Advanced glycation end products in skeletal muscle health and sarcopenia: A systematic review of observational studies

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\begin{abstract}
Background: Advanced glycation end products (AGEs) and AGEs receptor (RAGE) may play a role in sarcopenia.
This systematic review evaluated the associations between AGEs measured in tissues (skin) by autofluorescence (SAF) and/or circulation (blood, urine) and muscle health outcomes (strength, mass, function) and sarcopenia in observational studies.

Methods: MEDLINE, Embase, Scopus and Web of Science were searched for studies reporting associations between AGEs and muscle-related outcomes in community-dwelling adults aged $\geq 30$ years (until March 2022).

Results: Fourteen cross-sectional and one prospective study were included in the narrative summary. SAF was negatively associated with muscle strength, mass, and physical functioning in adults aged $\geq 30$ years (four studies), and muscle mass (three studies), strength, and sarcopenia (one study) in adults aged $\geq 65$ years. Circulating AGEs were negatively associated with muscle strength and physical functioning (four studies) and predicted the risk of walking disability (one prospective study), and sarcopenia (one study) in older adults. The role of RAGE in muscle health was inconclusive.

Conclusions: SAF and circulating AGEs were negatively associated with muscle-related outcomes in adults aged $\geq 30$ years in cross-sectional studies. This finding should be confirmed in well-designed prospective studies investigating sarcopenia, as AGEs represent a potentially modifiable target for intervention.
\end{abstract}

1. Introduction

Skeletal muscle is one of the most abundant and dynamic tissues in the human body and is involved in multiple body functions. These include energy production for locomotion and physical functioning, posture maintenance, breathing, heat production, and whole-body metabolism, where it serves as a reservoir of protein (amino acids) and carbohydrates (glucose) for other organs and during severe disruption of metabolic homeostasis, such as injury and chronic disease (Frontera and Ochala, 2015; Porter et al., 1995). Comprising about 40\% of total body weight and 50–75\% of total body protein (Frontera and Ochala, 2015), skeletal muscle experiences a profound change during ageing (Porter et al., 1995). Although highly plastic and responsive to a range of internal and external factors (e.g., diet, exercise, hormonal imbalance, inflammation) across the life course, the main change in muscle with ageing is muscle atrophy that starts in early mid-adulthood and accelerates in later life (Mitchell et al., 2012; Porter et al., 1995). Specifically, longitudinal studies have shown a rapid loss of muscle mass in older adults aged $\geq 75$ years at an annual rate of 0.64–0.70\% in men and 0.80–0.98\% in women (Mitchell et al., 2012), which is accompanied by even more pronounced loss of muscle strength, estimated to be 3–4\% in men and 2.5–3\% per year in women (Mitchell et al., 2012).

1.1. Muscle health with ageing and sarcopenia

Accelerated, generalised loss of muscle mass and function (strength, power, physical performance) above the rate of normal ageing is termed sarcopenia (reviewed in Cruz-Jentoft and Sayer, 2019). Current
Advanced glycation end products

Advanced glycation end products (AGEs) are a heterogeneous group of compounds and related adducts produced by glycation of macromolecules (protein, lipids, DNA) via the Maillard reaction. Protein glycation is a multistep process that happens spontaneously within and outside cells and involves non-enzymatic formation of covalent bonds between a carbonyl group of reducing sugars (e.g., glucose, fructose, ribose) and amino acids in proteins (reviewed in Chaudhuri et al., 2018; Gugliucci, 2017; Ramasamy et al., 2005; Reyaert et al., 2016; Rowan et al., 2018; Semba et al., 2010b). The possible involvement of glycation in pathophysiology of musculoskeletal ageing and disease has been discussed in several recent narrative reviews (e.g., Chen et al., 2018; Olson et al., 2021; Reyaert et al., 2018; Suzuki et al., 2022), including a critical appraisal of the current methodology for detection of AGEs and potential therapeutic strategies (Suzuki et al., 2022). However, a systematic review of evidence from observational studies about the role of glycation in muscle health and sarcopenia is lacking.

1.2. Advanced glycation end products

Advanced glycation end products (AGEs) are a heterogenous group of compounds and related adducts produced by glycation of macromolecules (protein, lipids, DNA) via the Maillard reaction. Protein glycation is a multistep process that happens spontaneously within and outside cells and involves non-enzymatic formation of covalent bonds between a carbonyl group of reducing sugars (e.g., glucose, fructose, ribose) and amino acids in proteins (reviewed in Chaudhuri et al., 2018; Gugliucci, 2017; Ramasamy et al., 2005; Reyaert et al., 2016; Rowan et al., 2018; Semba et al., 2010b). AGEs are ubiquitous and present in all body tissues and fluids with significant concentration of reducing sugars and their reactive metabolites (dicarboxyls), which cross-react with proteins in situ as a consequence of normal metabolism. Exogenous sources such as diet account for about 30% of in vivo AGEs in the circulation (i.e., dietary AGEs) although only 10% of dietary AGEs are absorbed through intestine, and one third of those are excreted via urine within 48 h. The remaining portion of circulating AGEs originates from defective glycosylation and insufficient clearance of AGEs, required to prevent AGE-related cytotoxicity (reviewed in Rowan et al., 2018). Depending on their composition and chemical properties (cross-linking and fluorescence), AGEs are categorised into: (a) fluorescent cross-linking AGEs (e.g., pentosidine), (b) non-fluorescent cross-linking AGEs (e.g., methylglyoxal-lysine dimers), and (c) non-cross-linking AGEs (e.g., N-carboxymethyl-lysine (CML)). Of those, pentosidine and CML are the most researched and abundant AGEs in human serum (or plasma), and foods. Because of the complexity and diversity of cross-linking AGEs, their chemical properties have not been fully elucidated (Chen et al., 2018; Rowan et al., 2018). For detection and quantification of the fluorescent AGEs accumulation in tissues, a non-invasive method using ultraviolet (UV) technology has been developed to detect AGEs in skin via skin autofluorescence (SAF) (Meerwaldt et al., 2004). SAF has been used as a proxy for accumulated tissue-levels of AGEs and validated against collagen-linked fluorescence and specific skin AGEs from skin biopsies (e.g., pentosidine, CML, and N-carboxymethyl-lysine (CML) in patients with and without diabetes mellitus (Meerwaldt et al., 2004).

