Glycative Stress Research

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Review article

Association between glycative stress, frailty, and sarcopenia

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Abstract

Frailty is a physical condition where physiological reserve declines and vulnerability to various stresses advances. The concept of frailty not only means the decline of physical functions, but also the comprehensive fragility of the elderly, which includes mental and psychological elements and also social elements such as solitary living and economic hardships associated with aging. The condition where muscle mass decreases and muscle strength declines with aging is called sarcopenia and is regarded as an important constitutional element of frailty. Multiple clinical studies show that sarcopenia develops in association with glycative stress from advanced glycation end products (AGEs) and leads to frailty. In the case of diabetes, it is considered that the formation and accumulation of AGEs are escalated by a chronic hyperglycemic state and oxidative stress which results in the pathological conditions of frailty and sarcopenia escalating. Whether or not frailty can be improved by suppressing glycative stress such as depletion of AGEs is an issue that should be investigated in the future.

***KEY WORDS*:** advanced glycation end products (AGEs), carboxymethyl-lysine (CML), frailty, sarcopenia, skin autofluorescence (SAF)

Introduction: Frailty and sarcopenia

In a super aged society, where further growth in the elderly population is expected, preventive care has become more and more important. Because functional decline in older adults may require the need for long-term nursing care, resulting in the robust increase in social medical expenses. The condition where physiological reserve declines with the advance of age and individuals become vulnerable to various stresses is defined as "frailty." As for the processes leading to the conditions requiring long-term care, there is a disease model related to disease and injury. Another model is a frailty model passing through the period of frailty, which is the period of preventive care (***Fig. 1***)[1]. Frailty is reversible; therefore, early and appropriate intervention is considered to prevent the conditions of requiring long-term care, lack of independence, falling, fracture and death.

The concept of frailty means not only the decline of physical functions, but also the comprehensive fragility of the elderly including mental and psychological elements as well as social elements such as solitary living and economic hardships associated with aging (***Fig. 2***)[2]. Meanwhile, the age related condition where muscle mass decreases and muscle strength declines is called sarcopenia[3]. Sarcopenia is regarded as an important constitutional element of physical frailty. Generally, Fried's frailty criteria firstly described in 2001 is used for diagnosis of physical frailty. In the case under three or more of the five factors of unintentional weight loss, self reported exhaustion, low physical activity, slow walking speed and weak grip strength, individuals are diagnosed as frailty[4]. Meanwhile, the cases of sarcopenia are diagnosed based on the low muscle mass in addition to the weak grip strength and/or slow walking speed (***Table 1***)[5]. The weak grip strength and slow walking speed are overlapped between both criteria of frailty and sarcopenia because frailty and sarcopenia are overlapped concepts, and many cases of frailty are considered being complicated with sarcopenia[6].

