradation, leading to muscle atrophy. Further contributing to muscle atrophy is NF-κB activation, which is mediated by the receptor activator of NF-κB (RANK). These mechanisms demonstrate the importance of inflammation in muscle breakdown and the development of muscle loss in diabetes conditions[14].

Role of AMPK in diabetic muscle atrophy:

AMPK (AMP-activated kinase) is a key intracellular energy sensor regulating metabolic homeostasis and it regulates energy balance, oxidative metabolism, and mitochondrial biogenesis by activating SIRT1(Sirtuin 1) to improve skeletal muscle function[33][34]. AMPK coordinates the both Anabolic and catabolic processes[35]. AMPK might be an important signaling step for glucose transport in response to exercise. Changes in the intracellular ratios of ATP to AMP, creatine phosphate to creatine, and intracellular pH all have an immediate effect on AMPK activation. AMPK activity surges in response to muscular contraction. AMPK modulates the processes of atrophy by altering the UPS [36].

Role of Advanced Glycation End Products (AGES) in diabetic skeletal muscle atrophy:

AGEs are toxic metabolites binding to receptors of AGEs (RAGE) to produce Reactive Oxygen Species (ROS)[37]. AGEs are involved in diabetic muscle wasting by increasing muscle breakdown and impairing muscle development both in vivo and in vitro. Tamura et al reported that AGE3 significantly raised MuRF-1 mRNA levels in myoblasts while decreasing MyoD mRNA levels. vitamin D had no effect on the amounts of MuRF-1 mRNA increased by AGE3 in myoblasts, it appeared to increase the levels of MyoD mRNA reduced by AGE3. Vitamin D may help with diabetic muscle wasting by improving myogenesis, which is inhibited by AGEs. In T1DM the children have less glycemic control leading to a decrease the aerobic muscle capacity and muscle area based on this T1DM and T2DM induce diabetic myopathy[38].

Role of the autophagy-lysosomal pathway in diabetic skeletal muscle atrophy:

Autophagy plays an important role in the degradation of protein, lipids, glycogens, and organelles in skeletal muscle, which decreases cellular abnormalities (mitochondrial damage and stress). In 2012, Lee et al. examined LC3, a key autophagosome molecule, and actin after 4 weeks of swimming exercise LC3 levels increased in diabetic (DM) rats but decreased exercise rat's actin levels remained unchanged. Diabetes enhances autophagy in lower limb muscles, and swimming exercise mitigates muscle atrophy by suppressing autophagy(36). FoxO3 is a vital regulator that activates autophagy and UPS pathways. Its activation increases muscle atrophy by regulating autophagy–lysosomal pathway markers like p62/SQSTM1, LC3- I, LC3-II, Apg12, Apg5, and Bnip3, which relate autophagy to muscle breakdown in diabetic conditions[16].In 2021 Choi et al reported that SFe administered to diabetic-induced mice reduced the level of LC3-I, LC3-II, and p62/SQSTM1, indicating autophagy reduction.LC3-I and LC3-II were lower in the STZ_SFe_250 group, but p62/SQSTM1 and LC3-II were lower in the STZ_SFe_500 group.Atg7, Beclin-1, and p-ULK1/ULK1 remained unaltered, indicating that SFe inhibits the autophagy-lysosomal pathway to prevent protein degradation[39].

Role of Mitochondrial Dynamics in diabetic skeletal muscle atrophy:

Skeletal muscles have two mitochondrial groups: subsarcolemmal (20%) under the myolemma and intermyofibrillar (80%) between myofibrils. Mitochondria control the metabolism, proliferation, and cell death[40]. Mitochondrial fusion (Mfn2, Opa1) and fission (Drp1, Fis1) play a crucial role in the pathogenesis of type 2 diabetes mellitus (T2DM), with Mfn2 and Opa1 downregulation in skeletal muscles leading to reduced mitochondrial mass and density, serving as an early indicator of metabolic disorders. Mfn2 dysfunction impairs substrate metabolism, while Mfn2 and Opa1 overexpression enhance mitochondrial respiration and glucose oxidation. This imbalance contributes to muscle atrophy through oxidative stress, as mitochondria play a dual role in energy generation and metabolic regulation. The study of diabetes emphasizes the link between cellular metabolism and disease progression, particularly the role of mitochondria in skeletal muscle atrophy. Mfn2-mediated mitochondrial fusion is essential for muscle health, and its downregulation in T2DM severely impacts function. Analyzing skeletal muscle samples from diabetic patients can provide deeper insights into these metabolic abnormalities. Additionally, exploring type 1 diabetes and the effects of high-fat diets on Mfn2 function can further elucidate mitochondrial dysfunction and its role in diabetes- associated muscle degeneration[41].In skeletal muscle, blocking autophagy reduces fat accumulation and protects against HFD-induced obesity and insulin resistance, according to muscle-specific Atg7 deletion research. Improved insulin sensitivity was connected to mitochondrial malfunction, which activated Fgf21 via Atf4 and the Unfolded Protein Response pathway, hence increasing glucose tolerance and insulin sensitivity[29].

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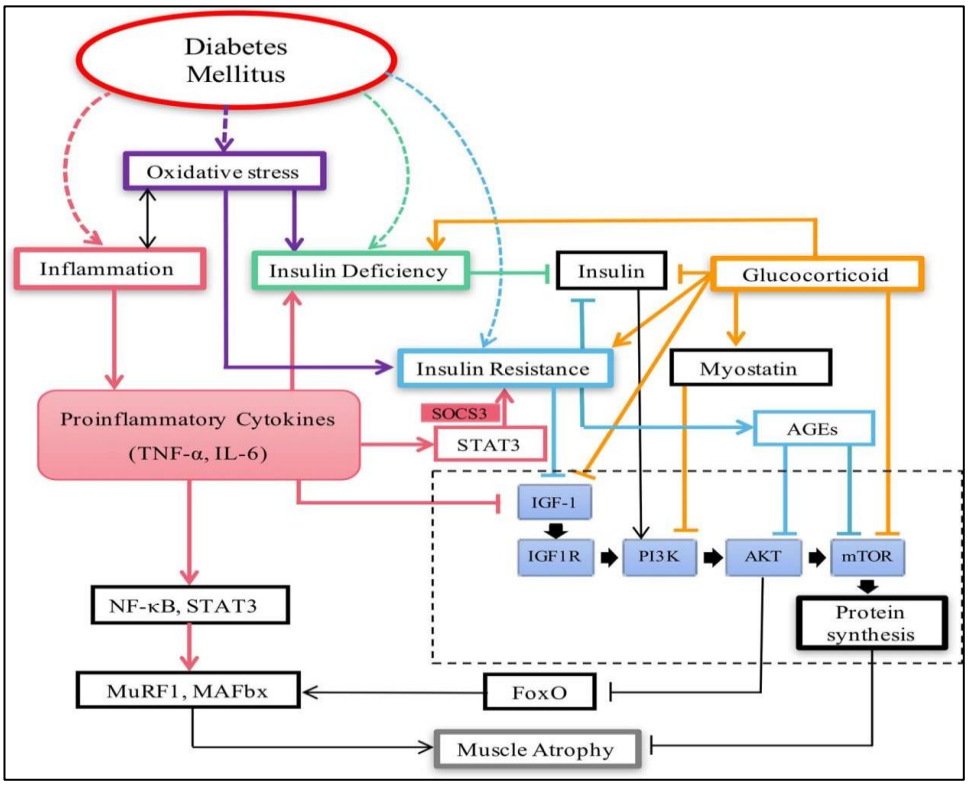

Figure 1: The signaling pathways of the diabetic skeletal muscle atrophy

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Role of KLF15 in diabetes-induced skeletal muscle atrophy and its regulation via the WWP1 pathway:

KLF15 belongs to the KLF transcription factor family, which controls carbohydrate, lipid, and protein metabolism and stimulates MuRF1 and atrogin-1 gene transcription using glucocorticoid receptor crosstalk. Hyperglycemia increases KLF15 in diabetic mouse models, and it directly impacts skeletal muscle by decreasing muscle mass. This is controlled by WW domain-containing E3 ubiquitin protein ligase 1 (WWP1), which is implicated in neural, infectious, and tumorigenic diseases as well as diabetic-induced pathological processes. Diabetes stimulates the WWP1/KLF15 pathway, which leads to skeletal muscle atrophy. WWP1 downregulation increases KLF15 levels, which aids in muscle atrophy. This pathway potential therapeutic strategy for preventing diabetes-induced muscle atrophy[42] or cAMP- PKA/CREB signaling[39].

Role of ROS-Dependent ER Stress in diabetics skeletal muscle atrophy:

Reactive oxygen species (ROS) cause endoplasmic reticulum (ER) stress, which activates the PERK pathway via self-phosphorylation. and increases nuclear activity, leading to the phosphorylation of FOXO1. FOXO1 promotes the expression of muscular atrophy F- box (MAFbx), which causes skeletal muscle atrophy. AGEs-RAGE binding produces ROS, which causes ER stress in type 2 diabetes mellitus (T2DM), which leads to insulin resistance (IR) and promotes muscle atrophy to evaluate this both in T2DM mouse model exposed to AGEs, where FOXO1 was silenced using siRNA. FOXO1 might be a possible therapeutic molecular target for IR in diabetes[37].

Role of FoxO Transcription Factors in Diabetic Muscle Atrophy and Metabolism:

The role of FoxO transcription factors in muscle atrophy and metabolism FoxO transcription factors control metabolism, stress reactions, and muscle atrophy, and their activity is inhibited by Akt signaling in response to insulin or IGF-1 stimulation. FoxOs are essential for insulin signaling in the liver, and their transcriptional activity is inhibited by phosphorylation. Insulin receptor (IR) knockout mice exhibit reverse gene expression alterations when FoxO1 is deleted in the liver. FoxOs control autophagy genes and atrophy- related genes such as Trim63 (MuRF1) and Fbxo32 (Atrogin1) in muscles. By deleting them, hunger and denervation-induced muscle atrophy is avoided. Further demonstrating their function in muscle protein breakdown and proteostasis, removing FoxO1, FoxO3, and FoxO4 in muscle prevents severe atrophy brought on by muscle-specific deletion of IR and IGF1R(Insulin-Like

Growth Factor 1 Receptor)[43].

Role of Ubiquitin-proteasome system in diabetic muscle atrophy:

Insulin production is low leading to increased muscle proteolysis through the ubiquitin-proteasome system. The ubiquitin-proteasome system degrades proteins, organelles, and cytoplasm, causing myofiber shrinkage (Muscle atrophy) due to net protein loss through ubiquitination, which is controlled by E3 ligases that facilitate ubiquitin transfer from E2 enzymes. This rate-limiting step determines proteasomal degradation. In muscle atrophy, E3 ligases such as Atrogin-1 and MuRF1 are increased and improve protein degradation unless de-ubiquitinating enzymes remove ubiquitin chains[29].In diabetic muscle, vitamin D deficiency promotes protein breakdown through the ubiquitin-proteasome pathway. Tamura et al reported diabetic mice, vitamin D deficiency increases Atrogin-1 and MuRF-1 mRNA levels, causing muscle atrophy. Vitamin D may protect against muscle loss by blocking degradation and improving early muscle differentiation, pointing to its potential significance in diabetic muscle health maintenance[38].