AGEs affect protein structure, function, and degradation, and disrupt regulation of the pathways responsible for protein signalling and quality control (Rowan et al., 2018), thus contributing to the ageing phenotype (Chaudhuri et al., 2018; Gugliucci, 2017; Ramasamy et al., 2005; Semba et al., 2010b). They also play a role in the pathogenesis of age-related diseases, including diabetes mellitus, Alzheimer’s disease, coronary heart disease and cancer via inflammation and oxidative stress (Chaudhuri et al., 2018; Gugliucci, 2017; Ramasamy et al., 2005; Reyaert et al., 2016; Rowan et al., 2018; Semba et al., 2010b). Furthermore, the receptor for AGE (RAGE) plays an important role in amplifying inflammatory responses in vivo. Upon binding with RAGE, a number of AGEs and their adducts (e.g., arginine and lysine modifications via methylglyoxal) activate pro-inflammatory signalling pathways (Chaudhuri et al., 2018; Reyaert et al., 2016; Riuuzzi et al., 2018) with direct and indirect biological consequences, including enhanced reactive oxygen species (ROS) production, reduced oxidative defense, impairment of the DNA repair mechanism, and altered biological activity of AGE-modified molecules (reviewed in Reyaert et al., 2016; Rowan et al., 2018). Conversely, truncated soluble versions of RAGE (sRAGE and endogenous soluble RAGE (esRAGE)) have been detected in several tissues and plasma, and are proposed to have scavenging capacity by serving as an extracellular decoy receptor for AGEs (Reyaert et al., 2016; Riuuzzi et al., 2018).

Similarly, several adverse biological consequences of AGEs and the AGE-RAGE signalling cascade have been proposed to play a role in skeletal muscle ageing and sarcopenia (Chaudhuri et al., 2018; Riuuzzi et al., 2018). Proposed mechanisms include AGEs effect on the structure and function of long-lived proteins such as collagen in the extracellular matrix by forming cross-links (Gautieri et al., 2017; Haus et al., 2007; Olson, 2021). AGEs may cause intracellular damage to key molecules and organelles (e.g., mitochondria) by amplifying inflammation (Gautieri et al., 2017; Riuuzzi et al., 2018; Suzuki et al., 2022) and oxidative stress via the RAGE-mediated intracellular signalling (Chaudhuri et al., 2018; Reyaert et al., 2016; Rowan et al., 2018; Ott et al., 2014) in muscle cells. Furthermore, AGEs may weaken other components of the musculoskeletal system (bone, cartilage, tendons, ligaments) through similar pathways, exacerbating, for example, stiffness and rigidity of connective tissues, apoptosis of the target cells, and increased expression of pro-oxidant and pro-inflammatory mediators, thus indirectly affecting muscle health and function in older adults (reviewed in Gautieri et al., 2017; Suzuki et al., 2022). Taken together, AGEs may play an important role in aetiology of sarcopenia but currently there is limited evidence from epidemiological studies.

1.3. Objective

To date, there has been only one systematic review of studies of the relationships between AGEs (tissue-bound and in circulation) and...
muscle-related outcomes (including muscle strength, mass, physical function), which was based on eight observational studies of community-dwelling adults and diabetes patients (reviewed studies up to January 2016) (Drenth et al., 2016). The objective of this review is to update the evidence, including the considerable further research on the role of AGEs in muscle health and sarcopenia in community-dwelling older adults published since (Drenth et al., 2016). The focus of the review was on observational studies with healthier participants that were not conducted in specific clinical populations.

2. Methods

2.1. Protocol and registration

This review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero) on 6 August 2020 as CRD42020202640.

2.2. Eligibility criteria

The inclusion and exclusion criteria for the selected studies are described in Appendix 1. Specifically, we included observational studies (cross-sectional and prospective longitudinal) with community-dwelling adults aged ≥ 30 years that examined at least one of the outcome measures (muscle strength, mass, function [including survey instruments with physical functioning domains such as the 12- or 36-Item Short Form Survey, the SF-12 or SF-36], and sarcopenia) in relation to at least one AGE, with concentrations assessed in tissues (skin, nails, hair, muscle tissue) or circulation (plasma, serum, urine). We excluded studies from clinical settings with specific clinical populations (e.g., diabetes mellitus, Alzheimer’s disease, amyotrophic lateral sclerosis, Duchenne muscular dystrophy, osteoarthritis, renal disease), and those examining dietary AGEs (from foods or in blood after a dietary intervention). Studies had to include at least 20 observations/participants in each group (exposed versus comparator group).

2.3. Information sources and search strategy

Electronic searching of four databases (MEDLINE, Embase, Scopus and Web of Science) was performed from the earliest date available up to 2nd March 2022. Reference lists from included studies and previously published review articles were also examined for potentially eligible papers.

The search strategy included a combination of free-text and MeSH terms relating to ‘AGEs’ and ‘muscle/sarcopenia’ which were developed through screening of previously published articles (e.g., titles, abstracts, keywords). We purposely used a combination of sarcopenia-specific and broader terms relating to muscle and physical function in order not to miss relevant articles. Full search terms and the complete search strategy for four databases are described in Appendix 2.

2.4. Study selection

All retrieved records were independently screened by two reviewers (AG, CH), and duplicates removed. To identify relevant studies, all records were initially screened for eligibility by title and abstract based on the inclusion and exclusion criteria. Irrelevant studies were removed before the full texts of the remaining records were retrieved and assessed for eligibility. Any disagreements between reviewers (AG, CH) during the study selection process were resolved by discussion until full consensus, or by consulting a third reviewer (LD).

