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Original article

Glycative stress and skeletal muscle dysfunctions; as an inducer of "Exercise-Resistance"

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Abstract

Skeletal muscle, the largest tissue in the body, is often overlooked for its role as a locomotor organ, however over the past few decades it has been revealed that it also has an important role as a metabolic organ. In recent years, its role as an endocrine organ that controls the homeostatic functions of organs throughout the body mediated by myokine secretion has come under close scrutiny. Skeletal muscle is indispensable for our daily life activities, and in order to maintain its function, it is necessary to understand the factors that deteriorate muscle function and establish a countermeasure. Glycative stress has recently received attention as a factor that impairs skeletal muscle function. Accumulation of advanced glycation end products (AGEs) in skeletal muscle impairs contractile function and myogenic potential. Furthermore, AGEs in the blood elicit inflammatory signals through binding to RAGE (Receptor for AGEs) expressed on muscle cells, resulting in muscle proteolysis. Habitual exercise is important to mitigate the negative effects of such glycative stress on skeletal muscle. On the other hand, it is known that the beneficial effects of exercise vary among individuals. The state in which the effects of exercise are difficult to obtain is called "exercise-resistance," and we hypothesize that glycative stress may be one of the causes of exercise-resistance. In this paper, we will discuss the possibility of glycative stress as an inducer of exercise resistance and summarize its impacts on skeletal muscle.

***KEY WORDS*:** glycative stress, advanced glycation end products (AGEs), skeletal muscle, exercise resistance, sarcopenia

Introduction: Importance of skeletal muscle in health maintenance and promotion

Skeletal muscle is the largest tissue in the body, accounting for about 40% of total body weight. In addition to its role as a locomotor that generates physical activity, skeletal muscle contributes significantly to our life-sustaining activities as a metabolic and endocrine organ. For example, 80% of the glucose in the blood is taken up by skeletal muscle and used for energy production or stored as glycogen. Therefore, a decline in skeletal muscle metabolic function leads to systemic glucose intolerance, which is a factor in triggering metabolic diseases, *i.e.*, diabetes. In recent years, it has become clear that myokines, bioactive substances secreted by skeletal muscle, are involved in the regulation of the functions of various organs in the body as well as skeletal muscle. After the age of 50, skeletal muscle mass declines by 1-2% per year and muscle strength by 1.5-5% [1)], and therefore, maintaining the quantity and quality of skeletal muscle is a prerequisite for healthy longevity (***Fig. 1***)

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Glycative Stress Research 2022; 9 (4): 199-205

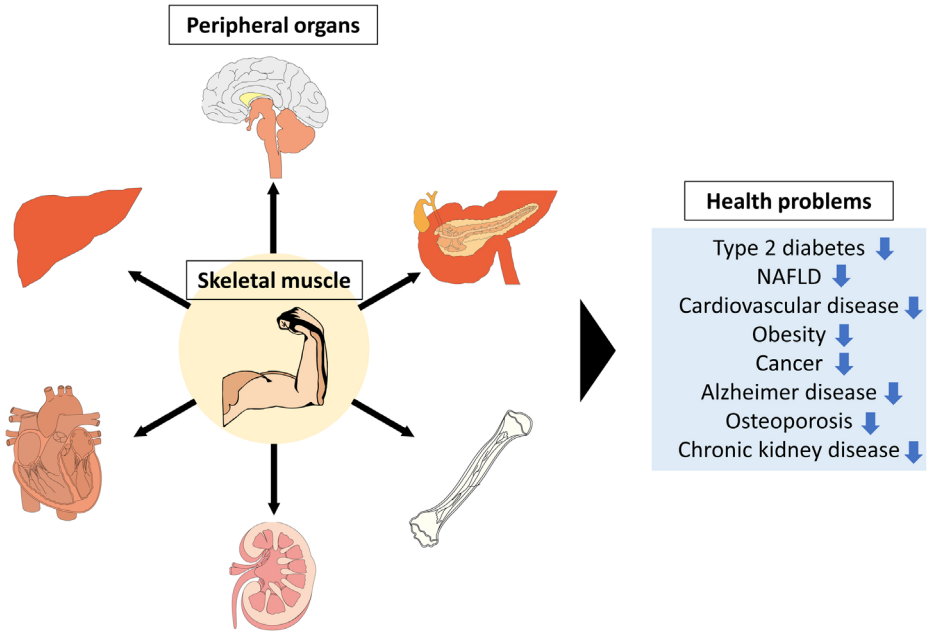

Fig. 1. **Skeletal muscle and metabolic health.**
Skeletal muscle has an important responsibility for maintaining our health as not only locomotor system but also metabolic and endocrine systems. NAFLD, non-alcoholic fatty liver disease.

