The role of AGEs in muscle ageing and sarcopenia

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Sarcopenia is an ageing-related disease featured by the loss of skeletal muscle quality and function. Advanced glycation end-products (AGEs) are a complex set of modified proteins or lipids by non-enzymatic glycosylation and oxidation. The formation of AGEs is irreversible, and they accumulate in tissues with increasing age. Currently, AGEs, as a biomarker of ageing, are viewed as a risk factor for sarcopenia. AGE accumulation could cause harmful effects in the human body such as elevated inflammation levels, enhanced oxidative stress, and targeted glycosylation of proteins inside and outside the cells. Several studies have illustrated the pathogenic role of AGEs in sarcopenia, which includes promoting skeletal muscle atrophy, impairing muscle regeneration, disrupting the normal structure of skeletal muscle extracellular matrix, and contributing to neuromuscular junction lesion and vascular disorders. This article reviews studies focused on the pathogenic role of AGEs in sarcopenia and the potential mechanisms of the detrimental effects, aiming to provide new insights into the pathogenesis of sarcopenia and develop novel methods for the prevention and therapy of sarcopenia.

Article focus

- The pathogenic role of advanced glycation end-products (AGEs) in sarcopenia and the potential mechanisms of the detrimental effects.
- A comprehensive review was conducted on the signalling pathways and molecular mechanisms through which AGEs contribute to sarcopenia development.

Key messages

- By binding with receptor for advanced glycation end products (RAGEs), AGEs can activate a series of intracellular signalling pathways in skeletal muscle cells related to the elevated levels of inflammation and oxidative stress, as well as impaired insulin/insulin-like growth factor-1 (IGF-1) signalling and mitochondrial biogenesis, which lead to reduced protein synthesis, increased protein degradation, intracellular lipid accumulation, changes in fibre type composition and muscle energy metabolism, and a higher rate of apoptosis, finally resulting in muscle atrophy and impaired regeneration abilities.
- Through directly targeted glycosylation, AGEs can damage the biological properties and functions of proteins which include the functional and structural proteins of skeletal muscle as well as collagens in ECM, resulting in muscle dysfunction such as impaired force production and increased stiffness. Furthermore, AGEs can also indirectly affect skeletal muscle by contributing to neuromuscular junction lesion and vascular disorders.

Bone & Joint Research

Strengths and limitations

- This article explores the promoting effect of AGEs on the occurrence and development of sarcopenia, which provides new insights into the pathogenesis of sarcopenia and develops potential methods for the prevention and therapy of sarcopenia.
- This article mainly reviews the basic research experiments, but there is a lack of discussion about clinical studies.

Introduction

Muscle ageing and sarcopenia

Skeletal muscle is one of the most vital organs in our body, accounting for approximately 40% of total body weight and containing 50% to 75% of total body proteins in humans. It plays a substantial role in maintaining our daily activities such as digestion, respiration, exercising, body posture maintenance, and joint and bone protection, among many other things.[1] Functioning as an important metabolic organ, skeletal muscle also contributes to the body's balance of sugar and fat metabolism,[2] as it makes up 80% of body glucose clearance.[3] Ageing muscle accompanies progressive muscle dysfunction such as muscle weakness and stiffness, presenting as low grip, slow movement, and decreased flexibility. Sarcopenia, namely the decline in muscle quality and function,[4] represents the most remarkable and visual of all changes during the ageing process. Since 2016, it has been recognized as a disease, code ICD-10-CM (M62.84), by the World Health Organization (WHO)'s International Statistical Classification of Diseases and Related Health Problems (ICD).[5] It refers to an asymptotic and systematic skeletal muscle disorder in the form of accelerated loss of muscle quality and function, which is linked to increased poor outcomes such as falls, fractures, frailty, cognitive decline, or even cardiovascular disease, leading to high hospitalization rates, elevated healthcare costs, and mortality.[6] Muscle mass and strength (parallel to bone density) peak in early adulthood, and after a plateau begin to gradually decline; strength declines more rapidly, especially over the age of 75 years.[7] With changing demographics and an ageing population, sarcopenia has gradually become a serious public health problem.[6] In order to propose more effective measures to improve the treatment and prognosis of this disease, many studies focus on illustrating the pathophysiological process of sarcopenia, aiming to develop novel diagnostic biomarkers, nutrition interventions, and drugs which enhance the beneficial effects of exercise.[6]

AGEs and sarcopenia

Sarcopenia causes a decline in both the size and number of skeletal muscle fibres, and the main histological findings are the type 2 or fast-twitch muscle fibres decreasing, and a change in the skeletal muscle extracellular matrix (ECM) such as the substantial infiltration of fibrous and adipose tissue.[8,9] Specifically, the weakened ability for aged muscle to regenerate, repair, and remodel is a key aspect of sarcopenia.[10] Ageing disturbs the homoeostasis of skeletal muscle, and multiple factors such as unbalanced protein metabolism, inflammation, oxidative stress, apoptosis, neuromuscular junction (NMJ) changes or motor neuron loss, satellite cell dysfunction, mitochondrial dysfunction, and microvascular changes can lead to sarcopenia.[6]

Advanced glycation end-products (AGEs), which originate from 'glycation' – a type of post-translational modification that usually occurs non-enzymatically and refers to a chemical reaction in which sugar binds to proteins, lipids, or nucleic acids – accumulate in various tissues in bodies with age and feature in the development of many chronic diseases such as obesity, diabetes, cardiovascular diseases (CVDs), osteoporosis, cognitive impairments, and cancer.[11] Many different types of AGEs exist in the human body, and over 20 different AGEs have been identified to date. These can be divided into fluorescent cross-linked AGEs, non-fluorescent cross-linked AGEs, and non-cross-linked AGEs. They have similarities in their biological efficacy, but there are also some slight differences. Currently, the most extensively studied AGEs are carboxymethyllysine (CML), pyrroline (both non-cross-linked), and pentosidine (fluorescent cross-linked).[11-13] In a cross-sectional analysis from 2,744 participants of northern European background whose mean age was 74.1 years, the authors found that higher skin AGEs were associated with a higher prevalence of sarcopenia.[14] Additionally, according to several studies, elevated serum AGE levels have been reported to be associated with adverse sarcopenia-related outcomes, such as poor grip strength, slow walking speed, and increased muscle weakness.[15-18] Research has shown that AGE accumulation could occur around the muscle fibres, within the cells, or in the muscle fibres of extensor digitorum longus in aged rats.[19] Although there is a lack of prospective studies to prove the causal relationship between AGEs and sarcopenia, the production and accumulation of AGEs in vivo is still recognized as a risk factor for the ageing-related loss of muscle mass and function, namely sarcopenia. AGEs are considered to cause or accelerate the pathological changes of sarcopenia based on partial current research,[20] and the mechanisms by which AGEs lead to sarcopenia are associated with the glycation-related cross-linking of intramuscular connective tissue and the raised levels of inflammation and oxidative stress in muscle caused by binding of AGEs to receptor for advanced glycation end products (RAGEs), followed by activating a string of intracellular signal transduction pathways.[21,22] The formation of AGEs is irreversible, and it is difficult for AGEs to decompose and metabolize in vivo. Currently, it is believed that the non-enzymatically regulated AGE cross-linking in collagenous tissues and the sustained activation of intracellular signalling pathways induced by the AGEs may be important reasons for the progressive development of sarcopenia.[11,21,23] This article mainly reviews the role of AGEs in the pathophysiological process of muscle ageing and sarcopenia, and aims to propose new insights into the pathogenesis and treatment methods of sarcopenia.