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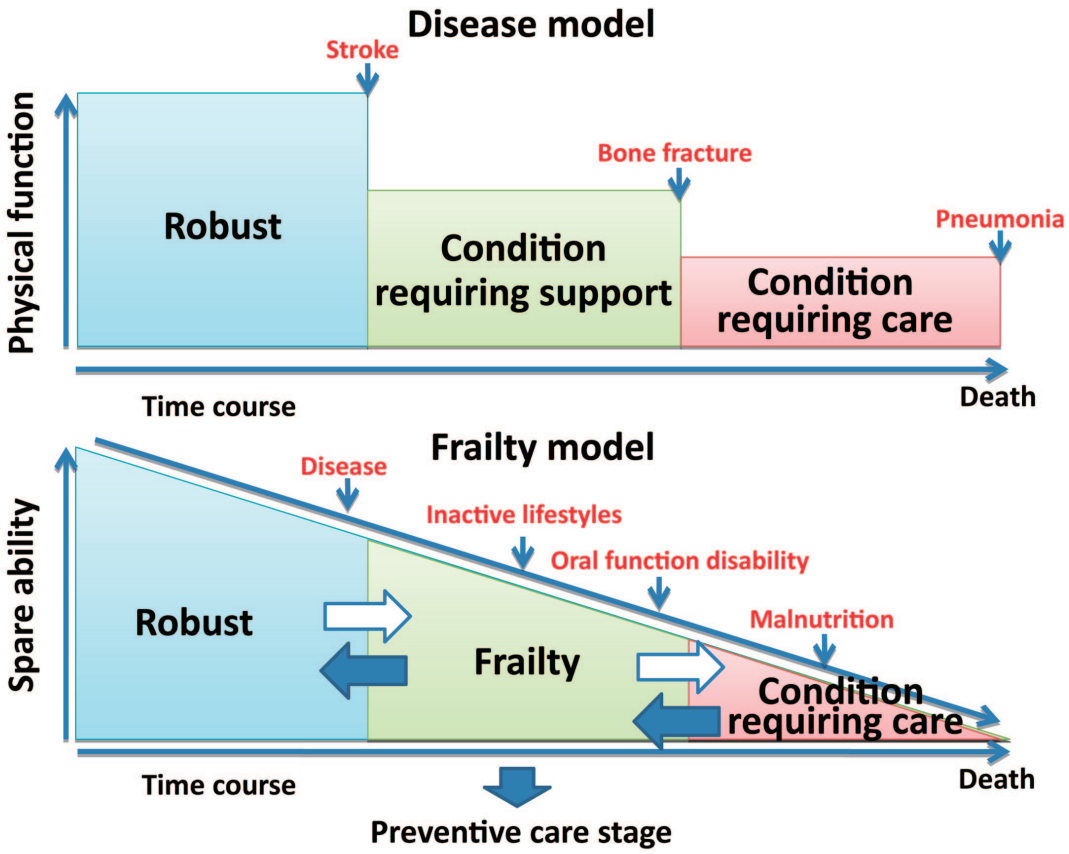

Fig. 1. **Disease model and frailty model which lead to the condition needed nursing care.**

By a conventional idea, the process declining of physical function from conditions needed nursing care to death in the elderly has been thought as if the condition was falling step by step, triggered by disease (the disease model). The frailty model, on the contrary, is a model in which the spare ability against a various stress declines successively. The frailty is located as a pre-stage of nursing care needed conditions from an initial stage of independence, then progresses associated with diseases, inactive lifestyles and declining oral function, leading to the nursing care needed conditions and eventually to death. In this model, the time course from the independent condition to frailty, needed nursing care, is considered to be reversible, thus it is possible to recover from the frailty condition if appropriate intervention is conducted. The figure is quoted from Reference 1.

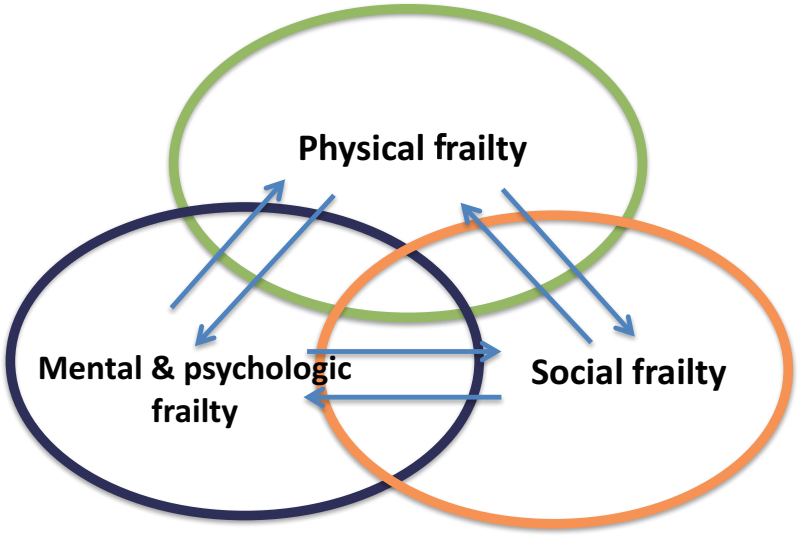

Fig. 2. **The versatility of frailty.**

The frailty consists of various components including physical factors, mental and psychological factors and social factors. They are partially overlapped and interacted with forming a "vicious cycle." The figure is quoted from Reference 2.