Role of myokines and osteokines in diabetic skeletal muscle atrophy:

Myokines and osteokines are important signaling molecules that regulate physiological processes muscle metabolism, bone health, inflammation, and energy homeostasis. It's released from muscle and bone cells. In diabetic conditions, Myokines and osteokines are involved in muscle and bone metabolism. Myokines a peptides or proteins released by skeletal muscle cells and their main function is muscle contraction or stress and act as signaling molecules to communicate with other tissues like adipose tissue, liver, and bone. osteokines are signaling molecules released by bone cells (osteoblasts and osteocytes). They are regulating bone remodeling and metabolic processes. Myokines and osteokines contribute to muscle atrophy. Myokines (myostatin and interleukin-6) initiate muscle degradation and inflammation, and irisin levels reduce muscle regeneration. Osteokines (osteocalcin) act in insulin sensitivity. The action of both myokines and osteokines in diabetic conditions (T1DM and T2DM) in the muscle-bone crosstalk will be reduced. It leads to increased muscle protein breakdown and decreased muscle mass resulting in muscle atrophy in diabetic patients. In diabetic BMP-7 increases muscle loss.FGF-21 maintains the metabolic balance of a diabetic state it leads to muscle waste due to affected energy metabolism[44][45].

Hydrogen sulfide (H_2S) in diabetic induced skeletal muscle atrophy:

H_2S is one of the important inter and intracellular signaling molecules like NO and CO that impact metabolic, inflammatory, and neurovascular processes.H_2S synthesis from L- cysteine or L-methionine by three main enzymatic contributors are CSE (cystathionine γ- lyase), CBS (cystathionine β-synthase) both are located in the cytoplasm, and 3-MST (3- mercapto pyruvate sulfurtransferase), which is located in the mitochondria expressed in human and rat skeletal muscles[15].In rat gastrocnemius muscle, the production of H_2S is 40% higher than that of the liver and 19% higher than that of the kidney. Compared to the kidney and liver, the levels of CBS and CSE are lower. 3-MST mRNA expression levels are comparable to the liver and two times higher than the kidney[46].In the diabetic rat model, the H_2S level was significantly lower compared to the control rats indicating the diabetic condition. Chronic administration of garlic to improve the H_2S level in diabetic rats[47]. Based on this study in 2018 Bitar et al reported that diabetic-induced rats confirm the endogenous H_2S deficiency which leads to muscle atrophy in diabetic rat models. NaHS is administered for one month daily to diabetic animal models it improves H_2S bioavailability, muscle mass, protein content, and grip strength in skeletal muscle. Also, increase insulin sensitivity and β-cell function in the pancreas[15].In 2020 Lu et al reported that the H_2S level was low in db/db mice the exogenous H_2S decreased skeletal muscle atrophy through the reduction of ROS production and ubiquitination level of MYOM1 and MYH4. Increased the S-sulfhydration of MuRF1. Mutating MuRF1 at Cys44 lowered its S-sulfhydration, inhibiting its interaction with MYOM1 and MYH4 to reduce skeletal muscle loss in diabetic conditions[48].

Impact of intramyocellular lipid accumulation on diabetic skeletal muscle atrophy:

Intramyocellular lipid droplets (IMCLs) are a dynamic organelle in skeletal muscle that assists in the metabolism of lipids, vesicle trafficking, and cell signaling. Insulin resistance causes excess fat to be released into the bloodstream from adipose tissue, and the liver leading to fat deposition in skeletal muscle. The accumulation of harmful lipid intermediates like ceramides and diacylglycerols (DAGs) activates the protein kinase C (PKC) and is involved in deteriorating muscle quality and reducing muscle mass. Palmitate-induced ceramide accumulation upregulated IF2α phospopulation and pro-atrophic genes (atrogin-1/MAFbx, FoxO3) and decreased protein synthesis in different cell lines. ceremide synthesis blockage prevents muscle atrophy, improves mTOR signaling, and reduces FoxO3 and atrogin-1/MAFbx expression. The high level of ceramide and DAG leads to reduced insulin response and mTOR signaling. Conversion of DAG to phosphatidic acid (PA) activated the mTOR signaling pathway and reported hypertrophy and Lipid intermediates are linked to insulin resistance and muscle atrophy for T2DM[49][50].