Formation and metabolism of AGEs

There are two sources of AGEs: endogenous and exogenous. Endogenous AGEs are a heterogeneous class of compounds derived from a series of glycosylation reactions. Maillard reaction is a non-enzymatic, multistep reaction, and occurs between the carbonyl group of a reducing sugar and the amino or N-terminal group of a protein or nucleic acid, such as adenine or guanine.[24] In the early stage of Maillard reaction, the condensation of the electrophilic carbon group of the reducing sugar with a free amino group (usually lysine or arginine) forms an unstable compound Schiff base, which is

chemically unstable due to its rapid and reversible production.[25] Over the course of several weeks, the Schiff bases may slowly rearrange to form the more stable ketoamine (Amadori products).[25] Resulting from subsequent oxidation, dehydration, or polymerization reactions, Amadori products eventually produce very stable AGEs, and during the process reactive oxygen species (ROS) are also produced.[25] In addition to the Maillard reaction, the formation of AGEs under physiological conditions can occur through the reactive carbonyl pathway, which derives from glucose autoxidation, glycolysis intermediates, and lipid peroxidation (Figure 1).[26] AGEs continually form covalent bonds with free amino groups on adjacent proteins to produce AGE cross-linking, resulting in the reticulation of proteins and their cross-linking, which usually happens in the ECM and increases rigidity of tissues.[27,28] AGEs usually generate slowly and constantly in intracellular and extracellular environments, unless the organism in a state of ageing, inflammation, hyperglycaemia, or oxidative stress, when the rate of AGE accumulation is significantly accelerated.[28] In addition, AGEs can be formed exogenously, as a result of environmental factors such as diet and smoking. Direct intake of diets rich in AGEs substantially contribute to the AGEs in blood circulation. The formation of AGEs in food generally depends on several factors such as temperature, water content, pH status, cooking time, and method. Foods processed or chronically cooked or stored at high temperatures or pH, as well as fried or grilled foods, are all thought to contain plenty of AGEs.[24] It should be noted that apart from dietary AGEs, cigarette smoke has been reported to contain a certain amount of reactive glycation products, which pose a risk of increasing the accumulation of AGEs in the tissues and circulating blood of smokers.[29] The amounts of exogenous AGEs, which are thought to be closely related to the metabolism of AGEs in vivo,[30] are usually much higher than those of endogenous AGEs. Therefore, ingestion of food high in exogenous AGEs may cause more health problems than endogenous AGEs. Both types have similar biological functions, and thus can act analogously to stimulate inflammation, oxidative stress, and other cellular disturbance, leading to deleterious pathophysiological phenomena.[24]

The kidney and small intestine are the essential organs for metabolizing AGEs. Most orally administered dietary AGEs have two ways of leaving the body after they are directed to the gastrointestinal tract. Absorbable AGEs enter the bloodstream and their remains (about one-third of AGEs) are excreted through urine, while non-absorbable compounds enter the lower intestine where they are partially digested by gut microbiota and the remains are discharged from the body with faeces.[31] The mechanism of the clearance of AGEs remains unclear, whereas available data suggest that AGEs, especially endogenously formed AGEs, are probably metabolized by either inborn defence or intracellular degradation after receptor-dependent uptake.[31] The residual AGEs can cause many pathological changes in the body, including disrupting glucose metabolism homeostasis,[32] exacerbating inflammatory response,[33] aggravating endothelial damage,[34] and escalating oxidative stress injury.[33]

AGE-RAGE axis

Accumulating intracellularly and extracellularly in tissues and body fluids, AGEs can cross-link with certain macromolecules (such as proteins, nucleic acids, and lipids), thus the AGE-modified macromolecules undergo structural and functional alterations that do direct harm to their normal biochemical performance.[35] Besides the direct impact of AGEs on the ECM and proteins, AGEs regulate organismal pathophysiological functions principally through the AGE-RAGE axis pathway. RAGE exists on the cell surfaces of many tissues including heart, lung, and skeletal muscle.[36] Bound to AGEs to form the AGE-RAGE axis, RAGEs can activate intracellular signalling pathways and initiate a string of intracellular reactions. RAGEs are typically upregulated in muscles which are rich in the deposition of AGEs, since the deleterious effects of AGEs on muscle tissue are mediated in part by their interaction with RAGEs.[37] Known as a multiligand receptor, RAGE belongs to the immunoglobulin (Ig) superfamily (including Igs, cell surface receptors, and adhesion molecules).[38,39] RAGE is named for its interaction with AGEs, but its family of ligands includes AGEs, high mobility group box 1 (HMGB1), amyloid-P peptide, and S100 family members. Although typically expressed at low levels in normal tissues, RAGE is upregulated regardless of where its ligand accumulates.[40] AGE-RAGE interaction causes various physiological and pathological processes mediated by triggering intracellular signalling cascades. These signalling pathways include the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway, p38 mitogen-activated protein kinase (p38 MAPK), extracellular signal-regulated protein kinases 1 and 2 (ERK 1/2), and c-Jun N-terminal kinase (JNK), followed by the activation of nuclear transcription factor-κB (NF-κB) and interferon-stimulated response elements (ISRE).[11] After the activation of the NF-κB pathway, RAGE in turn gets a positive feedback effect in its expression, thus further accelerating the process of inflammation and becoming trapped in a vicious circle.[41] The excessive amounts of AGEs lead to the overexpression of RAGE, and their ligation is supposed to cause further ROS production via the NAPDH pathway.[42] Meanwhile, there is another class of AGE cell surface receptors that play a converse role compared with RAGE, and is involved in AGE detoxification, including macrophage scavenger receptors class A, type II (MSR-AII), and class B, type I (MSR-BI, CD36), as well as AGE receptors 1, 2, and 3 (AGE-R1, -R2, and -R3).[24,43] These receptors can mediate the catabolism and clearance of AGEs by modulating endocytosis and degradation.[44,45] For instance, the first identified AGE receptor, AGER1, possesses intrinsic anti-inflammatory properties that mediate oxidative stress reduction through three distinct mechanisms: 1) suppression of MAPK/NF-κB signalling pathway activity; 2) enhancement of AGE degradation; and 3) attenuation of cellular ROS production.[46–48] However, RAGE and AGE-R1 expression seems to depend positively and negatively on AGE levels. As observed in a study by Mastrocola et al,[49] the gastrocnemius muscle of high fructose diet (HFRT) mice that had a higher level of CML accumulation tended to have a higher level of RAGE expression and a lower level of AGE-R1 expression, in contrast with the control group.