2.5. Data extraction and synthesis

Data were extracted from eligible studies into a custom-made spreadsheet by the lead author with a second investigator checking the extracted data for accuracy (CH/LD). We extracted the following data related to: (a) study design and location; (b) sample characteristics (sample size, mean age or age range, sex); (c) the type of AGE and method of assessment (e.g., SAF, enzyme-linked immunosorbent assay [ELISA]); (d) primary outcome measures (muscle health-related outcome such as muscle strength, mass, function, sarcopenia); (e) the strength of association between AGEs and muscle-related outcomes or sarcopenia (e.g., correlation coefficients [r], β coefficient, odds ratios [OR], risk ratios [RR], hazard ratios [HR]) in the exposed versus comparator group. For the studies not reporting any association coefficient, effect sizes (Cohen’s d) were calculated from the available data as described in Appendix 3. Extracted and calculated data items are presented in Table 1, and the main findings summarised in Table 2. Because of substantial heterogeneity among the studies selected for the review, no meta-analysis was conducted.

2.6. Quality assessment and risk of bias

Risk of bias for each included study was independently assessed by two authors (CH and LD) according to the Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2013). The studies were assessed as having low, moderate, or high risk of bias for the following domains: study participation, prognostic factor measurement, confounding measurement and account, outcome measurement, analysis, and reporting (Appendix 4). If one or more domains were evaluated as having a high risk, an overall ‘high’ risk score was assigned to the study. Any disagreements were resolved by discussion to reach consensus.

3. Results

3.1. Study selection

A modified version of a PRISMA diagram for the study selection process and the reasons for exclusion is presented in Fig. 1. A total of 998 records were identified through electronic and hand searches, and 615 were screened by title and abstract after the removal of duplicates. Thirty-one full-text articles were further assessed for eligibility against inclusion and exclusion criteria (Appendix 1) of which 16 were excluded. The predominant reason for articles being excluded was no relevant outcome measure reported in the studies. Fifteen observational studies (Dalal et al., 2009; Drenth et al., 2018; Ebert et al., 2019; Eguchi et al., 2021; Kato et al., 2017; Kim et al., 2018; Momma et al., 2011; Moriwaki et al., 2021; Tabara et al., 2019; Semba et al., 2010a; Sun et al., 2012; Waqas et al., 2022; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019) were included in the narrative synthesis (Fig. 1).

3.2. Risk of bias

Appendix 4 shows the risk of bias evaluation (low, moderate, high) for each included study across six criteria described above (Section 2.6) based on the QUIPS tool (Hayden et al., 2013). Fourteen studies were evaluated as having low risk of bias (Dalal et al., 2009; Drenth et al., 2018; Ebert et al., 2019; Kato et al., 2017; Kim et al., 2018; Momma et al., 2011; Moriwaki et al., 2021; Tabara et al., 2019; Semba et al., 2010a; Sun et al., 2012; Waqas et al., 2022; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019), and one as having high risk of bias (Eguchi et al., 2021).

3.3. Characteristics of the included studies

There were several sources of heterogeneity across the studies, including sample characteristics, AGEs type, and outcome measures. We
Table 1

Characteristics of the studies examining the association between advanced glycation end (AGE) products, muscle health and sarcopenia.