Table 1. Diagnosis of sarcopenia.

① Low SMI	Male: <7.0 kg/m² Female: <5.7 kg/m² (BIA) : <5.4 kg/m² (DXA)
② Weak grip strength	Male: <26 kg, Female: <18 kg
③ Slow walking speed	Average walking speed <0.8 m/s

① only → Pre-sarcopenia
① and (② or ③) → Sarcopenia

Diagnosis by Asian Working Group for Sarcopenia (AWGS). The figure is quoted from Reference 5. SMI, skeletal muscle index; BIA, bioimpedance analysis; DXA, dual-energy X-ray absorptiometry.

Frailty, sarcopenia and advanced glycation end products (AGEs)

In pathological conditions such as frailty and sarcopenia, fatty tissues are replaced in the parts where muscles shrank, and as a result, it is considered that this phenomenon is accompanied with glycative stress and chronic inflammation in the same way as observed in increased visceral fat tissue of patients with metabolic syndrome.

In vivo protein is uniformly glycated with aging and forms aging protein with a high risk of organ failure called advanced glycation end products (AGEs). The formation and accumulation of AGEs are known to be accelerated by glycative stress and chronic inflammation. It is well known that glycative stress from AGEs is involved not only in diabetes accompanied by a chronic hyperglycemic state, but also various age-related diseases including complications of cardiovascular disease, osteoporosis, Alzheimer's disease, cancer and non-alcoholic steatohepatitis (NASH). In the elderly with frailty and sarcopenia where oxidative stress and chronic inflammation have also advanced, AGEs are considered to exacerbate pathological conditions of frailty and sarcopenia.

Haus *et al*. quantified pentosidine, a type of AGEs, in muscle targeting 20 young subjects (mean 25 ± 3 years) and 22 elderly subjects (mean 78 ± 6 years, age range of 70 ~ 93). They reported that pentosidine levels of the elderly group with mean age of 78 were higher than those of the young group with mean age of 25 and that the accumulation of AGEs was correlated to muscle weakness with aging (***Fig. 4***)[7].

In the Women's Health and Aging Study I (WHAS I) targeting 559 older women with serious disability living in Baltimore, the serum levels of carboxymethyl-lysine (CML), a kind of AGEs, were divided into four quantiles and their relationship with grip strength was investigated.

The grip strength of the quantile of the highest CML was lower than those of other three quantiles (***Table 2***)[8]. However, no significant relationship between grip strength and the soluble receptor for AGEs (sRAGE) or the endogenous soluble receptor for AGEs (esRAGE) was recognized. Therefore, the mechanism by which glycative stress starting from AGEs is involved in the decrease in muscle strength has not been clarified yet.

Regarding the relationship between AGEs and walking speed, in the InCHIANTI study targeting the elderly older than 65 years old conducted in Italy, they were examined by being divided into four quantiles based on CML levels. By using a multiple logistic regression model, it was shown that the walking speed of the quantile of the highest CML was lower than those of other three quantiles. There remained significant differences even after the data were corrected for age, education history, cognitive function and smoking. What is noteworthy is that a significant relationship was observed between CML and walking speed even after patients with diabetes were excluded, and it showed that the high levels of CML are an independent risk factor of the decrease in walking speed (***Table 3***)[9].

It was reported that in the extensor digitorum longus (EDL) of Fischer344 Brown Norway (F344BNF1) hybrid rats, more AGE accumulation was recognized in aged rats than in young rats by immunohistological staining[10].