Detrimental effects of AGEs to skeletal muscle

AGEs promote muscle atrophy

Muscle atrophy refers to the loss of muscle mass and strength, which is the consequence of an imbalance between skeletal

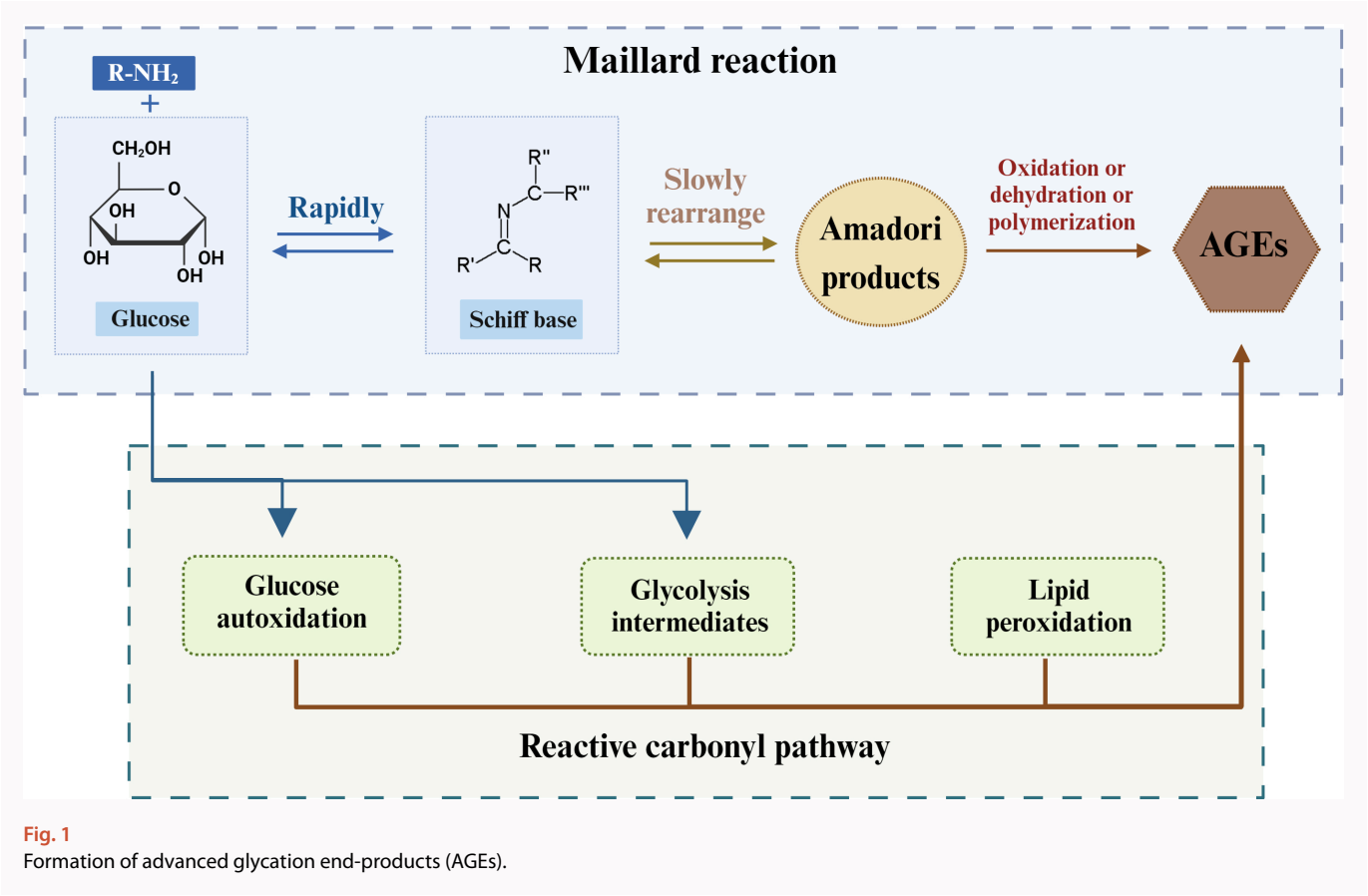

Fig. 1
Formation of advanced glycation end-products (AGEs).

muscle protein synthesis and degradation or changes in the functions of intramuscular proteins.[50] It is generally accepted that insulin/insulin-like growth factor-1 (IGF-1) signalling plays an important role in skeletal muscle protein synthesis.[51] However, continuous low-grade inflammation, chronic increased oxidative stress, and impaired mitochondrial function are usually linked with skeletal muscle atrophy by accelerating protein degradation in skeletal muscle and damaging its energy supply. Meanwhile, ubiquitin proteasome system, autophagy lysosome system, caspase system, and calpain system are considered as the four major downstream pathways during the process.[50,52–54] Additionally, skeletal muscle atrophy is also correlated with other muscle alterations such as changes in myofibre types or myosin isoforms, as well as intramuscular and intermuscular fatty infiltration.[6,50,55]

IGF-1 signalling is of great significance to maintaining skeletal muscle mass, and promotes protein synthesis by sequentially activating: phosphoinositide 3-kinase (PI3K); the serine/threonine kinase Akt, also known as protein kinase B (PKB); mammalian target of rapamycin (mTOR); and ribosomal protein S6 kinase, 70 kda (p70S6K).[51] The impaired IGF-1 signalling of skeletal muscle could cause abnormal protein metabolism and finally lead to muscle wasting,[51] while this process is partially related with the accumulation of AGEs in the body, especially in some conditions that promote AGE accumulation such as ageing and diabetes. A recent ex vivo experiment by Egawa et al[56] found that treatment with AGEs lowers the phosphorylation level of the majority of the phosphorylation sites in insulin/IGF-1 signalling. Such an effect has also been observed in their in vivo study, which showed that long-term AGEs intake in rodents reduced the phosphorylation of Akt and p70S6K.[56] Thus, they suggested that AGEs may play a part in ageing-related skeletal muscle loss by inhibiting protein synthesis through downregulating IGF-1 signalling. Additionally, Chiu et al[57] found that the accumulation of AGEs is associated with muscle atrophy and weakness in diabetic mice and elderly diabetic patients, showing a decrease in average muscle fibre cross-sectional area (CSA) and an increase in Atrogin-1/muscle atrophy F-box protein (MAFbx) compared with normal mice and the elderly, respectively. In their study, they used an OxiSelect AGE ELISA kit to assess the level of AGEs in serum, histological assessments, and western blot to detect the AGEs in skeletal muscle tissues and whole-cell protein extracts.[57] In further research, they proved that AGEs promote muscle atrophy in myotubes via a RAGE-mediated activation of AMP-activated protein kinase (AMPK), which leads to decreased Akt phosphorylation. The activated AMPK can increase protein degradation through the ubiquitin-proteasome pathway,[58] while Akt plays a role in protein synthesis,[59] both of which promote the catabolism of muscle protein and result in the reduction of muscle tube size. However, this process could be drastically reversed by treatment with Ala-Cl (an AGEs cross-link breaker), sRAGE (the soluble circulating form of RAGE), IGF-1, and compound C (an AMPK inhibitor).[57] The reduction of the sensitivity of target tissue to insulin, defined as insulin resistance, is the major characteristic of type 2 diabetes,[60,61] which certainly has negative effects on skeletal muscle since it accounts for a considerable part of total body protein and glucose clearance.[62] The increased formation of AGEs in the body under a circumstance of chronic hyperglycaemia seems to intensify insulin resistance.[63,64] Cassese et al[63] found that

human glycated albumin (HGA) could induce the formation of a multimolecular complex consisting of RAGE, protein kinase C α (PKCα), and Src in L6 cells; this phenomenon has also been observed in skeletal muscle from the dietary insulin-resistant high-AGE diet (HAD) fed mice. Further, the activated PKCα and Src may suppress insulin action through the serine/threonine phosphorylation of insulin receptor substrate (IRS), as observed in L6 cells.[63,65] Therefore, AGEs may inhibit insulin action in skeletal muscle cells by the formation of this RAGE/IRS-1/Src/PKCα complex ex vivo and probably in vivo. However, an interesting study proposed a novel methylglyoxal (a highly reactive AGEs precursor)-derived AGEs inhibitor, MK-I81, which could regain insulin sensitivity and alleviate the effect of insulin resistance caused by AGE-mediated downregulation of insulin signal transduction in skeletal muscle to an extent;[66] this is a potential therapeutic compound for the future.