| Ref. | Study design and location | Sample characteristics | AGES type and methodology | Outcome | Results |
|------|--------------------------|------------------------|---------------------------|---------|---------|
| **Skin autofluorescence (SAF)** | | | | | |
| Momma et al. (2011) | cross-sectional; Tohoku, Japan; | adult healthy men; n = 232 with SAF measurement tertiles; median age (interquartile range) 46.0 (37.0-56.0) years; | SAF; AGE Reader (Diagnosticon, Groningen, The Netherlands); excluding those with skin reflection < 10%; in arbitrary units (AU); | muscle strength: grip strength (GS) and leg extension power (LEP); | (a) adjusted mean GS (kg) lower in higher tertiles of SAF: 44.5 (95% CI: 43.2-45.9) kg in T1; 42.0 (40.6-43.3) kg in T2; 41.7 (40.3-43.1) kg in T3; all p < 0.01; ES (T1 vs. T3) = 0.46 *; (b) adjusted LEP (W/kg) lower in higher tertiles of SAF: 17.8 (16.6-19.1) W/kg in T1; 17.5 (16.4-18.7) W/kg in T2; 16.0 (14.9-17.1) W/kg in T3; all p = 0.04; ES (T1 vs. T3) = 0.45 *; (c) higher levels of SAF in low BMI group: 2.4 ± 0.3 AU in low BMI (n = 31) versus 2.1 ± 0.3; p < 0.01 in normal BMI group (n = 101) (b) SAF independent risk factor for low BMI; OR = 15.70 (95% CI: 1.85-133.01), p = 0.01; (c) the AUC for SAF: 0.86, p < 0.01; at SAF cut-off 2.45 AU, the sensitivity and specificity for predicting low BMI: 0.75 and 0.91, respectively; |
| Kato et al. (2017) | cross-sectional; Tokyo, Japan; | middle-aged and older men and women; n = 132; mean age 57 ± 10 years (men), 60 ± 11 years (women); | SAF; AGE Reader (Diagnosticon, Groningen, The Netherlands); in AU; | appendicular skeletal muscle mass index (SMI; kg/m² height) by DXA; the Asian Working Group for Sarcopenia (AWGS) cut-offs for low SMI (<7.0 kg/m² (men) and < 5.4 kg/m² (women); | (a) higher levels of SAF associated with less active days/week: β = -0.21 (95% CI: -0.35 to -0.07, p = 0.04) in adjusted model (b); lower compliance with the Dutch physical activity guidelines in those with higher SAF; OR = 0.76 (0.62-0.94), p = 0.01 (c) lower physical functioning (RAND-36) in those with higher SAF; β = -1.60 (-2.64 to -0.54), p = 0.003 in adjusted models; (a) a linear relationship between SAF quartiles and the frequencies of low BMI (Q1: 14.2%; Q2: 16.1%; Q3: 21.1%; Q4: 24.8%; p < 0.001) (b) Q4 of SAF independently associated with low BMI; OR = 1.48 (95% CI: 1.23-1.78), p < 0.001 in all participants and those aged ≥ 60 years (OR = 1.85 (1.26-2.72), p = 0.002 (c) Q4 associated with weak grip strength (OR = 1.98 (1.26-3.11), p = 0.003), hip flexion strength (OR = 1.50, p = 0.01), and hip abduction strength (OR = 1.78, p = 0.001); (a) SAF inversely associated with ASMI (β = -0.062, 95%CI (-0.092 to -0.032), GS (-0.051 (-0.075 to -0.026), and gait speed (-0.074 (-0.116 to -0.033)) all p < 0.001) in all participants (b) one unit increase in SAF associated with higher odds of probable sarcopenia (OR = 1.36, 95% CI (1.09-1.68)); and confirmed sarcopenia (2.01 (1.33-3.06), p = 0.001) in adjusted analyses; (c) no associations with gait speed; |
| Drenth et al. (2018) | cross-sectional; The Netherlands North; | community-dwelling older adults aged ≥ 65 years in the LifeLine Cohort Study, n = 5624; | SAF; AGE Reader (Diagnosticon, Groningen, The Netherlands); in AU; those with skin reflection values < 10% excluded; | active days per week (the Short Questionnaire to Assess Health Enhancing Physical Activity, SQUASH); Dutch Physical Activity Guidelines (30 min of moderate intensity for 5 days/week); physical functioning (RAND-36 questionnaire or SF-36); | (a) adjusted mean GS (kg) lower in higher tertiles of SAF: 44.5 (95% CI: 43.2-45.9) kg in T1; 42.0 (40.6-43.3) kg in T2; 41.7 (40.3-43.1) kg in T3; all p < 0.01; ES (T1 vs. T3) = 0.46 *; (b) adjusted LEP (W/kg) lower in higher tertiles of SAF: 17.8 (16.6-19.1) W/kg in T1; 17.5 (16.4-18.7) W/kg in T2; 16.0 (14.9-17.1) W/kg in T3; all p = 0.04; ES (T1 vs. T3) = 0.45 *; (c) higher levels of SAF in low BMI group: 2.4 ± 0.3 AU in low BMI (n = 31) versus 2.1 ± 0.3; p < 0.01 in normal BMI group (n = 101) (b) SAF independent risk factor for low BMI; OR = 15.70 (95% CI: 1.85-133.01), p = 0.01; (c) the AUC for SAF: 0.86, p < 0.01; at SAF cut-off 2.45 AU, the sensitivity and specificity for predicting low BMI: 0.75 and 0.91, respectively; |
| Tabara et al. (2019) | cross-sectional; Japan; | community-dwelling adults; n = 9203; mean age 57.8 ± 12.4 years; the Nagahama Prospective Cohort for Comprehensive Human Bioscience study; | SAF; the AGE sensor RQ-AG01J (SHARP Lifesciences Co., Kobe, Japan) | appendicular skeletal muscle mass index (SMI; kg/m² height) by bioimpedance; grip strength; gait speed over a 1.2-m course; the maximum isometric strength of knee extension; hip flexion strength; hip abduction strength; | (a) higher levels of SAF associated with less active days/week: β = -0.21 (95% CI: -0.35 to -0.07, p = 0.04) in adjusted model (b); lower compliance with the Dutch physical activity guidelines in those with higher SAF; OR = 0.76 (0.62-0.94), p = 0.01 (c) lower physical functioning (RAND-36) in those with higher SAF; β = -1.60 (-2.64 to -0.54), p = 0.003 in adjusted models; (a) a linear relationship between SAF quartiles and the frequencies of low BMI (Q1: 14.2%; Q2: 16.1%; Q3: 21.1%; Q4: 24.8%; p < 0.001) (b) Q4 of SAF independently associated with low BMI; OR = 1.48 (95% CI: 1.23-1.78), p < 0.001 in all participants and those aged ≥ 60 years (OR = 1.85 (1.26-2.72), p = 0.002 (c) Q4 associated with weak grip strength (OR = 1.98 (1.26-3.11), p = 0.003), hip flexion strength (OR = 1.50, p = 0.01), and hip abduction strength (OR = 1.78, p = 0.001); (a) SAF inversely associated with ASMI (β = -0.062, 95%CI (-0.092 to -0.032), GS (-0.051 (-0.075 to -0.026), and gait speed (-0.074 (-0.116 to -0.033)) all p < 0.001) in all participants (b) one unit increase in SAF associated with higher odds of probable sarcopenia (OR = 1.36, 95% CI (1.09-1.68)); and confirmed sarcopenia (2.01 (1.33-3.06), p = 0.001) in adjusted analyses; (c) no associations with gait speed; |
| Wijas et al. (2022) | cross-sectional; Rotterdam, The Netherlands | community-dwelling adults aged ≥ 55 (RS-I, RS-II) and ≥ 45 years (RS-III), n = 2744; The Rotterdam Study (RS); | SAF; AGE Reader (Diagnosticon, Groningen, The Netherlands); in AU; | components of sarcopenia (GS, walking (gait) speed, appendicular skeletal muscle mass index by DXA (ASMI; kg/m² height)); sarcopenia (defined by EWGSOP2) | (a) increased risk of slow walking speed (mobility disability) in the highest quartile of CML (Q4) compared with lower three |
| **Circulating AGES/RAGE** | | | | | |
| Sembast et al. (2010b) | cross-sectional; Tuscany, Italy; | community-dwelling older adults aged ≥ 65 years, n = 944; InCHIANTI study; | plasma carbamoylmethyl-lysine (CML); enzyme-linked immunosorbent assay (ELISA); | walking speed over 4 m course | (continued on next page) |
Table 1 (continued)