Role of NLRP3 in diabetic skeletal muscle atrophy:

Nucleotide-binding and oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) is a crucial inflammasome associated with metabolic disorders such as type 2 diabetes and inflammatory reactions. It has a role in the development and effects of diabetes; in diet-induced diabetes, knockout mice show better insulin sensitivity and glucose tolerance. In diabetic cardiovascular and endothelial cells, NLRP3-mediated pyroptosis stimulates the release of pro-inflammatory substances, whereas reducing it decreases inflammatory atrophy and increases muscular strength. NLRP3 significantly modulates the metabolism of skeletal muscle. NLRP3 inhibitor, in the diabetic skeletal muscle atrophy condition, improves glucose absorption, and muscular function, and decreases muscle atrophy. This study reveals that NLRP3 inhibitors are used in the treatment of muscle atrophy and diabetic muscular atrophy[51].

Diagnostic of diabetic skeletal muscle atrophy:

There are no specific diagnostic methods to detect diabetic skeletal muscle atrophy but some methods are bioelectrical impedance analysis, Screening for grip strength and gait speed, and measuring SMI by dual-energy x-ray absorptiometry, a-SMI is binary logistic regression analysis. its new diagnostic approved by AWGS 2019(52). and computed tomography are currently adopted to assess muscle mass. However, these methods have limitations including a low sensitivity for early detection of muscle atrophy, the risks of radiation exposure, and high cost[17]. Muscle oxygen saturation (SmO2) was measured in deep tissue by using dual-wavelength NIRS with a light emitter and two sensors placed over the medial head of the right gastrocnemius muscle.SmO2 was determined at the wavelengths of 733 nm and 809 nm, which estimated deoxygenated and the sum of deoxygenated and oxygenated hemoglobin. The maximal isokinetic strength (peak torque) of the flexors and extensors at the knee and ankle was determined by using an isokinetic dynamometer, and patient peak torques were compared with healthy reference participants. MRI is an important method to diagnose muscle activity and structure 1 week before taking iso-kinetic testing. The images are analyzed with the help of a custom-built software toolbox. Image segmentation was performed by using ITK-SNAP based on Dixon water images[53].

BIOMARKERS FOR DIABETIC SKELETAL MUSCLE ATROPHY:

Pentadecanoic acid, 5'-MTA, ADMA, glutamine, and Isoxanthohumol were identified as potential biomarkers for diabetic sarcopenia (muscle atrophy). The concentrations of alkanoic acid, 5'-MTA, ADMA, and glutamine were significantly increased and Isoxanthohumol was significantly decreased in the diabetic sarcopenia[54].

Titin is a large elastic protein (molecular spring) in muscle and degradation by calpains and MMPs during muscle injury or atrophy. serum titin is used to diagnose myocardial injury and skeletal muscle atrophy. Urinary titin is used to diagnose elevated muscular dystrophy and ICU muscle atrophy. It's used as a biomarker for early muscle atrophy detection[55].

TREATMENTS AND THERAPEUTIC DRUGS:

Non-Pharmacological Approaches:

Diabetic patients benefit from exercise because it protects against oxidative stress. It improves muscle function and lessens problems from diabetes by upregulating insulin-like growth factors and heat shock proteins, which have anti-inflammatory, anti-oxidative, and anti- atrophic properties. Chen et a reported in diabetic rats the body weight, and muscle mass are decreased, and increase the concentration of blood glucose levels, Exercise training significantly increased the body weight, serum glucose concentration, muscle weight, muscle fiber size, decreased TBARS levels, and increased SOD activity. STZ induced diabetic the level of citrate synthase activity in the gastrocnemius is low after the exercise training the citrate synthase activity and MuRF1 expression in a diabetic rat is significantly increased after exercise training reduced MuRF1 expression in mRNA level and the protein level[56]. Yan et al. reported That exercise training (Treadmill training) in diabetic rats increased the BGL, body weight, HbA1c, and gastrocnemius skeletal muscle weight. The number of myonuclei, GAP- 43, and KIF5B protein levels in the rat gastrocnemius skeletal muscle fibers decreases in diabetic conditions[57]. This report shows exercise training improves skeletal muscle atrophy in diabetic condition.