As above, although there are multiple reports regarding AGEs and sarcopenia, only a few reports have been presented concerning the relationship between AGEs and frailty with a broader concept than sarcopenia. Whitson *et al*. followed up 3,373 participants in the Cardiovascular Health Study for 14 years, where CML levels were measured during the period from 1996 to 1997, and the relationship between the onset of frailty meeting the criteria that Fried described above and CML levels were examined by logistic regression analysis. The high levels of CML in the cases of males significantly increased the risk of developing frailty (odds ratio, 1.30 per standard deviation; 95% confidence interval, 1.14 ~ 1.48; $p < 0.001$, ***Table 4***)[11]; however, the significant difference disappeared after the data were corrected for cognitive function, kidney function, complications in rheumatoid arthritis and others. In the cases of females, no significant difference was observed between the onset of frailty and CML. Regarding gender differences in the relationship among frailty, sarcopenia and AGEs, there remain many issues to be solved in the future.

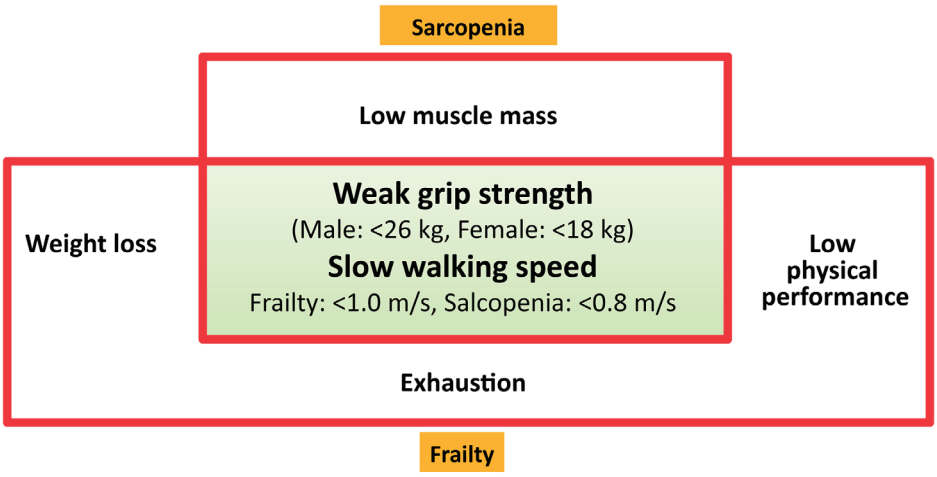

Fig. 3. **The interrelationship between frailty and sarcopenia.**

Standard values for walking speed are rather different in diagnosis between frailty and sarcopenia, however, the items are common for weak grip strength and low waking speed. The concepts of two diseases are supposed to be overlapped. The figure is quoted from Reference 6.