Muscle homeostasis can be influenced under a circumstance of low-grade chronic inflammation, which has been reported to suppress antagonist muscle activation and contribute to age-related muscle weakness.[67] With ageing, the amassing of AGEs and the expression of RAGE in muscle tissue were pathologically increased,[1] which would also happen in other cells that express RAGE like monocytes, resulting in a sustained activation and release of proinflammatory factors and contributing to the systemic chronic low-grade inflammatory state.[40] The AGE-RAGE interaction can activate NF-κB, and subsequently leads to the increased expression of numerous inflammatory gene products and the establishment of an inflammatory niche.[68,69] Inflammatory mediators upregulated by AGE-RAGE-NF-κB pathways include tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and CRP.[70] These inflammatory factors also activate the NF-κB pathway, further raising inflammation levels and thereby reactivating the ubiquitin-proteasome system (UPS) and autophagolysosomal system, leading to protein degradation.[71] High levels of TNF-α could stimulate myostatin expression through a NF-κB-dependent pathway, while the exposure to myostatin could induce production of IL-6.[72] Excess IL-6 could induce the dephosphorylation of Akt thus inhibiting its activation, resulting in increased protein degradation and decreased protein synthesis in muscle.[72,73] Myostatin, a member of the transforming growth factor-β (TGF-β) family of secreted proteins, is mainly expressed in skeletal muscle, and can be activated by proteolysis or free radical stimulation and induce muscle loss. The excessive released myostatin can bind to the high-affinity type 2 activin receptor (ActRIIB) on the sarcolemma, leading to the activation of type 1 activin receptor serine kinases ALK4 or ALK5, which phosphorylate Smad2/3 thus stimulating the gene transcription linked with UPS.[50,74] Moreover, application of TNF-α has been proved to initiate the apoptotic signalling pathways in the mature cultured muscle cells, thus promoting catabolism.[75] Further, inflammatory cytokines can also deactivate the PI3K/Akt/mTOR pathway, mediating insulin resistance thus resulting in the reduction of protein synthesis.[74,76] Reduced Akt dephosphorylation stimulates muscle proteolysis by activating caspase-3 and UPS, since caspase-3 produces substrates for UPS cleaving actomyosin and increases proteasoma-mediated proteolysis. Additionally, the activation of forkhead box O3 (FOXO3) after activation of the NF-κB pathway can induce the expression of the muscle-specific ubiquitin ligases atrogin-1/MAFbx and muscle RING finger-1 (MuRF-1), and at the same time autophagy-associated proteins (Atgs), leading to selective proteolysis of myosin and other thick filament proteins, as well as actin and other thin filament proteins.[76–79] Inflammatory cytokines can also induce cyclooxygenase-2 (COX-2), which plays a part in skeletal muscle cachexia.[80] It is reported that increased COX-2 messenger RNA (mRNA) expression is followed by upregulated MuRF1 and atrogin-1 expression in the gastrocnemius of rats.[81]

Oxidative stress is another considerable factor linked with age-related muscle wasting. Research work has demonstrated that muscle tissue from those with obesity and older subjects showed increases in immunostaining of CML and RAGE, which was positively correlated with immunostaining of markers of oxidative stress and inflammation.[82] Oxidative stress refers to a state that means the imbalance of oxidative and antioxidative effects in vivo, which usually results from a rise in ROS and a reduction in antioxidant function.[83] The age-related decline in cellular antioxidant defences, coupled with elevated ROS production and compromised clearance mechanisms, leads to a progressive net accumulation of ROS within biological systems over time.[84] ROS are involved in AGE synthesis through glycoxidation, which promotes the synthesis of highly reactive carbonyl intermediates such as glyoxal and methylglyoxal, which can further react with different molecules to produce AGEs.[85] ROS contribute to skeletal muscle atrophy through a series of ways: activating the UPS and leading to the waste of muscle mass through intensifying proteolysis and reducing muscle protein synthesis; reducing the calcium release from sarcoplasmic reticulum by impairing excitation-contraction coupling; inducing modifications of actin and myosin structures; and dramatically decreasing the cross-bridge cycling within the myofibrillar apparatus.[85,86] Besides, there are other common cell damages caused by ROS such as mitochondrial damage, cellular apoptosis, inflammation, and lipid peroxidation.[87] The AGE-RAGE interaction increases oxidative stress by activating NADPH oxidase, which is a main source of ROS and could cause NF-κB stimulation.[42,88] ROS can also activate NF-κB through the Ras-ERK1/2 and Rac1-MKK6 pathways, and can accelerate muscle protein damage through a Ca^{2+}-dependent pathway.[89] Besides, binding of AGE-RAGE also facilitates oxidative stress through other pro-oxidative stress pathways such as protein kinase C (PKC) pathways.[90] It has been reported that elevated activities of the PKC pathway could stimulate ROS-generating enzymes such as NADPH oxidases and lipoxygenases; both of them can aggravate the cellular oxidative environment.[91] Cai et al[92] found that the skeletal muscle of mice with long-term oral methylglyoxal-AGE showed severe deficiency of AGE-R1 and survival factor sirtuin 1 (SIRT-1), elevating basal oxidative stress/inflammation and increasing susceptibility to metabolic abnormalities of insulin resistance. Worse still, the stronger oxidative environment will further accelerate the formation of AGEs, leading to a vicious circle.[11] Blocking the receptor for RAGEs enhances antioxidant capacity, as it has been verified in a previous study that RAGE-deficient mice have an increased superoxide dismutase and sirtuin mRNA expressions.[93] Moreover, high oxidative stress may also promote muscle atrophy through upregulating

myostatin, which has been observed in chronic kidney disease (CKD).[94]

Mitochondria are extremely important organelles for skeletal muscle, since they participate in the regulation of many critical cellular processes such as energy provision, calcium homeostasis, ROS production, and regulation of apoptosis.[95] Mitochondrial respiratory dysfunction, reduced muscle mitochondrial mass, and reduced skeletal muscle energy supply all contribute to the development of muscle atrophy. Plenty of evidence indicates that AGEs do harm to mitochondrial respiration and oxidative phosphorylation, while the downstream effects caused by AGE-RAGE binding may play a significant role in this process. Some studies carried out in cardiomyocyte mitochondria may provide further evidence for this. For instance, incubation of AGEs in different cell lines promoted the dissipation of $\Delta\psi m$ and the reduction of intracellular adenosine triphosphate (ATP) levels, while the RAGE null mice had higher cardiac ATP levels than their littermates.[43] Additionally, compared with the normal high-fat diet mice, RAGE-deficient mice showed better mitochondrial quality control by facilitating removal of damaged mitochondria.[93] AGEs and ROS can be induced by reducing oxidase and mitochondrial protein oxidation change to influence mitochondrial function, leading to protein degradation and loss of function and mitochondrial volume density and mitochondrial DNA copy number of reduction.[96] Moreover, AGE-induced oxidative stress and inflammation may do damage to mitochondrial biogenesis.[96] Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α is thought to play the most important cooperative role in mitochondrial biogenesis, and is viewed as a marker of mitochondrial biosynthesis.[97] PGC-1α and mitochondrial protein content in skeletal muscle have been reported to decrease with age,[98] while oxidative stress and inflammation decrease PGC-1α expression and increase the mitochondria number in muscle.[99] Yabuuchi et al[37] found that AGEs-aptamer ameliorated the reduction of succinate dehydrogenase (SDH) activity and PGC1-α in the gastrocnemius muscle of 5/6 Nx CKD model mice, which implies that AGE may cause deteriorating effects on mitochondrial energy production and biosynthesis in part by lowering SDH activity and PGC1-α levels. Similarly, Mastrocola et al[49] found that mean SDH activity per oxidized muscle fibre was reduced in HFRT mice compared with the mice fed a standard diet, which could be improved by the supplement of pyridoxamine, a potent inhibitor of the dicarbonyl compound precursor of AGEs. The hypothesis of fructose-derived AGE-induced mitochondrial damage had been verified by further assays, which showed reduced mitochondrial membrane potential in HFRT gastrocnemius muscle as well as reduced sarcomere mitochondrial creatine kinase (sMtCK) content in HFRT gastrocnemius muscle extracts.[49] However, pyridoxamine treatment could almost totally reverse this AGE-induced mitochondrial damage.[49]