Pharmacological therapy:

There is no specific drug or therapy for treating skeletal muscle and diabetic induced skeletal muscle atrophy. The possible therapeutic are:

1. drug therapy (Chemical drugs, Active substances of traditional Chinese Medicine, Antioxidants, Hormone drugs, Hormone drugs)

2. Nutrition Support (Protein, Essential amino acid, ß-hydroxy-ß-methyl butyrate, Creatine, Vitamin D)

3. Physical therapy (Electrical Stimulation and Optogenetic Technology, Electroacupuncture, Low-level Laser Therapy, Heat Therapy)

4. Gene Therapy (Gene medicine, Gene Overexpression, and Knockdown Non-coding RNAs)[58] but this is how effective skeletal muscle atrophy in the diabetic condition is not clear taking only an anti-diabetic drug does not give muscle recovery properly so in recent times many research ongoing in diabetic skeletal muscle atrophy using already available drugs in different disease conditions and traditional medicine like a plant substance or extraction.

T2DM animal model used for diabetic skeletal muscle atrophy:

SUBSTANCE	TEST ANIMAL	TEST DRUG DOSE	DIABETIC INDUCED	MECHANISM	REFERENCE
Centella asiatica	Sprague-Dawley rats (150–180 g)	(500 and 1000 mg/kg)	Feed 10% fructose solution and single intraperitoneal (ip) injection of low- dose streptozotocin (STZ) at 40 mg/kg	Reduced blood glucose level Elevated skeletal muscle glycogen content. Increase the level of PFK (7-fold), FBPase (23%), GS (27%), GP (50%).	(59)
Salbutamol	Sprague Dawley rats (aged 8–10 weeks and	6 mg/kg/da y for 4 weeks)	High-fat diet ad libitum for two weeks and injected as a single low dose	Increased grip strength and lean muscle mass. increased levels of antioxidants. Reduced inflammatory markers.	(3)
	weighing 200 ± 30 g)		of 35 mg/kg of streptozotocin (STZ) intraperitoneally (i.p.)	Increased pro-inflammatory cytokines and muscle markers (myostatin, creatine kinase)	
Fucoidan	Sprague-Dawley rats (4 weeks, 80 ± 20 g)	50, 100, and 200 mg/kg/da y	HFD and injection of low- dose STZ 35 mg/kg	Promote muscle protein synthesis, suppress muscle protein degradation, and improve glucose metabolism through the regulation of PI3K/ Akt signaling pathway	(60)
Magnoflorine and *T. cordifolia*	Wister rats (6 weeks old, weight- 180-220 gm)	. cordifoli a (TC) (250 mg/kg/day) and magnofl orine (2 mg/kg/day) for three weeks.	treated with an intraperitoneal injection of nicotinamide (110 mg/kg b.w.) (Mojani et al., 2014) followed by STZ (70 mg/kg b.w.)	Reduced the degradation of the protein (decreased (CK) levels, increased MyHC-β levels. Decreased the expression of ubiquitin-proteasomal E3-ligases (Fn-14/TWEAK, MuRF1, and Atrogin1), autophagy (Bcl-2/LC3B), and caspase related genes, increased expression of TNF-α and IL-6, Increased the activity of superoxide dismutase, GSH-Px, decreased the activities of β-glucuronidase, LPO	(61)
extracted a proteoglycan from *Ganoderma lucidum*	Sprague Dawley Rats and db/db mice	-	HFD was given a single injection of STZ 40 mg/kg	Reduction of the cross-sectional area of muscle fibers and overexpression of muscle atrophic factors	(34)