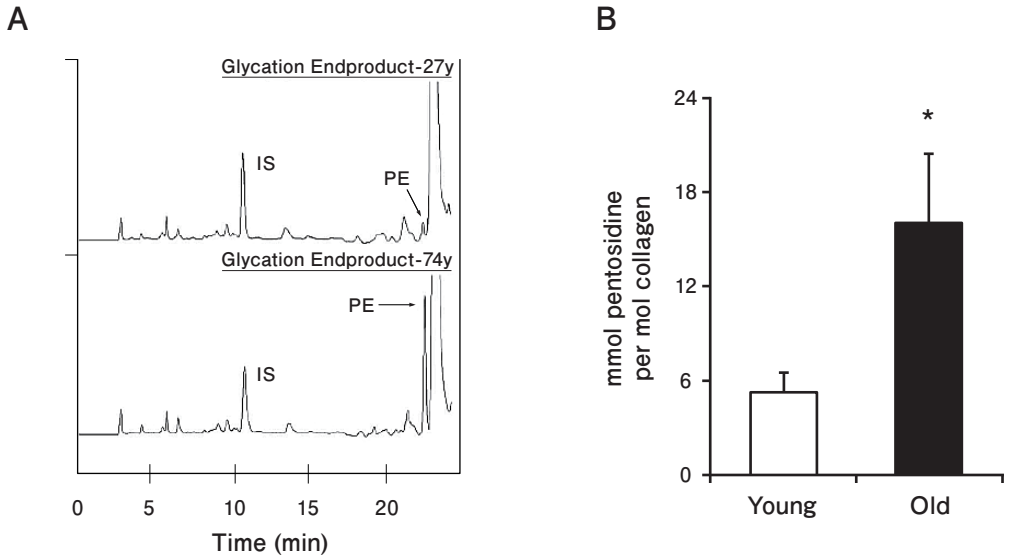

Fig. 4. **Comparison of pentosidine (one of AGEs) between the young and old.**

A: Representative chromatographs for each of the connective tissue assays performed in human skeletal muscle. Aging samples displayed increases in AGEs. **B:** Intramuscular AGEs described by the concentration of pentosidine. *p < 0.05 from young. AGEs, advanced glycation end products; PE, pentosidine. The figures are quoted from Reference 7.

Table 2. Association of grip strength with CML, sRAGE and esRAGE.

Characteristics*	Beta	SE	p
Serum CML, highest quartile versus lower three quartiles	-1.31	0.61	0.03
Serum sRAGE (ng/mL)	0.44	0.27	0.10
Serum esRAGE (ng/mL)	1.16	1.30	0.38

The table shows Multivariate linear regression models of serum CML, sRAGE, and esRAGE with grip strength. *Separate models were fit for serum CML, sRAGE, and esRAGE, and each model was adjusted for age, race, BMI, Mini-mental State Examination score <24, depression, and diabetes. Multi regression analysis adjusted for age, race, cognitive function, depression and diabetes reveals that the gripping strength of the quantile of the highest CML was significantly lower than that of other three quantiles. The gripping strength is not significantly correlated with sRAGE or esRAGE. The table is quoted from Reference 8. CML, carboxymethyl-lysine; RAGE, receptor for advanced glycation end product; sRAGE, soluble RAGE; esRAGE, endogenous secretory RAGE; BMI, body mass index; SE, standard error.

Table 3. Association of plasma CML with walking speed.

		Model adjusted for age, sex			Model adjusted for age, sex, education, smoking, MMSE			Model adjusted for age, education, smoking, MMSE, depression, and chronic diseases**		
		OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Plasma CML***	All participants (n = 944)	1.51	1.10-2.25	0.04	1.52	1.01-2.28	0.04	1.6	1.02-2.52	0.04
	Participants without diabetes (n = 828)	1.76	1.13-2.73	0.01	1.75	1.12-2.74	0.01	1.87	1.15-3.04	0.01

Multivariate logistic regression models of the relation of plasma CML with slow walking speed * in adults, aged >65 years and above, in the InCHIANTI Study. * Slow walking speed defined as the lowest quintile of walking speed. **Chronic diseases were hypertension, heart failure, peripheral artery disease, stroke, diabetes, and renal insufficiency. ***Odds ratios expressed per for highest quartile of plasma CML versus lower three quartiles in separate logistic regression models in which slow walking speed is the dependent variable. Multiple logistic regression model reveals that the risk lowering the walking speed is significantly marked in the quantile of the highest CML. The risk remains significant after adjustment for age, education history, cognitive function, smoking and other chronic diseases. The significant correlation is noted between the walking speed and CML except for diabetes. The table is quoted from Reference 9. CML, carboxymethyl-lysine; OR, odds ratio; CI, confidence interval; MMSE, Modified Mini-Mental State examination.

Table 4. Association of CML with frailty onset.

Model	Women (n = 2,007)			Men (n = 1,332)		
	OR	95% CI	p	OR	95% CI	p
Model 1	1.06	0.91-1.23	0.44	1.30	1.14-1.48	<0.001
Model 2	1.06	0.90-1.24	0.47	1.24	1.07-1.45	0.004
Model 3	0.91	0.77-1.07	0.27	1.10	0.92-1.32	0.29

Results shows association of serum CML (per SD increase [225 mg/mL]) with frailty in women and men. Model 1: age, sex, race, field center, and education. Model 2: above plus BMI, diabetes, alcohol consumption, smoking status, total cholesterol, albumin, and status of hypertension, CHD, CHF, stroke, and claudication. Model 3: above plus arthritis, Modified Mini-Mental State examination (MMSE) score, and eGFR. CML, carboxymethyl-lysine; OR, odds ratio; SD, standard deviation; BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate. The table is quoted from Reference 11.