| Ref.          | Study design and location | Sample characteristics | AGEs type and methodology | Outcome | Results |
|--------------|---------------------------|------------------------|---------------------------|---------|---------|
| Ebert et al. (2019) | cross-sectional; Halle, Germany; community-dwelling men and women aged 43–83 years; n = 1770; the CARLA Study; | plasma AGE; sRAGE; AGE-related fluorescence measured three times with a FLUOstar OPTIMA reader (BMG Labtechnologies, Offenbourg, Germany); ELISA kit (Quantikine; R&D systems), respectively; | physical functioning (SF-12) assessed by a physical functioning subscale of SF-36; | (b) higher level of AGES associated with lower physical functioning in women: OR = 0.86 (95% CI: 0.74–0.98) | (a) higher level of AGES associated with lower physical functioning in women: OR = 1.54 (95% CI: 1.02–2.38), p = 0.04 in all participants; and in those without diabetes 1.87 (1.15–3.04), p = 0.01 in adjusted models; |
| Dalal et al. (2009) | cross-sectional; Baltimore, Maryland, USA; community-dwelling older women age ≥ 65 years with walking disability; n = 559; The Women’s Health and Aging Study (WHAS I); | serum CML, sRAGE, and esRAGE; a competitive ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany), a sandwich ELISA (Quantikine Human RAGE Immunoassay; R&D Systems, Minneapolis, MN), and ELISA (B-Bridge International, Mountain View, CA, USA, respectively); serum CML, sRAGE, and esRAGE; | muscle strength (GS); | (a) adjusted mean GS (kg) lower in the highest quartile (Q4) of CML versus three lower quartiles (Q1–Q3): 18.6 kg versus 20.0 kg, p = 0.002 | (b) those in Q4 had higher risk of poor GS in adjusted model: β (SE) −1.31 (0.61), p = 0.03 |
| Sun et al. (2012) | prospective; 30 months follow-up; Baltimore, Maryland, USA; community-dwelling older women aged ≥ 65 years with walking disability at baseline; n = 394; The Women’s Health and Aging Study (WHAS I); | serum CML, ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany); | walking disability (not able to walk or walking speed < 0.4 m/s over 4 m course); | highest CML quartile associated with increased risk of developing severe walking disability: (a) in all women with missing data censored: HR = 1.46 (95% CI: 0.95–2.23), p = 0.08; (b) all women with missing data treated as developing some disability prior to death: 1.54 (1.04–2.29), p = 0.03; (c) multiple simulations (imputed missing data): 1.63 (1.06–2.49), p = 0.03; | |
| Whiton et al. (2014) | cross-sectional analysis of a prospective study; USA; community-dwelling Medicare recipients; n = 3373; mean age 78.1 ± 4.8 years; The Cardiovascular Health Study; | serum CML; ELISA (Microcoat, Penzberg, Germany); | physical frailty components including low GS and slow walking speed; | (a) adjusted mean CML higher in men with three frailty criteria (low GS, low physical activity, and exhaustion) compared with men without frailty components; CML in low vs. normal GS: 665 ± 245 ng/ml vs. 636 ± 240 ng/ml (b) odds of frailty increased by SD increase of CML in men (OR = 1.30 (95% CI: 1.30 (1.14–1.48), p < 0.01); | (b) low sRAGE independent risk factor for low ASMB (in all participants: OR = 0.25 (95% CI: 0.11–0.61), p = 0.002; in men: 0.1 (0.02–0.52), p = 0.006); |
| Kim et al. (2018) | cross-sectional; South Korea; community-dwelling adults aged ≥ 40 years; n = 390; the Korean Sarcopenic Obesity Study; | serum sRAGE; R&D Systems Inc., Minneapolis, Minnesota; appendicular muscle mass normalized by BMI (ASMB); | (a) positive correlation between sRAGE and ASMB (r = 0.109, p = 0.04) (b) low sRAGE independent risk factor for low ASMB (in all participants: OR = 0.25 (95% CI: 0.11–0.61), p = 0.002; in men: 0.1 (0.02–0.52), p = 0.006); | (a) only GS in women significantly correlated with uCML (r = −0.32, p = 0.04) (b) adjusted GS decreased by 1.73 kg per unit increase in natural log-transformed uCML (p = 0.004) in women; (c) no associations between uCML, muscle mass, TUG, walking speed, or GS in men (d) a combined effect of more than 50th percentile of uCML and poor TUG on risk of sarcopenia (OR = 13.76 (95% CI: 1.03–183.83), p < 0.05); | |
| Yang et al. (2019) | cross-sectional; Taiwan; community-dwelling older adults aged ≥ 65 years; n = 104; | urinary CML (uCML); ELISA (Circulea, MBL International Corporation, Nagoya, Japan); height- and weight adjusted SMI assessed by DXA; GS; 5-m walk test; Timed Up-and-Go test (TUG); sarcopenia (defined by the AWGS); | components of sarcopenia (appendicular skeletal muscle mass by BIA (ASM, kg/m²) | (a) sRAGE level associated with lower ASM (β = −164.04, 95% CI (36.02–292.06), p = 0.012), and (continued on next page) | (c) no associations between uCML, muscle mass, TUG, walking speed, or GS in men (d) a combined effect of more than 50th percentile of uCML and poor TUG on risk of sarcopenia (OR = 13.76 (95% CI: 1.03–183.83), p < 0.05); | |
Table 1 (continued)