MCC950(C20 H24N2O5S)	C57BLKS/J Gpt db/db	(10 mg kg−1)	-	Combined MCC950	

inhibitory effect on the NLRP3	mice (six weeks of age)			treatment with exercise exhibits glucose uptake capacity, muscle performance. Reduced NLRP3- mediated inflammatory factors (cleaved-Caspase-1, GSDMD-N) and prevented apoptosis and pyroptosis in atrophic GAS.	
bavachin and corylifol A from *Psoralea corylifolia L.* seeds	C57BLKS/J -db/db mice (Twelve week old)	10 mg/kg/day for 40 days,	-	enhanced muscle strength, and suppressed inflammatory cytokine(IL-6 and TNF-α)by downregulating nuclear factor-κB phosphorylation. Decreased the muscle atrophic factor (myostatin, atrogin-1, and muscle RING finger-1). Activated the AKT synthetic signaling pathway.y increased mitochondrial biogenesis and dynamic factor (optic atrophy-1, mitofusin-1/2, fission, mitochondrial 1, and dynamin 1- like).o improved mitochondrial quality by upregulating the mitophagy factor (p62, parkin, PTEN-induced kinase-1, and BCL2-interacting protein-3) expression levels	(62)
semaglutide	male diabetic KK-Ay mice aged	subcutan eous injection of semaglut	-	Protected hepatic injury through increased production of IGF-1 and reduced accumulation of ROS. Decreased proinflammatory cytokines leading to suppression	(63)

	10 weeks old	ide (3 nmol/kg)		of ubiquitin-proteosome muscle degradation. Inhibiting the amino acid starvation-related stress signaling. stimulating GLP-1R in myocytes. Induced cAMP-mediated activation of PKA and AKT. enhanced mitochondrial biogenesis. inhibition of NF-κB/myostatin-mediated ubiquitin-proteosome.	

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T1DM animal model used for diabetic skeletal muscle atrophy:

SUBSTANCE	TEST ANIMAL	TEST DRUG DOSE	DIABETIC INDUCED	MECHANISM	REFERENCE
CURCUMIN, The active ingredient of turmeric	C57BL/6 J mice (8–10 weeks of age)	150, 450, and 1500 mg /kg/ day	I.P. injection of STZ 200 mg (kg bodyweight)−1	Decrease Ubiquitination of protein and muscle-specific ubiquitin E3 ligase atrogin-1/MAFbx and MuRF1. Decrease the NF-κB, TNF-α and IL-1βactivation.	(64)
Schisandrae chinensis Fructus	C57BL/6 mice	250 mg/kg and 500 mg/kg	STZ was intraperitoneally injected at a dose of 150 mg/kg	Decreased the expression of atrophic factors (MuRF1 and atrogin-1). No alter the expression of muscle synthetic factors. Downregulation of the CREB-KLF15-mediated UPS system and the p62/SQSTM1-mediated autophagy–lysosomal pathway. No changes in Atg7, Beclin-1, or ULK-1	(39)
Puerarin	Sprague-Dawley (SD) rats (160−190 g)	100 mg/kg/da y puerarin for 8 weeks	STZ was intraperitoneally injected at a dose of 65 mg/kg	Down-regulation of Atrogin-1 and Murf-1 and the up regulation of MyHC. Increased the muscle fiber area of fast-twitch glycolytic type IIB fibers but reduced the area of slow oxidative type I fibers. up regulated phosphorylation of ULK1, p62 expression. downstream targets p70S6K and 4EBP1.promoted Akt/mTOR while inhibited LC3/p62 signaling pathway.	(65)
Gallic acid	C57BL/6 mice (male, 20 ± 2 g)	20 mg/kg/da y	STZ was intraperitoneally injected at a dose of 200 mg/	Enhancing fibre size and grip strength. FBXO-32 and TRIM-63 expressions is decreased. Improve mitochondria function (enhanced NRF-1 and PGC-1α expressions). Increased BAX and decreased BCL-2 expressions to suppress apoptosis.	(66)