Relationships between frailty, sarcopenia and AGEs from diabetes

In the case of diabetes, it is considered that the formation and accumulation of AGEs are escalated by a chronic hyperglycemic state and oxidative stress, and the pathological conditions of frailty and sarcopenia are advanced.

Kalyani RR *et al*. followed up 984 patients with diabetes (25 ~ 96 years) who participated in a Baltimore Longitudinal Study of Aging, for a period of 7.5 years. They were divided into four quantiles based on HbA1c levels. This study demonstrated that blood glucose was related to knee extensor muscle strength and leg lean mass, and that the higher HbA1c was, the lower both muscle strength and muscle mass were [12]. This study also revealed that the development of diabetic peripheral neuropathy affected muscle strength and muscle mass.

Recently, Mori *et al*. reported that, in the investigation of 36 patients with type 1 diabetes, AGEs levels measured by skin autofluorescence (SAF) had a significant negative relationship with knee extensor muscle strength. However, no significant relationship existed between AGEs and skeletal muscle mass index (SMI: skeletal muscle divided by the square of height) and, when using muscle mass and muscle strength, the results did not always coincide with each other (***Fig. 5***) [13].

Meanwhile, Kato *et al*. measured the SAF of 132 participants in an anti-aging dock (medical check-up) (70 males, 62 females, mean 59 ± 11 years). They found that SAF in the group with low-level SMI was at the higher level and that even after the data of high-level SAF were corrected for age, gender, HDL-C, creatinine and blood glucose using multivariate logistic regression analysis, a significant relationship between high-level SAF and low-level SMI was recognized (odds ratio, 15.7; 95% confidence interval, 1.85 ~ 133.01; p = 0.012, ***Table 5***) [14]. In addition, a significant relationship between SAF and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in urine, a marker of oxidative stress, was recognized in this study, suggesting that oxidative stress contributes, at least in part, to the relationship between the decrease in muscle mass and the accumulation of AGEs (***Fig. 6***) [14].

Conclusion

The relationship between oxidative stress exemplified by AGEs and frailty was organized with emphasis on sarcopenia based upon recent reports. Frailty means not only physical frailty represented by weight loss and muscle

weakness but also has the broader concept including mental, psychological and social frailties. Glycative stress has been reported relating with almost all age-related diseases such as diabetes, cardiovascular complications, osteoporosis, Alzheimer's disease and cancer. It is easily understood that all of these disease states exacerbate frailty in various directions. Diabetes, in particular, is recognized as synergistically forming a vicious cycle between frailty and itself. In addition to direct mechanisms such as chronic inflammation and oxidative stress, the progress of diabetic complications such as nephropathy, neuropathy, and retinopathy accelerates the progression of sarcopenia.

Meanwhile, it is known that existing anti-diabetic agents including DPP-4 (dipeptidyl peptidase-4) inhibitors and PRAR-γ (peroxisome proliferator-activated receptor γ) agonists have the action of inhibiting AGEs-related signaling pathways [15,16]. However, it has not been well examined whether these drugs can reduce the incidence of the frailty, that is supposed to be reversible in diabetic patients. So further clinical and basic investigations are required to clarify this issue.

Conflict of interest

The authors declare no conflicts of interest in this study.