| Ref. | Study design and location | Sample characteristics | AGEs type and methodology | Outcome | Results |
|------|--------------------------|------------------------|---------------------------|---------|---------|
| Moriwaki et al. (2021) | cross-sectional; Japan; | community-dwelling middle-aged and older adults (men: 75.0 ± 8.9 years; women: 73.6 ± 8.1 years); n = 254; the GAINA study; Hino, Japan; | urinary pentosidine (u-pentosidine); ELISA (MARKIT-M urinary pentosidine, SB Bioscience Co., Ltd., Tokyo, Japan); | skeletal muscle index (SMI, kg/m² height) by BIA, GS, gait speed; | (a) u-pentosidine correlated with GS (r = -0.363) and gait speed (r = -0.364) in men (all p < 0.001) (b) u-pentosidine correlated with GS (r = -0.305) and gait speed (r = -0.387) in women (all p < 0.001) (c) GS and gait speed associated with u-pentosidine in multivariate regression models (p = -0.179 95%CI (-0.203 to -0.003), p = 0.043; -0.254 (-0.099 to -0.001)) in men (d) GS and gait speed associated with u-pentosidine in multivariate regression models (p = -0.215 95%CI (-0.089 to -0.024), p = 0.001; -0.182 (-0.006 to -0.001), p = 0.017) in women (e) no associations with SMI |
| Ebuchi et al. (2021) | cross-sectional; Japan; | community-dwelling older women seen in outpatient clinic; n = 70; women with sarcopenia (n = 47) aged 72.7 ± 10.1 years, controls (n = 23) aged 77.2 ± 7.2 years. | SAF, serum and urine pentosidine; AGE Reader (Diagnostic, Groningen, The Netherlands) and ELISA (Fushimi Pharmaceutical Co. Kagawa, Japan), respectively. | SMI (kg/m²) estimated by bioimpedance; low appendicular SMI of <5.75 kg/m² (here termed sarcopenia). | (a) only serum pentosidine differed between sarcopenic and non-sarcopenic women (0.063 ± 0.019 µg/ml vs. 0.055 ±0.012 µg/ml, p = 0.049); ES = 0.50 * (b) only serum pentosidine negatively correlated with SMI (r = -0.269, p < 0.05). |

AUC, area under the curve; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle index; AWGS, Asian Working Group for Sarcopenia; Chen et al., 2020; BMI, body mass index; CARLA Study, the CARDiovascular disease, Living and Ageing in Halle study; DXA, dual-energy X-ray absorptiometry; ES, effect size; esRAGE, endogenous soluble receptor for advanced glycation end product; EWGSOP2, revised European Working Group for Sarcopenia in Older People (Cruz-Jentoft et al., 2019; Cruz-Jentoft and Sayer, 2019); GAINA, the Good Ageing and Intervention Against Nursing Care and Activity Decline study; GS, grip strength; InCHIANTI study, ‘Ageing in the Chianti Area’; RAND-36, 36-item Short Form Survey, RAND corporation, Santa Monica, California, USA; SE, standard error; SMI, skeletal muscle index; sRAGE, soluble receptor for advanced glycation end product; vs, versus. *Calculations described in Appendix 3.

Examined 14 cross-sectional studies (Drenth et al., 2018; Dalal et al., 2009; Ebert et al., 2019; Ebuchi et al., 2021; Kato et al., 2017; Kim et al., 2018; Momma et al., 2011; Moriwaki et al., 2021; Tabara et al., 2019; Semb a et al., 2010a; Waqas et al., 2012; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019) and one prospective longitudinal study (Sun et al., 2012) (Table 1), and grouped them by the type of exposure: SAF (Drenth et al., 2018; Kato et al., 2017; Momma et al., 2011; Tabara et al., 2019; Waqas et al., 2022) (SAF and muscle-related outcomes), circulating AGEs and RAGEs (in blood plasma or serum, urine) (Dalal et al., 2009; Ebert et al., 2019; Kim et al., 2018; Moriwaki et al., 2021; Semb a et al., 2010a; Sun et al., 2012; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019) (Circulating AGEs/RAGE and muscle-related outcomes), and multiple AGEs (i.e., AGEs from different sources) (Ebuchi et al., 2021) (Multiple AGEs and muscle-related outcomes).

The sample size ranged from 70 (Ebuchi et al., 2021) to 9203 (Tabara et al., 2019) participants. Eleven studies included men and women (Drenth et al., 2018; Ebert et al., 2019; Kato et al., 2017; Kim et al., 2018; Moriwaki et al., 2021; Tabara et al., 2019; Semb a et al., 2010a; Wu et al., 2021; Yang et al., 2019) (Table 1).
Overview of the associations between advanced glycation end products (AGEs), receptors for AGE (RAGE) and muscle-related outcomes.

A. Granic et al.

A. Granic et al. (men), 5.5 kg/m² (women); gait speed: 0.8 m/s (men and women) (Cruz-Jentoft et al., 2019).

Physical frailty were examined in two studies (Drenth et al., 2018; Ebert et al., 2019; Moriwaki et al., 2011; Tabara et al., 2019; Waqas et al., 2022) used the AGE Reader (DiagnOptic, Groningen, The Netherlands), and one used a prototype for the AGE sensor RQ-AG01 (SHARP, Lifesciences Co., Kobe, Japan) (Tabara et al., 2019) to measure SAF in arbitrary units (AU), either from the skin of the forearm or a fingertip, respectively. The SAF values measured by Skin Autofluorescence (SAF) was also assessed in eight studies (Eguchi et al., 2021; Kato et al., 2017; Moriwaki et al., 2011; Waqas et al., 2022) used the AGE Reader (DiagnOptic, Groningen, The Netherlands), and one used a prototype for the AGE sensor RQ-AG01 (SHARP, Lifesciences Co., Kobe, Japan) (Tabara et al., 2019) to measure SAF in arbitrary units (AU), either from the skin of the forearm or a fingertip, respectively. The SAF values measured by Skin Autofluorescence (SAF).