Sinapic acid	ICR mice (8 weeks old, 20±2 g)	40 mg/kg/da y for 8 weeks	STZ was intraperitoneally injected at a dose of 200 mg/kg	Enhanced grip strength, modulation of mitochondrial function (NRF-1, PGC-1α), moderation of ER stress (CHOP, GRP-87), and suppression of apoptosis (inhibit BAX promotes BCL-2)	(67)
Cumin Chitosan nanoparticles	rats	200 µL of CE and 200 µL of CECNs	STZ was injected intraperitoneally with 65 mg/kg body weight.	Increased grip strength, reduction of damage to the pancreas, reduced the inflammatory response (interleukin (IL)-6 and IL-1β).	(68)
Resveratrol	C57BL/6mi ce (male), 6 to 7 weeks old	100 mg/kg/da y for 8- weeks	Intraperitoneal injection of STZ 200 mg/ kg body weight	Improves Muscle Function. Inhibits the Ubiquitin–Proteasome System((MAFbx)/atrogin-1 and MuRF-1), Autophagy, and Apoptosis increase in mitochondrial biogenesis, inhibition of the activation of mitophagy, Inhibits Mitochondrial Fission and Fusion.	(69)
Ellagic Acid	Male ICR mice (20±2 g)	(100 mg/kg/da y for 8 weeks	Intraperitoneal STZ	Reduced CK and LDH levels, reduced muscle-specific E3 ubiquitin ligases, enhance NRF-1 and PGC-1α expressions, regulation of ER stress (reduces CHOP and GRP-78 expressions), apoptosis (inhibit BAX promotes BCL-2)	(70)
Niclosamide ethanolamine	Male C57BL/6J mice	10 g/kg NEN for 8 weeks	STZ intra- peritoneal	Enhance the grip strength, increase	(71)
			injection 55 mg/kg body weight for 5 consecutive days.	the numbers of type II fibers in SOL muscle. Increase the serum insulin level, reduce the overexpression of autophagy proteins (p-AMPK (Thr172), FoxO3a, p-ULK1 (Ser555), LC3B II, and p- p38)	
Juzentaihoto	ICR mice (8 weeks old, male)	JTT was mixed with normal feed at a rate of 4% (w/w).	STZ was intraperitoneally injected at a dose of 150 mg/kg	Decrease Serum TNF-α levels and increase IL-10 levels. Decrease Ubiquitin Ligase mRNA Expression (MuRF1 and Atrogin1 levels).	(72)
Nicotinamide	12-week- old male C57BL/6J mice	400 mg/kg/da y for four weeks	streptozotocin (STZ) (50 mg/kg, i.p.) injection on five consecutive days	NAM does not show a significant impact of BW or BG. Restored grip strength. down-regulated MuRF1 and Atrogin1. TGF-b1 was not significantly influenced, with no effect on Smad2 expression. smad2 phosphorylation significantly repressed. de- activation of TGF-b/Smad2 signaling	(73)

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CONCLUSION:

Diabetic mellitus in a chronic stage leads to complications in the skeletal muscle and is called diabetic skeletal muscle atrophy. Skeletal muscle is one of the important organs for energy metabolism, and movement of the body parts. In this review the chronic diabetic patients, skeletal muscles are affected by various muscle mass-controlling like cortisol and plasminogen affect the skeletal muscle in diabetic conditions. IGF-1/Akt pathways control protein synthesis and protein degradation in diabetics it affects the skeletal muscle mass and strength. Pro-inflammatory cytokines TNF-alpha, IL-6, and IL-15 are elevated in diabetic conditions and contribute to insulin resistance in skeletal muscle. AGES bind to the RAGE to produce the ROS and lead to endothelial reticulum stress which activates the PERK pathway causing diabetic skeletal muscle atrophy. Glucocorticoids to induce skeletal muscle atrophy. Mitochondrial dynamics the mitochondrial fusion (Mfn2, Opa1) and fission (Drp1, Fis1) this imbalance is contributing the muscle atrophy in diabetic conditions. H_2S, NLRP3, and IMCLs are also reasons for diabetic skeletal muscle atrophy. This review to understand the diabetic skeletal muscle atrophy-related molecular level mechanisms, and to identify the specific site to treat diabetic muscle atrophy in the future perspective to reduce the skeletal muscle atrophy condition.

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