Apart from the above points, AGEs can also promote muscle atrophy through the following mechanisms. First, AGEs can directly target skeletal muscle intracellular proteins to change their biological functions. AGEs generated in the Maillard reaction, while changing the structure and activity of proteins, also reduce their susceptibility to degradation.[100,101] Snow et al[19] observed the number and types of age-modified proteins in the extensor longus muscle of young (eight months), old (33 months), and very old (36 months) rats. According to their study, intracellular proteins creatine kinase, β-enolase, carbonic anhydrase III, and voltage-dependent anion selective channel 1 (VDAC1) are targets for AGEs, and are of great importance to skeletal muscle energy supply. In addition, structural proteins of skeletal muscle are also targets for AGEs, as the actin has been identified by the AGE immunoreactive bands.[19] The AGE-modified actin reduces actin polymerization, thus having a detrimental effect on myofibril contraction.[102,103] Ramamurthy et al[104] found that glucose reduced the speed of myosin movement in a dose-dependent manner, while glutathione reversed the effects of glucose on myosin function. Glycosylation of myofibrils (myosin, actin) has been reported to reduce adenosine triphosphatase (ATPase) activity in an ex vivo experiment.[105] Additionally, targeting glycosylated respiratory chain complex I and IV components and catalase will impair cellular energy metabolism and the entire antioxidant defense system, respectively.[43] Second, AGEs can contribute to lipid accumulation in muscle cells. A study by Mastrocola et al[49] showed that there is a higher level of triglyceride, and the adipogenic sterol-regulatory element binding protein (SREBP) cleavage-activating protein SCAP/SREBP pathway is strongly activated in the skeletal muscle homogenate of HFRT mice compared with the standard diet mice. As SIRT-1 was viewed as the inhibitor of SREBP-1c activity and could be upregulated by AGE-R1,[106] the authors found that HFRT diet can reduce not only the levels of AGE-R1 but also expression of SIRT-1, while both could be effectively prevented by pyridoxamine treatment.[49] Third, AGEs may cause changes in fibre type composition and muscle metabolism. Since the myogenic regulatory factors (MRFs) involved in muscle structural protein reprogramming were thought to be regulated by the activity of SREBP-1c,[107] AGEs may contribute to age-related muscle fibre switch. Uribarri et al[106] found that in the gastrocnemius muscle of HFRT mice, there was a higher content of slow-switch fibre of myosin heavy chain (MyHC) 1 and 2 and a lower content of fast glycolysis fibre of MyHC2b, which impaired the contractile function of the muscle as a whole. However, pyridoxamine had also been found in their study to effectively preserve the composition of MyHC.[106] The molecular mechanisms of AGEs leading to skeletal muscle atrophy are summarized in Figure 2.

AGEs impair muscle regeneration

Satellite cells (SCs) play a central part in skeletal muscle regeneration. When skeletal muscle is damaged, they can be activated and become myoblasts that differentiate into myocytes. Myocytes fuse to form myotubes or integrate with existing muscle fibres to regenerate skeletal muscle.[35] Pax7 (pairing domain transcription factors) and MRFs are in regulation of myogenesis. Pax7 is expressed and labelled in resting stem cells (SCs) to prevent their premature differentiation, which is important for the proliferation and survival of myogenic progenitors. In myoblasts, the expression of Pax7 and myogenic regulatory factors (MRFs) demonstrates mutual exclusivity, as downregulation of Pax7 is required to enable terminal differentiation of muscle cells.[108] MRFs (namely Myf5, MyoD, myogenin, and MRF4) are activated timely in myoblasts to modulate downstream targets such as MyHC, MCK (creatine