Studies varied widely by outcome measures (Table 1). Muscle strength (grip strength, leg/knee extension power, hip flexion/abduction strength) was evaluated in eight studies (Dalal et al., 2009; Momma et al., 2011; Moriwaki et al., 2021; Tabara et al., 2019; Waqas et al., 2022; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019). Muscle mass (total muscle mass, appendicular muscle mass, skeletal muscle mass) was also assessed in eight studies (Eguchi et al., 2021; Kato et al., 2017; Kim et al., 2018; Moriwaki et al., 2021; Tabara et al., 2019; Waqas et al., 2022; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019). Physical functioning measures (walking/gait speed, severe walking disability (walking <0.4 m/s or not walking), Timed Up-and-Go test (TUG), physical functioning domain of SF-36 or SF-12) were used in nine studies (Drenth et al., 2018; Ebert et al., 2019; Moriwaki et al., 2021; Sembia et al., 2010a; Sun et al., 2012; Wu et al., 2021; Yang et al., 2019). Sarcopenia was evaluated in three studies (defined by the EWGSOP2, the Updated AWGS (grip strength: kg (men), 16 kg (women); appendicular skeletal muscle index: 7.0 kg/m² (men), 5.5 kg/m² (women); gait speed: 0.8 m/s or not walking), Timed Up-and-Go test; uCML, urinary carboxymethyl-lysine).

Table 2
Overview of the associations between advanced glycation end products (AGEs), receptors for AGE (RAGE) and muscle-related outcomes.

| Ref. | Muscle strength | Muscle mass | Physical functioning | Sarcopenia | Other muscle outcomes |
|------|-----------------|-------------|----------------------|------------|------------------------|
| Momma et al. (2011) | ↓ grip strength | — | — | — | — |
| Kato et al. (2017) | ↓ leg extension power | — | — | — | — |
| Drenth et al. (2018) | ↓ skeletal muscle index | — | — | — | — |
| Tabara et al. (2019) | ↓ grip strength | ↓ skeletal muscle index | ↓ gait speed | — | — |
| Wu et al. (2021) | ↓ hip flexion strength | ↓ hip abduction strength | ↑ with AGES/sRAGE ratio | (women) | — |
| Dalal et al. (2009) | ↓ grip strength | ↑ with sRAGE and esRAGE | — | — | — |
| Sun et al. (2012) | ↓ appendicular skeletal muscle index | — | ↑ with higher SAF† | — | — |
| Kim et al. (2018) | ↓ appendicular muscle mass and sRAGE | — | ↑ risk of low muscle mass with low sRAGE | — | — |
| Yang et al. (2019) | ↓ grip strength (women) | — | — | — | — |
| Wu et al. (2021) | ↓ grip strength with higher sRAGE (all participants, women) | — | ↑ appendicular muscle mass with higher sRAGE (all participants, men) | — | — |
| Moriwaki et al. (2021) | ↓ grip strength | — | ↓ gait speed | — | — |
| Multiple AGEs | — | ↓ skeletal muscle index | — | ↑ risk of combined higher uCML & poor TUG* | — |
| Eguchi et al. (2021) | — | ↓ appendicular skeletal muscle mass | — | ↑ risk with higher SAF† | — |

† positive association; ‡ negative association; ↔ no association; — not assessed. esRAGE, endogenous soluble receptor for advanced glycation end product; RAND-36, 36-item Short Form Survey, RAND corporation, Santa Monica, California, USA; ref, reference; SF-12, 12-item Short Form Survey; sRAGE, soluble receptor for advanced glycation end product; TUG, Timed Up-and-Go test; uCML, urinary carboxymethyl-lysine.

3.4. SAF and muscle-related outcomes

Of the five cross-sectional studies examining the association between SAF and muscle-related outcomes, three were conducted in Japan (Momma et al., 2011; Kato et al., 2017; Tabara et al., 2019), and two in The Netherlands (Drenth et al., 2018; Waqas et al., 2022). The Japanese studies were conducted in community-dwelling adults aged ≥ 30 years, and the Dutch studies in older adults (≥ 65 years) (Drenth et al., 2016) and in those ≥ 45 years (mean age 74 years) (Waqas et al., 2022). The number of participants ranged from 132 (Kato et al., 2017) to 9203 (Tabara et al., 2019). Four studies (Drenth et al., 2018; Kato et al., 2017; Momma et al., 2011; Waqas et al., 2022) used the AGE Reader (DiagnOptic, Groningen, The Netherlands), and one used a prototype for the AGE sensor RQ-AG01 (SHARP, Lifesciences Co., Kobe, Japan) (Tabara et al., 2019) to measure SAF in arbitrary units (AU), either from the skin of the forearm or a fingertip, respectively. The SAF values measured by the AGE Reader (Drenth et al., 2018; Kato et al., 2017; Momma et al.,
Muscle-related outcomes included muscle strength (upper and lower limb strength) (Momma et al., 2011; Tabara et al., 2019; Waqas et al., 2022), muscle mass (SMI; appendicular skeletal muscle mass / height^2, kg/m^2) (Kato et al., 2017; Tabara et al., 2019; Waqas et al., 2022), physical functioning (SF-36, gait speed) (Drenth et al., 2018; Tabara et al., 2019; Waqas et al., 2022), sarcopenia (Waqas et al., 2022), and additional related measures (e.g., meeting the national physical activity guidelines) (Drenth et al., 2018). No prospective studies could be found to evaluate the predictive value of SAF for muscle health decline.