Glycative stress and impairment of motor and skeletal muscle function

Advanced glycation end product (AGE) modification of proteins is an irreversible reaction that is essentially metabolized by the proteolytic system. However, as the protein turnover function declines with age, the accumulation of AGEs in the body progresses over time, adversely affecting biological functions. The relationship between age-related AGE accumulation and motor and skeletal muscle function was first reported by a research team led by Dr. Richard Semba, Johns Hopkins University, Baltimore, MA, USA, who found that elevated blood N^{ε}-(carboxymethyl) lysine (CML) levels were a risk factor for impaired muscle strength and walking ability [2-4]. Subsequent epidemiological studies in middle-aged and elderly subjects have confirmed that elevated blood AGEs and subcutaneous AGEs (skin autofluorescence: SAF) correlate with impaired muscle strength and physical function (***Table 1***). The accumulation of AGEs in the body is considered to be a biomarker of reduced motor and skeletal muscle function.

Recent studies have confirmed that an association exists between subcutaneous AGE accumulation status and impaired motor and skeletal muscle function in middle-aged and older adults as well as in children and young adults. In a study of 1,075 children (6-8 years), a Swiss research team found that children with higher levels of SAF had lower endurance capacity [5]. Also, our study of 20 college students (18-20 years) confirmed a negative correlation between SAF and leg muscle strength [6]. Namely, the impacts of glycative stress on motor and skeletal muscle function may occur regardless of age. Whereas, a study of 1,542 adolescents reported that low muscle strength promotes AGE accumulation rather than AGE accumulation induces muscle weakness [7], thus, further research is needed to clarify the causal relationship between the two.

Molecular mechanisms of glycation-induced decrease in motor and skeletal muscle function

The first factor that causes AGE accumulation to impair motor and skeletal muscle function is that muscle contractile proteins, i.e., myosin, actin, tropomyosin, are modified by glycation, resulting in impaired contractile function [8-11]. It has also been suggested that changes in extracellular matrix structure, decreased ATPase activity [9,12], and impaired motor neurotransmission [13] are also involved (***Fig. 2***).

Our recent study reports that myogenesis and protein synthesis signaling are affected by glycative stress. In this study, mice fed a diet containing 5 times the normal level of AGEs for 16 weeks showed decreased expression of myogenic factor 5 (Myf5) and myogenic differentiation 1 (MyoD), which play a role in promoting myogenesis; furthermore, insulin-like growth factor 1 (IGF-1) signaling, which plays a role in promoting protein synthesis, was attenuated, resulting in decreased muscle mass [14,15]. In an experiment using mice intaking methylglyoxal (MGO), a precursor of AGEs, for 20 weeks, gene expression of the inflammatory cytokines interleukin (IL)-1β and IL-6 increased in association with