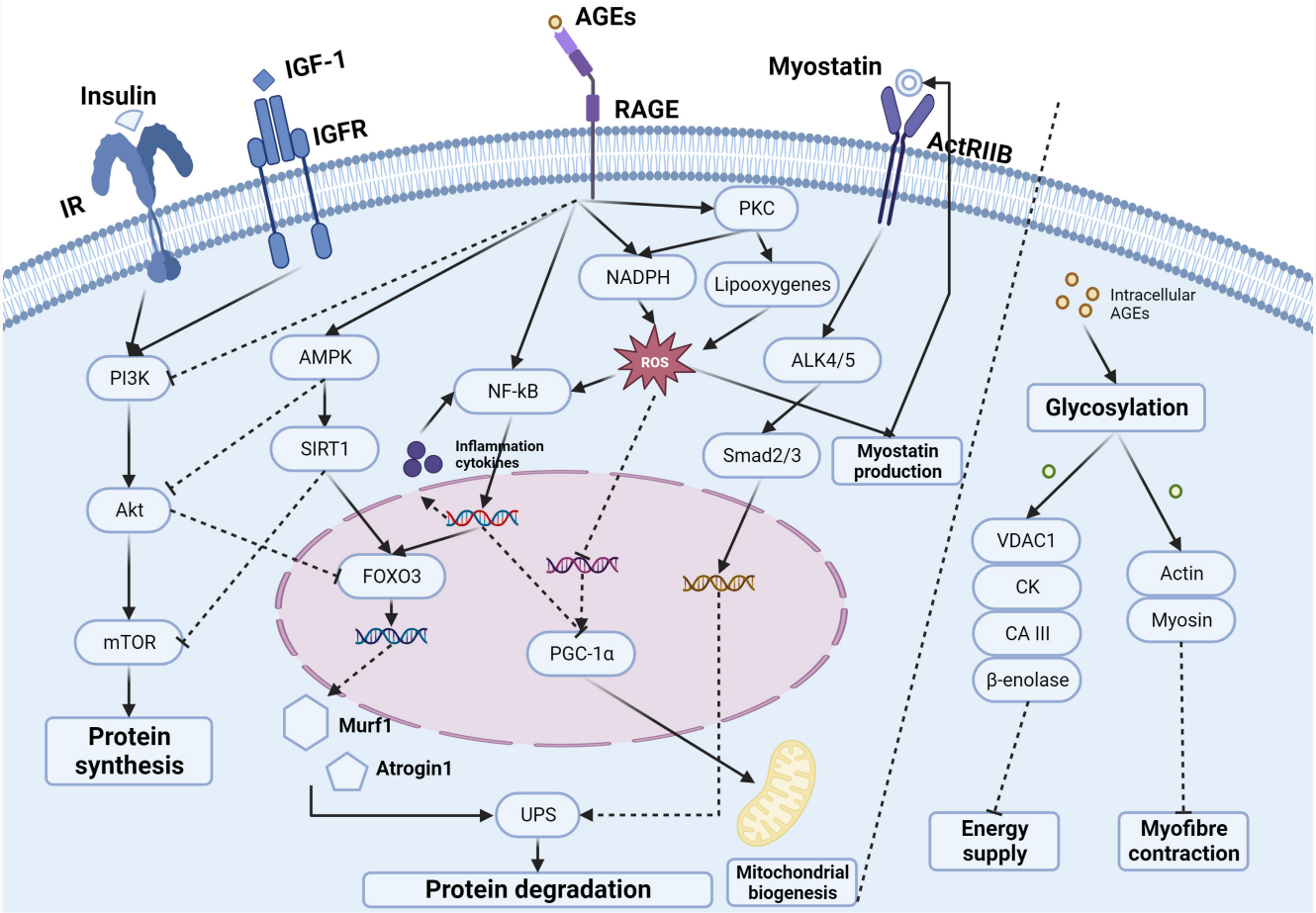

Fig. 2
Molecular mechanisms of advanced glycation end-products (AGEs) leading to skeletal muscle atrophy. Arrows (→) indicate activation and stub lines (T) indicate inhibition. ActRIIB, type 2 activin receptor; Akt, serine/threonine kinase; ALK4/5, activin receptor-like kinase 4/5; AMPK, adenosine 5′-monophosphate; CAIII, carbonic anhydrase III; CK, creatine kinase; FOXO3, fork head box O3; IGF-1, insulin-like growth factor-1; IGFR, receptor for IGF-1; IR, receptor for insulin; mTOR, mammalian target of rapamycin; Murf1, muscle RING finger-1; NADPH, nicotinamide adenine dinucleotide phosphate; NF-kB, nuclear factor-κB; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RAGE, receptor for AGEs; ROS, reactive oxygen species; Smad2/3, mothers against decapentaplegic 2/3; SIRT1, sirtuin1; UPS, ubiquitin-proteasome system; VDAC1, voltage-dependent anion selective channel 1. Created with BioRender.com, with permission.

kinase), and troponin T, which are required for terminal differentiation and functional muscle fibre generation.[109,110]

RAGE signalling plays a significant role in skeletal muscle regeneration, especially in the process of acute damage in skeletal muscle.[76] During the early stages of differentiation, activated myoblasts respond to S100B via RAGE to enhance proliferation via ERK1/2, and simultaneously initiate myogenic processes via p38 MAPK.[111] During the later stages of differentiation, HMGB1 stimulates the upregulation of myogenin through the RAGE-dependent p38 MAPK pathway, preparing for myoblast fusion by inhibiting Pax7.[112] However, when the AGEs are pathologically upregulated under certain circumstances such as ageing, high glucose conditions, or long-term chronic high levels of inflammation and oxidative stress, the pathologically upregulated AGE-RAGE signalling dominates the natural RAGE course, leading to the abnormal differentiation of SCs.[76] Chiu et al[57] witnessed that AGEs impaired the regeneration of damaged muscle in the mice and stimulated collagen deposition in the regenerated muscle. AGE-BSA (bovine serum albumin) treatment reduces myogenic protein and MyHC expression through phosphorylation of AMPK and dephosphorylation of Akt, thereby adversely affecting myoblast differentiation and fusion, which can be reversed by the treatment of Ala-Cl, sRAGE, IGF-1, and compound C.[57] Takata et al[113] found that AGEs derived from glyceraldehyde (an intermediate of glucose/fructose metabolism) strongly induced C2C12 cell death, manifested as the vitality of C2C12 cells treated with glyceraldehyde dropped in a dose-dependent manner. However, this detrimental effect can be completely inhibited by pretreatment with aminoguanidine, a depressant of AGE production. Similarly, Adachi et al[114] found that both AGE2 and AGE3, derived from glyceraldehyde and glycolaldehyde, respectively, could apparently inhibit the mRNA expression of MyoD, myogenin, endogenous IGF-1, and total Akt in C2C12 cells, and all these conditions could be reversed by co-treatment with IGF-1. In addition, treatment with AGE2 and AGE3 greatly promoted the apoptosis of C2C12 cells, while co-incubation of IGF-I with AGE2 or AGE3 counteracted the cytotoxic effects of AGE2 and AGE3.[114] Furthermore, the authors found that a hyperglycaemia environment accelerates the impairment of AGEs through upregulating the expression of RAGE.[114] Similarly, a study by Tanaka et al[115] found that AGE2 or AGE3 treatment could suppress the myoblastic

differentiation of C2C12 cells, probably by suppressing the expression of MyoD and myogenin proteins in C2C12 cells, while 1,25D (a sort of active vitamin D) could, to an extent, reverse such harmful effects. Apart from the SCs, human mesenchymal stem cells (MSCs) may also have a role in differentiating into mature musculoskeletal tissues after tissue damaging. Research by Kume et al[116] showed that treatment with AGEs could inhibit MSC proliferation, induce apoptosis, and prevent cognate differentiation, which might result in the loss of MSC mass which would manifest as tissue repair disorders. They also found that this detrimental effect of AGEs on MSCs may be partially attributed to the AGE-RAGE interaction, since the antiserum against RAGE discouraged the AGE-induced MSC events to a certain extent.[116] Although many studies have shown the association between AGEs and impaired muscle regeneration ability, there are few studies that have focused on the specific molecular mechanisms. STAT3 signalling is known to be upregulated in older SCs, while suppression of it might lead to an increasing number of SCs, which is conducive to the repair of muscle tissue and improved functional performance.[117] A study by Egawa et al[56] found that AGE treatment increased STAT3 Tyr705 phosphorylation in skeletal muscle, which was verified in both in vivo and ex vivo experiments, presenting that AGE-induced suppression of muscle regeneration may be partially through activation of STAT3 signalling. Additionally, ERK, as a member of the mitogen-activated protein kinase family and involved in the differentiation of skeletal muscle cells,[118] also plays a crucial regulating role in myogenesis.[119] Egawa et al[56] found that the presence of AGEs exacerbated the age-related attenuation of ERK signalling, since they observed that the AGE treatment decreased ERK Thr202/Tyr204 phosphorylation in C2C12 cells, and the long-term AGEs intake also lowered the ERK phosphorylation in rat skeletal muscle.