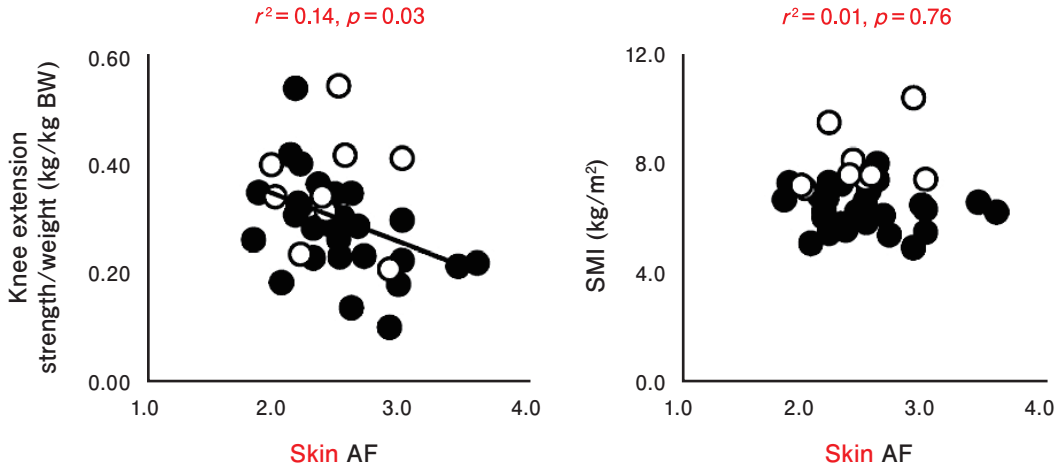

Fig. 5. **The correlation between knee extension strength/weight, skeletal muscle mass index (SMI) and skin autofluorescence (AF) in men (open circle) and women (closed circle).**

SAF shows a significantly negative correlation to knee extension strength, while no correlation to SMI. Results of muscle mass and strength are not coincident. The figures are quoted from Reference 13.

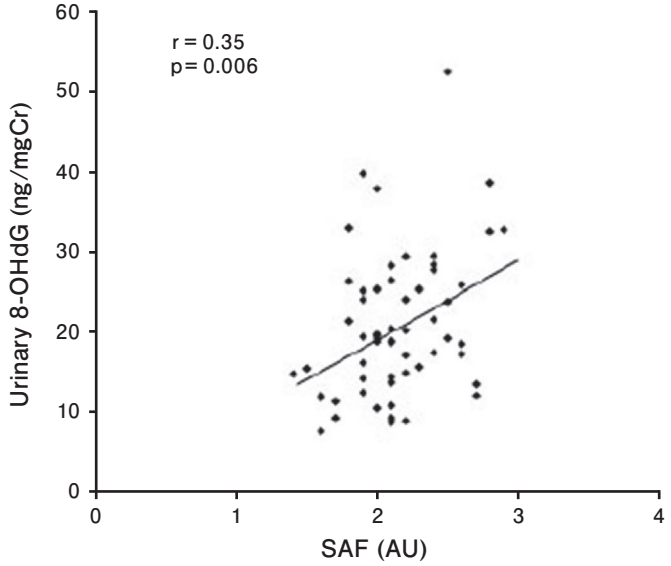

Fig. 6. **Relationship between SAF and urinary 8-OHdG.**

SAF, skin autofluorescence; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; Cr, creatinine. The figure is quoted from Reference 14.

Table 5. Multivariate logistic regression analysis of low SMI.

Variable	OR	95% CI	p
Age	0.97	0.92-1.04	0.455
Sex	0.92	0.15-5.47	0.937
HDL-C	1.03	0.98-1.09	0.271
Cr	1.14	0.01-96.20	0.950
FBS	0.96	0.91-1.02	0.202
SAF	15.7	1.85-133.01	0.012

Multivariate logistic regression analysis of low SMI. Multivariate logistic regression analysis using the forward selection method with likelihood ratio was carried out for age, sex, HDL-C, Cr, FBS and SAF as exploratory variables, and low SMI as a dependent variable. SMI, skeletal muscle index; OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; Cr, creatinine; FBS, fasting blood glucose; SAF, skin autofluorescence. The table is quoted from Reference 14.

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