Table 1. Association between glycative stress and muscle function

Reference	Characteristics	AGE type	Impacts on muscle function
Dalal et al., 2009 [2]	women, age ≥ 65 years (n = 559)	serum CML	lower grip strength
Semba et al., 2010 [3]	age ≥ 65 years (n = 944)	plasma CML	slower walking speed
Momma et al., 2011 [30]	men, median age 46.0 years (n = 232)	SAF	lower grip strength and leg extension power
Sun et al., 2012 [4]	women, age ≥ 65 years (n = 394)	serum CML	severe walking disability
Whitson et al., 2014 [31]	mean age 78.1 ± 4.8 years (n = 3,373)	serum CML	physical frailty
Kato et al., 2017 [32]	men, mean age 57 ± 10 years; women, 60 ± 11 years (n = 132)	SAF	lower muscle mass
Mori et al., 2017 [33]	mean age 55.7 ± 10.3 years (n = 36)	SAF	lower knee extension strength
Drenth et al., 2018 [34]	age ≥ 65 years (n = 5,624)	SAF	lower physical function
Ebert et al., 2019 [35]	aged 43–83 years (n = 1,770)	plasma AGE	lower physical function
Eguchi et al., 2019 [36]	women with sarcopenia, age 72.7 ± 10.1 years (n = 47); controls, age 77.2 ± 7.2 years (n = 23)	serum pentosidine	lower muscle mass
Mori et al., 2019 [37]	mean age 63.2 ± 12.3 years (n = 166)	SAF	ower muscle mass, strength, and physical performance
Yang et al., 2019 [38]	age ≥ 65 years (n = 104)	urinary CML	lower grip strength
Tabara et al., 2019 [39]	mean age 57.8 ± 12.4 years (n = 9,203)	SAF	lower muscle mass and grip strength
Moriwaki et al., 2021 [40]	men, 75.0 ± 8.9 years (n = 157); women, 73.6 ± 8.1 years (n = 97)	urinary pentosidine	walking disability and lower grip strength

Results are expressed as mean ± SD. AGE, advanced glycation end product; CML, N^{ε}-(carboxymethyl) lysine; SAF, skin autofluorescence; SD, standard deviation.

muscle mass loss [16], suggesting that glycative stress may induce protein catabolism through inflammatory signals.

The changes observed in these studies occurred primarily in fast-twitch muscle, suggesting that there may be a muscle-type specificity in the effects of glycative stress on skeletal muscle. These impairments in myogenesis, protein synthesis, and inflammation-induced catabolism that occur predominantly in fast-twitch muscle may be triggers for the age-related selective loss of fast-twitch muscle function, so-called sarcopenia.

Whereas, another of our studies reported that glycative stress is involved in disuse muscle atrophy, which occurs mainly in slow muscle [17]. In this study, mice subjected to a 1-week hindlimb suspension induced disuse atrophy, resulting in slow-twitch muscle-dominant atrophy and increased receptor for AGEs (RAGE) expression. In addition, the administration of RAGE antagonists decreased the accumulation of AGEs in muscle and partially relieved disuse muscle atrophy. In short, disuse muscle atrophy is thought to be induced by increased RAGE-dependent glycative stress.

Glycative stress as an inducer of exercise resistance

There is no doubt that exercise is a powerful health-promoting biological stimulus. Indeed, habitual exercise is also effective in reducing glycative stress [18, 19]. However, it is also true that there are individual differences in the health-