AGEs disrupt the normal structure of skeletal muscle ECM

Skeletal muscle ECM is of great significance for the transmission, maintenance, and adjustment of muscle fibre force.[120] The ECM of skeletal muscle is usually divided into endomysium, perimysium, and epimysium, which is a connective tissue scaffold surrounding individual muscle fibres, muscle bundles, and the entire muscle.[21,120] The principle composition of skeletal muscle ECM is collagen. This provides a scaffold for remaining muscle-tendon integrity and is involved in the transmission of muscle force, as the elastic properties of collagen are partly responsible for the production of passive force in skeletal muscle.[121]

Since the formation of AGEs is a lengthy stochastic process that depends on the concentration and probability of monosaccharides in an open-loop conformation, it is easier for AGEs to accumulate in long-lived proteins such as collagen.[122,123] Moreover, collagen contains lots of lysine and arginine amino acids, which potentiates AGE formation.[122] Previous research shows that glycosylation of myofibrillar proteins increases with age,[124] and locally formed AGEs can change the biomechanical properties of skeletal muscle, increasing stiffness and decreasing elasticity through cross-linking in the connective tissue, making it more resistant to enzymatic degradation, and finally impairing the muscle and body functions.[69,125] Differing from enzymatically mediated collagen cross-linking such as non-reducing collagen pyridinium cross-links, non-enzymatically regulated AGE cross-linking is another form of biochemical linkage that results from the spontaneous non-enzymatic bond formed between a reducing sugar and a protein residue.[21] Once formed, AGEs can only be metabolized if the proteins to which they are linked are degraded.[126] The increases in collagen concentration, pyridine cross-linking of hydroxycollagen, and AGE cross-linking have been reported to closely relate to increased muscle rigidity and reduced muscle flexibility, since the increased AGE cross-linking can harm the elastic properties of collagen thus affecting the passive viscoelastic properties of skeletal muscle.[69,121,125,127] Research by Haus et al[21] confirmed that intramuscular collagen concentration and enzyme-mediated collagen cross-linking are under rigorous regulation, as similar concentrations are observed in the skeletal muscle of young and old individuals. In contrast, AGE cross-linking in muscle has been observed to increase in healthy, sedentary older adults. In their study, the authors witnessed a 200% increase of pentose glycoside in the elderly which may have affected the stiffness of the tissue and the passive viscoelastic properties of the muscle, thereby contributing to the decline in muscle function.[21] Bartling et al[128] had demonstrated that AGE-collagens impair efficient cell adhesion and migration, as well as matrix degradation since collagen proteolysis and AGE level of the individual collagen samples showed an inverse correlation. However, during tensile loading, the cross-linked collagen triple helix undergoes local micro-unfolding, thereby increasing the number of proteolytic sites as well as susceptibility to collagenase digestion.[129] Thus, the accumulation of AGEs in skeletal muscle may be partially attributed to the decline of collagen turnover rate, which may result from the lack of a regular and robust tissue turnover stimulus such as exercise.[130,131] In their study, Maessen et al[130] made a comparison of dicarbonyl stress and AGEs in lifelong endurance athletes (ATH) versus sedentary controls. Their study found that ATH tend to have lower levels of dicarbonyl stress while have higher levels of circulating AGE markers such as CML and carboxyethyllysine (CEL), thus they proposed a possible explanation that exercise improves collagen turnover, which breaks and prevents AGE cross-linking in the tissue, leading to larger amounts of circulating AGEs.

AGEs contribute to neuromuscular junction lesion and vascular disorders

The NMJ is the synapse between an α motor neuron and a skeletal muscle fibre, which is a microenvironment under strict modulation.[123] However, impaired NMJ can influence the stability of the microenvironment of synapse, or even cause the collapse of the motor unit spatial domain, presenting as the low speed of muscle contraction and loss of muscle strength.[132] During the maturation process of NMJ, the microenvironment in the region of the motor end plate comprises mostly of collagen type IV and laminin; it is under careful regulation and thought to participate in NMJ development.[123] A previous study showed that non-enzymatic glycosylation of laminin inhibited neurite outgrowth in cultured neuroblastoma cells.[133] It has been shown that at high glucose concentrations, non-neuronal cells derived from the sciatic nerve express elevated mRNA levels of fibronectin and collagen types I and IV,[134] and increased collagen IV synthesis may form massive microfibril deposits between the perineurial

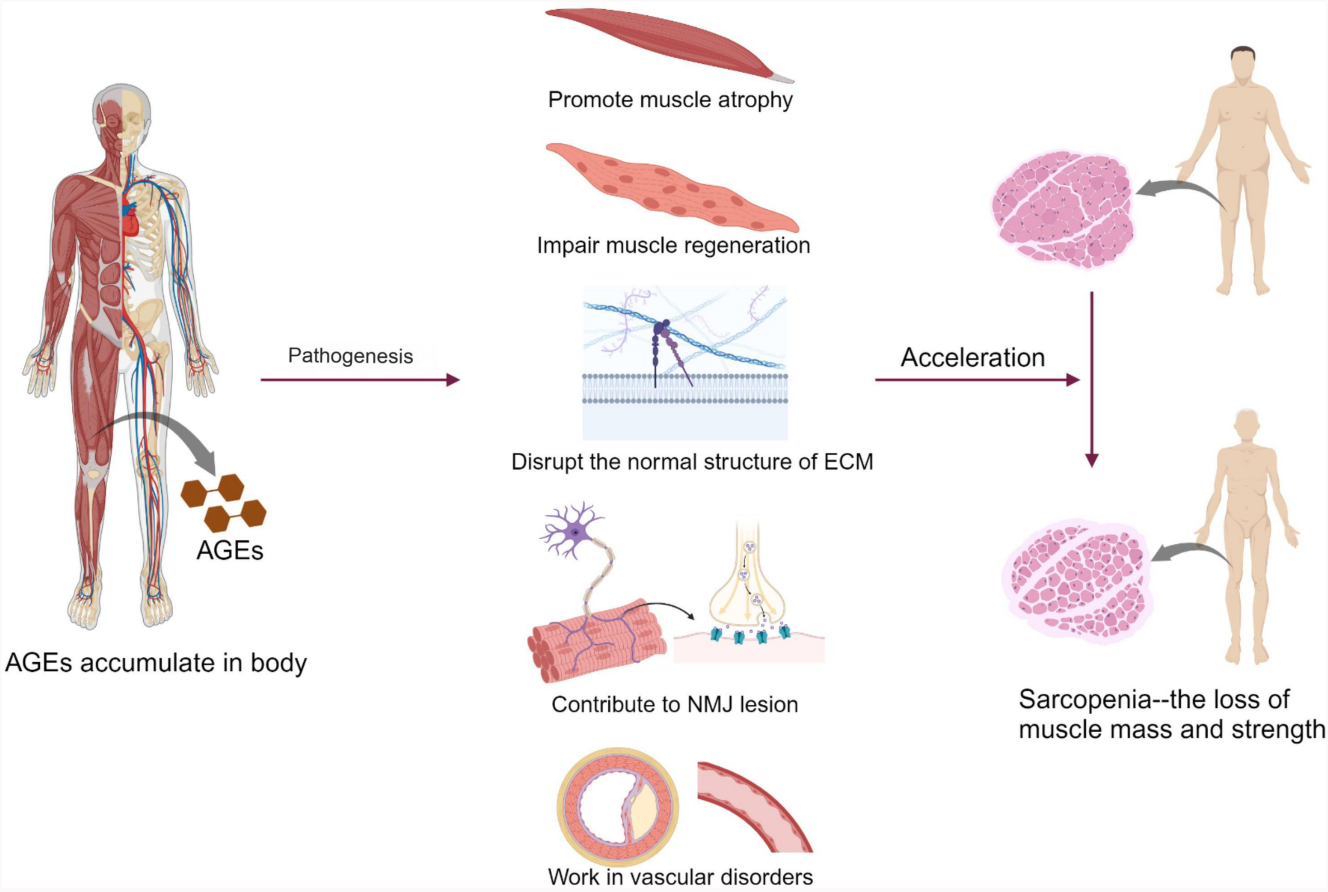

Fig. 3
The pathogenic role of advanced glycation end-products (AGEs) in skeletal muscle. ECM, extracellular matrix; NMJ, neuromuscular junction. Created with BioRender.com, with permission.