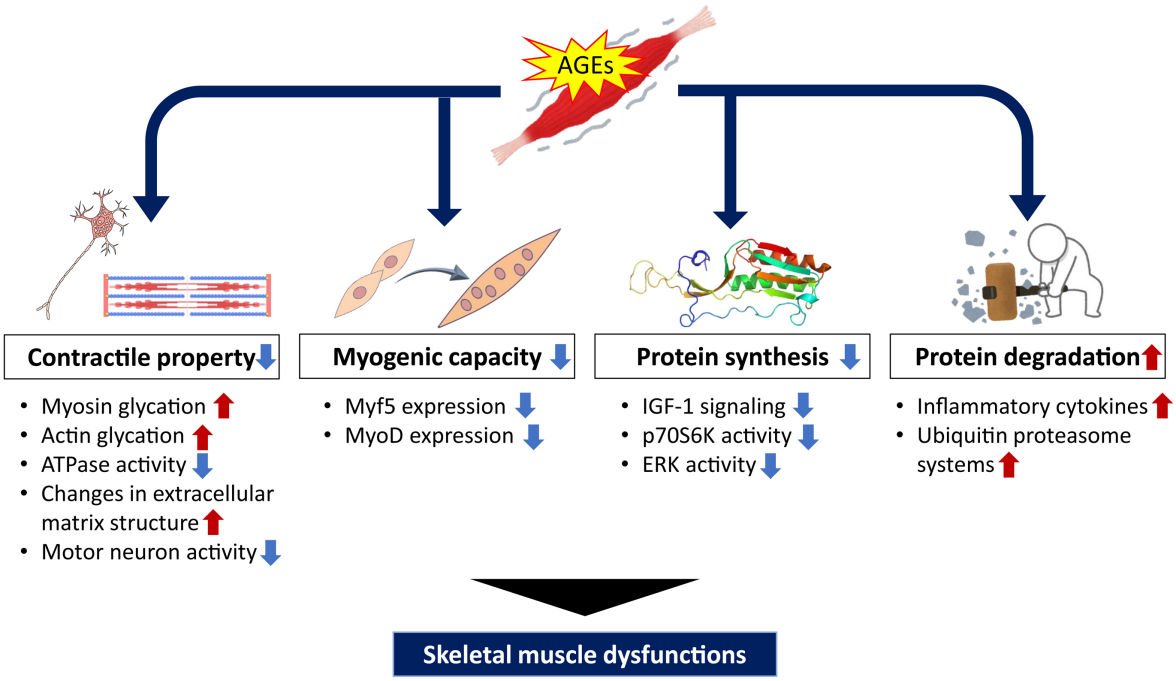

Fig. 2. **Molecular mechanisms underlying AGEs-induced muscle dysfunctions.**
Myf5, myogenic factor 5; MyoD, myogenic differentiation 1; IGF-1, insulin-like growth factor 1; p70S6K, 70kDa ribosomal protein s6 kinase; ERK, extracellular signal-regulated kinase.

promoting effects of exercise. Concurrently, a wide range of individual differences are observed among diabetics and the elderly, and it is known that about one out of every five people is unable to obtain sufficient exercise benefits [20-23]. Such a condition in which it is difficult to obtain the benefits of exercise, namely the condition in which physical adaptation to exercise is difficult to occur, is called "exercise-resistance", and those who are less likely to develop it are called "non-responder". The factors thought to mediate exercise resistance include congenital factors, *e.g.*, age, race, genetic predisposition, and acquired factors, *e.g.*, type and intensity of exercise, dietary habits, sleep habits, insulin sensitivity [20, 23]. Their definitions, however, are not clear.

For this factor, we focus on methylglyoxal (MGO), one of the products of the glycolytic system. MGO is a highly reactive dicarbonyl compound and is 20,000 times more reactive than glucose in glycation reactions [24]. It has also been reported that MGO induces mitochondrial dysfunction and inflammation in skeletal muscle cells and other tissues [25, 26], suggesting that it may be a factor that interferes with normal adaptive changes in the body. In our study in which MGO-administered mice underwent spontaneous running training for 4 weeks, the increase in mitochondrial respiratory chain complexes in skeletal muscle associated with exercise training was suppressed, despite no difference in locomotor activity compared to control mice that did not receive MGO [27] (***Fig. 3***). Also, the same was true for peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) expression, a master regulator of mitochondrial biosynthesis, and citrate synthase activity. This means that mitochondrial adaptation is less likely to occur during exercise in the presence of higher-than-normal levels of MGO. Other findings include a broad attenuation of adaptive responses induced by exercise, such as increased phosphorylation of insulin signaling molecules, increased expression of heat shock protein (HSP72), and increased expression of glyoxalase 1, a MGO-metabolizing enzyme. Although the molecular mechanism by which MGO causes such exercise resistance is not clear, this is the first evidence that glycative stress may influence the health-promoting effects of exercise.

Our results on the effects on strength training are also interesting. In a mouse muscle training model in which compensatory hypertrophy of the plantaris muscles of the lower limb was induced by synergist muscle ablation, the administration of glyceraldehyde-derived AGEs (0.5 mg/g/day) once a day for one week before treatment resulted in inhibition of compensatory muscle hypertrophy and increase in myonuclei [28]. This means that AGEs have exercise resistance properties that interfere with the effects of muscle training. Unexpectedly, a part of mice treated with AGEs showed disruption of muscle cell membranes with muscle hypertrophy (Egawa et al., unpublished data). In a study using cultured skeletal muscle cells, it was also confirmed that the addition of AGEs causes weakening of muscle cell membranes, suggesting that glycative stress causes exercise resistance and concurrently damages muscle cell structure.

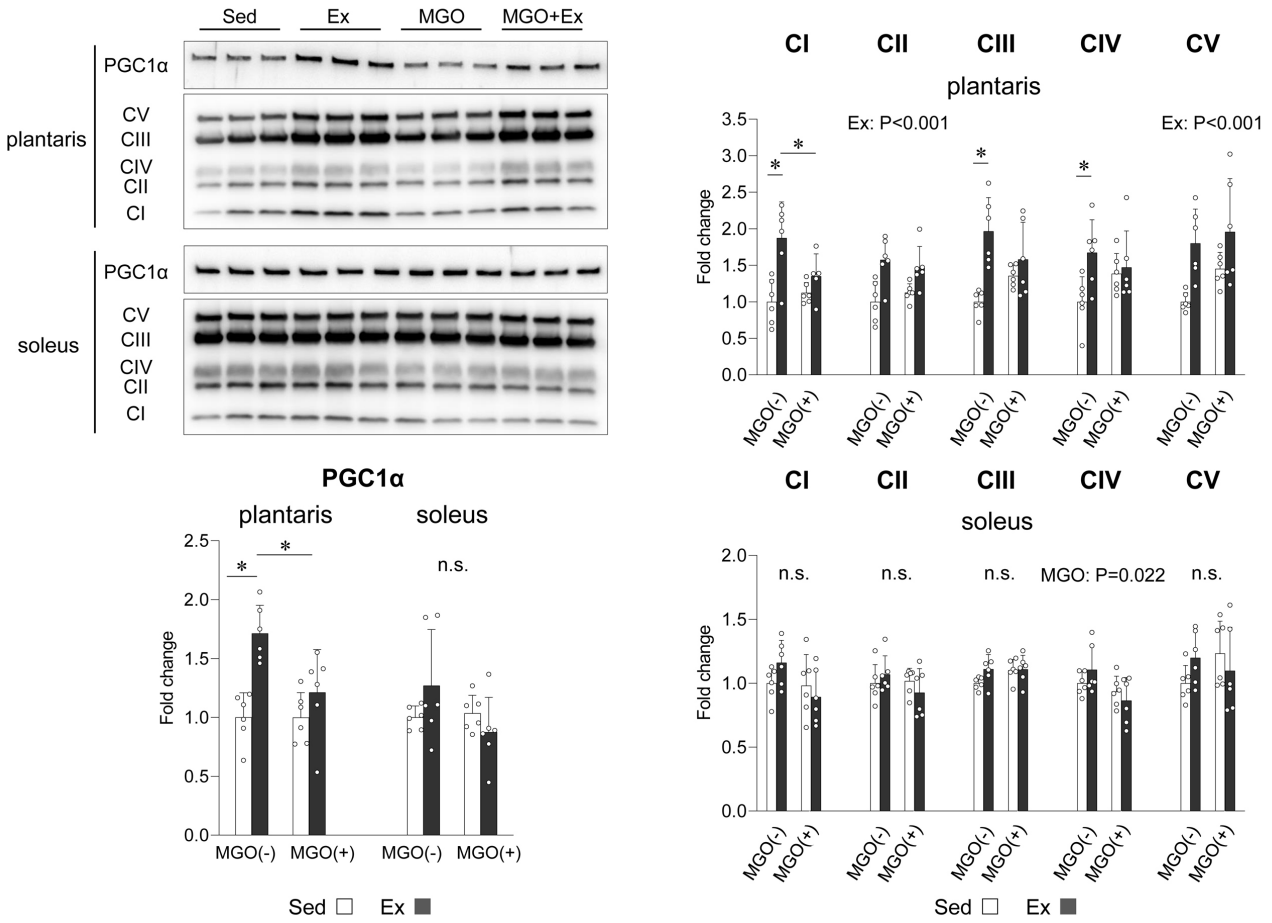

Fig. 3. **Methylglyoxal suppresses exercise-induced mitochondrial adaptations in skeletal muscle.**

Methylglyoxal (MGO) intake (1% drinking water) suppressed 4-week voluntary exercise-induced upregulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α) and mitochondria complex proteins (CI, CII, CIII, CIV, and CV) in plantaris muscle but not in soleus muscle. Data are presented as mean ± SD (n = 6 per group). Individual data points are indicated on the bar graph. Representative immunoblots are shown. Statistical significance was analyzed using two-way ANOVA with exercise and MGO treatment as main factors. *: $P < 0.05$ with simple effects tests, n.s.: not significant. Sed, sedentary control group; Ex, voluntary exercise group. This figure was adapted from Egawa et al.[27] with permission of the publisher.