cell layers.[135] At the same time, deposition of collagen fibres themselves may also prevent nerve regeneration.[136] Furthermore, glycated collagen is suggested to increase under diabetic conditions and be resistant to protease digestion, which may do harm to axon regeneration, thereby contributing to neuropathy in diabetic patients.[136] Collagen deposition around neurones may act as a compressive lesion or, on the other hand, may interfere with diffusion, transport, and binding of neuropeptides and monoamines.[125] In short, it is clear that NMJ lesions can be driven by AGE-cross-linked ECM components. Furthermore, it has been reported that AGEs exhibit high cytotoxicity on Schwann cells through P38 MAPK and NF-κB pathways, which could lead to the demyelination of the motor nerves.[137,138] Moreover, deposition of AGEs would enhance local oxidative stress and produce more ROS that act on NMJ. Specifically, ROS were suggested to prevent the generation of an action potential of the sarcolemma by reducing acetylcholine release in synaptic cleft, and persistent oxidative stress has been thought to reduce the amount of innervation and fibres, thus altering the morphology of the NMJ.[85]

A healthy vasculature surrounding skeletal muscle is designed to ensure its nutrient supply and waste product removal.[3] AGE accumulation is associated with micro- and macrovascular disorders, which may do harm to skeletal muscle metabolism and regeneration.[3,139] AGEs have been reported to affect the vascular endothelium by inducing adverse biological events such as foam cell formation, calcium deposition, inflammation, oxidative stress, and apoptosis; these processes together lead to vascular calcification and progression of atherosclerotic plaques.[140] Koike et al[141] demonstrated that AGE-induced apoptosis of vascular smooth muscle cells (VSMCS) could be the result of NADPH oxidase activation and ROS generation. Moreover, Otero et al[142] found that albumin-derived AGEs could disrupt the vascular endothelial cadherin (VE-cadherin) complex in cultured human and murine endothelial cells (ECs), one of the most important regulators of EC integrity and intercellular communication,[143] while the loss of VE-cadherin complex components was linked to increased vascular permeability and EC migration, leading to the unstable adhesion of ECs.[34] The microvascular system is of great importance to maintaining the delivery of oxygen and nutrients of skeletal muscle, especially during periods of increased activity. Capillary rarefaction may lead to skeletal muscle fatigue,[34] as a lower capillary-to-fibre ratio was observed in biopsy samples of the lateral thigh muscle from haemodialysis patients who showed impaired exercise capacity.[144] A study by Yabuuchi et al[37] found that the AGE-aptamer could, to an extent, restore the capillary rarefaction in the gastrocnemius muscle of 5/6 Nx CKD mice. Asymmetric dimethylarginine (ADMA) is an endogenous depressant of nitric oxide (NO) synthase that is correlated with endothelial disability.[145] Plasma ADMA levels were negatively correlated with endothelial function, as measured

by flow-mediated vasodilation, but increased with serum AGE levels.[145] Ando et al[145] found that AGEs decreased mRNA levels of dimethylarginine dimethylaminohydrolase (DDAH)-II, an ADMA degrading enzyme, and decreased its total enzyme activity thereby increasing ADMA, which may contribute to ROS generation mediated by AGE-RAGE signalling in ECs, while these effects could be completely blocked by the antioxidant N-acetylcysteine. Thus, the AGEs may contribute to capillary rarefaction and ischaemia in the skeletal muscle mediated by ADMA through reducing NO synthesis and bioavailability.

Conclusion and future prospects

The accumulation of AGEs in the body can accelerate the progression of sarcopenia in many ways. In this article, we reviewed the potential mechanisms of the detrimental effects based on existing studies. On the one hand, by binding with RAGE, AGEs can activate a series of intracellular signalling pathways in skeletal muscle cells related to the elevated levels of inflammation and oxidative stress, as well as impaired insulin/IGF-1 signalling and mitochondrial biogenesis, which leads to reduced protein synthesis and increased protein degradation, intracellular lipid accumulation, changes in fibre type composition, and muscle energy metabolism as well as a higher rate of apoptosis, finally resulting in muscle atrophy and impaired regeneration abilities. On the other hand, by directly targeted glycosylation, AGEs can damage the biological properties and functions of proteins that include the functional and structural proteins of skeletal muscle and collagens in ECM, resulting in muscle dysfunction such as impaired force production and increased stiffness. In addition, AGEs can also indirectly affect skeletal muscle by contributing to NMJ lesions and vascular disorders (Figure 3).

Since AGEs are a link in the pathophysiological process of muscle ageing and sarcopenia, there are some corresponding measures and treatments that people can take to prevent its progression. Limiting the exogenous intake of AGEs is of great importance, and specific measures include reducing intake offried or baked food, a low-fat and low-sugar diet, quitting smoking, and adding lemon or vinegar to lower the local pH of food.[29,146] AGE precursor-derived AGE formation inhibitors such as aminoguanidine,[113] pyridoxamine,[49] and MK-I81[66] have been reported to be effective in alleviating the toxicity of AGEs by reducing their endogenous formation. A previous study in animal models showed that AGE cross-link breakers (e.g. Ala-Cl) and soluble circulating RAGE are effective in reducing AGE accumulation in tissues,[57] but whether it can be applied in clinic needs further verification. Ex vivo experiments have demonstrated that IGF-1, compound C, and 1,25D are effective in decreasing myotube atrophy and recovering the regeneration activities of skeletal muscle cells,[57,115] which may offer a way of thinking to novel therapy development. Suppressing the activity of RAGE seems to be an effective way to avoid part of the toxic effects of AGEs, control inflammation and oxidative stress levels, and protect the skeletal muscle to some extent.[76] Some RAGE inhibitors such as TTP488[147] and FPS-ZM1[148] have been developed and were well tolerated in human trials, and both have been reported to reduce or abrogate the pathogenic effects caused by RAGE activity by reducing AGE-RAGE interactions in animal models. However, the application of RAGE inhibitors still needs further clinical studies to guarantee its effectiveness, and determine the appropriate dose since the complete inhibition of RAGE may damage the regeneration of skeletal muscle.[76] Exercise is a well-established and effective way to reverse or delay the progression of sarcopenia, which could get further support from the useful effects of exercise on decreasing the AGE-induced detrimental effects on skeletal muscle. One mechanism by which exercise reduces AGE accumulation is improving glucose tolerance and lipid levels, to reduce the raw materials of the glycation response such as sugars and aldehydes.[20] Moreover, exercise can enhance AGE degradation by stimulating protein turnover, especially the collagen in the ECM of skeletal muscle, thereby improving muscle flexibility by reducing AGE cross-linking.[130,131] It has also been reported that exercise could reduce AGE-RAGE binding by reducing RAGE expression,[149] and increase the gene expression of enzymes responsible for the degradation of precursor glycosylation product.[150] Furthermore, exercise is effective in counteracting the pro-inflammation and pro-oxidative stress effects of AGEs.[151] Exercise also inhibits myostatin signalling, thereby repressing the transcription of atrogenes and reducing the consequent protein degradation.[151] Moreover, exercise can stimulate protein synthesis by increasing the internal IGF-1 levels and promote mitochondrial biogenesis by inducing the transcription of PGC-1α.[151] The specific mechanism of AGEs involved in the occurrence and development of sarcopenia needs to be further elucidated, in order to facilitate further research and develop treatment methods and drugs for sarcopenia.

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Data sharing

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