Summary and conclusion

Musculoskeletal diseases, as typified by sarcopenia, are important factors that lead to conditions requiring long-term care. As an endocrine organ, skeletal muscle communicates with various organs throughout the body to maintain physiological functions. Namely, quantitative and qualitative deterioration of skeletal muscles leads to deterioration of the entire body. As shown in this text, glycative stress appears to adversely affect skeletal muscle regardless of age. We speculate that glycative stress in skeletal muscle, which begins in youth, causes continuous and gradual damage to metabolic molecules and muscle cell structures, and that this damage accumulates in old age, eventually leading to muscle atrophy and loss of muscle function. Therefore, countering glycative stress is an issue that should be addressed from young adulthood, not from middle age. The first strategy to counteract this stress in skeletal muscle would be exercise. However, since glycative stress causes exercise-resistance, exercise under increasing stress may not be sufficiently effective (***Fig. 4***). Fortunately, in our report, muscle strength training three times a week for 12 weeks in male university students showed a muscle-strengthening effect regardless of their glycative stress status [29]. In conclusion, expectedly, taking measures against glycative stress centered on exercise from young age will lead to the prevention of glycative stress-related diseases that become apparent in old age.

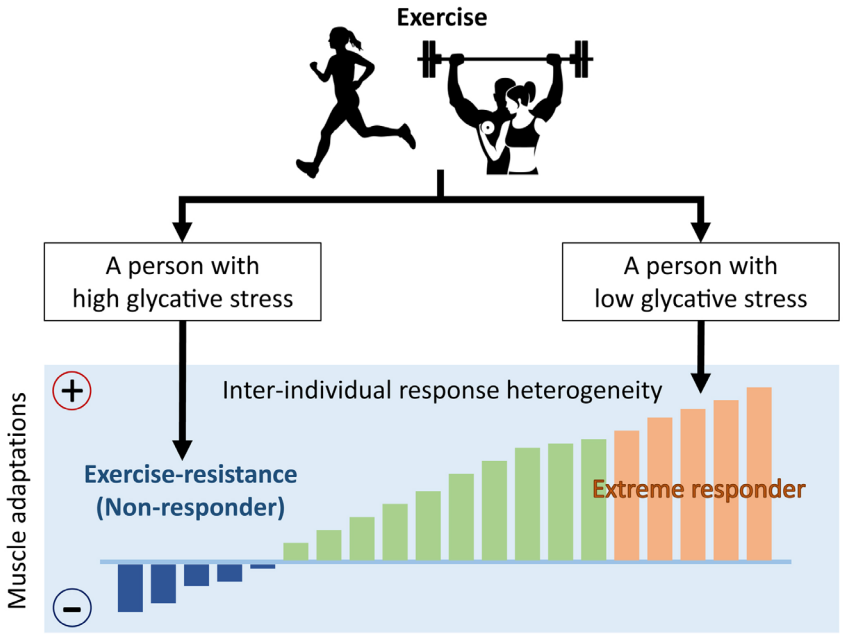

Fig. 4. **Possible involvement of glycative stress in exercise resistance.**
Exercise-induced skeletal muscle adaptations may not occur in some cases, a condition known as exercise-resistance (also called non-responder). Exercise-resistance means that adaptive responses driven by exercise are diminished due to the heterogeneity of factors such as endogenous factors (age, sex, etc.), exogenous factors (exercise intensity, duration, etc.), and molecular responses (proteins, genes, metabolites, etc.). Glycative stress may be a new exogenous factor that reflects exercise-resistance.

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Conflict of interest declaration

All authors declare that they have no conflicts of interest.

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