### 3.4.1. Muscle strength, mass, and sarcopenia

All three Japanese cross-sectional studies (Momma et al., 2011; Kato et al., 2017; Tabara et al., 2019) reported negative associations between muscle strength and/or muscle mass and SAF levels. Higher values of SAF (the AGE Reader) were associated with lower mean grip strength and leg extension power in 232 middle-aged men, showing a gradient effect of SAF on muscle strength with a moderate Cohen’s d ES for both outcomes (Momma et al., 2011). The associations were independent of lifestyle factors and chronic diseases, including diabetes mellitus and kidney disease. Similarly, the highest sex-specific quartile of SAF from a fingertip was associated with lower grip strength, hip flexion strength, and hip abduction strength, but not with gait speed in over 1900 older adults aged ≥60 years from the Nagahama study (Tabara et al., 2019). The study also observed a significant association between the highest SAF quartile and low SMI (defined by the AWGS cut-offs from bioimpedance) in both middle-aged and older adults, independent of several muscle-related biomarkers (e.g., serum albumin, markers of inflammation, and insulin resistance). Taken together, the authors suggest that SAF could be considered as an independent marker of lower muscle strength and mass and not a phenomenon modulated by glycemia and other factors (Tabara et al., 2019). Comparable results were observed in a smaller study that used DXA to estimate SMI in relation to SAF (the AGE Reader) in 132 middle-aged and older adults. Higher SAF was an independent risk factor for low SMI, and the sensitivity and specificity of predicting low SMI were 0.75 and 0.91, respectively with the SAF cut-off at 2.45 AU (Kato et al., 2017).

In a Dutch cross-sectional study of 2744 middle-aged and older adults (aged ≥45 years) participating in the Rotterdam Study (RS-I, RS-II, and RS-III), SAF (the AGE Reader) was negatively associated with ASMI, grip strength, and gait speed (all p < 0.001) after adjusting for sex, age, percent body fat, height, renal failure, diabetes, and smoking status. A one unit increase in SAF was associated with 36% increased odds of probable sarcopenia (sex-specific low grip strength of <27 kg in men and <16 kg in women), and a two-fold increase in odds of confirmed sarcopenia (EWGSOP2) (Waqas et al., 2022). The authors highlighted the need for longitudinal studies to explore the role of SAF as a potential biomarker of sarcopenia.

### 3.4.2. Physical functioning and related outcomes

Examining other outcomes related to physical functioning, another Dutch study with over 5600 older adults (aged ≥65 years) found a significant association between the higher levels of SAF (the AGE Reader) and fewer physically active days, lower physical functioning (SF-36), and lower adherence to the Dutch physical activity guidelines, independent of diabetes mellitus (or levels of glucose), cardiovascular diseases (CVD), and BMI (Drenth et al., 2018). The results partially support the hypothesis that SAF accumulation contributes to worse motor function.

### 3.5. Circulating AGEs/RAGE and muscle-related outcomes

Seven studies (six cross-sectional and one prospective longitudinal) investigated the association between plasma or serum AGEs (CML, total plasma fluorescent AGEs, pentosidine) and/or RAGEs in relation to muscle outcomes including sarcopenia (Dalal et al., 2009; Ebert et al., 2019; Kim et al., 2018; Semba et al., 2010a; Sun et al., 2012; Whitson et al., 2011; Waqas et al., 2022) were comparable, ranging from the mean of 2.1–2.41 AU.
et al., 2014; Wu et al., 2021). Two cross-sectional studies investigated the association between urinary AGEs, uCML (Yang et al., 2019) and pentosidine (u-pentosidine) (Moriwaki et al., 2021) and muscle outcomes. Four studies examined the role of AGE receptors (i.e., circulating sRAGE, and esRAGE) and AGEs/sRAGE ratio in muscle health (Dalal et al., 2009; Ebert et al., 2019; Kim et al., 2018; Wu et al., 2021). Two studies were conducted in Europe (Ebert et al., 2019; Semb et al., 2010a), three in the USA (Dalal et al., 2009; Sun et al., 2012; Whitson et al., 2014), and four in Asia (Kim et al., 2018; Moriwaki et al., 2021; Wu et al., 2021; Yang et al., 2019). Six studies examined older adults (≥ 65 years) (Ebert et al., 2019; Dalal et al., 2009; Sun et al., 2012; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019), and the remaining three also included those aged ≥ 40 years (Ebert et al., 2019; Kim et al., 2018; Moriwaki et al., 2021). The number of participants ranged from 104 to 3373, and all except two studies (Dalal et al., 2009; Sun et al., 2012) included both sexes. Most studies used immunological methods (i.e., ELISA) to measure the concentration of AGEs or RAGEs but varied in terms of the muscle outcomes measured. Studies using ELISA to measure CML (in blood) reported the assay to be validated, specific, and showing no cross-reactivity with other compounds (e.g., Microcoat, Penzberg, Germany). The intra- and inter-assay analytical coefficients of variation for blood CML were reported at < 5% (Dalal et al., 2009; Semb et al., 2010a; Sun et al., 2012; Whitson et al., 2014), and at < 7.4% and < 15.2%, respectively, for uCML (Kim et al., 2018), and for u-pentosidine at < 5% (Moriwaki et al., 2021). The studies measuring sRAGE (Wu et al., 2021), and both serum and urine pentosidine (Eguchi et al., 2021) with ELISA did not report assay specifications.

3.5.1. Muscle strength, mass, and sarcopenia

In a study of 559 older women with moderate to severe disability belonging to the highest quartile of circulating CML (≥0.68 μg/ml) was associated with a higher risk of low grip strength independently of BMI, diabetes mellitus, and antioxidants, when compared with the three lower quartiles, but no associations were found between the AGE receptors (sRAGE, esRAGE) and grip strength (Dalal et al., 2009). However, low sRAGE was an independent risk factor for low appendicular skeletal muscle mass normalised by BMI (ASM_BMI), independent of plasma glucose, insulin resistance, and C-reactive protein in 390 Korean adults aged ≥ 40 years (Kim et al., 2018). Serum CML was higher in older men than in women in the Cardiovascular Health study including over 3300 Medicare recipients. This was especially evident in men with three criteria for frailty (low grip strength, low physical activity, and exhaustion) regardless of age, lifestyle factors, and CVD (Whitson et al., 2014). In a cross-sectional study of 314 Taiwanese older adults (aged ≥ 65 years), sRAGE was significantly associated with low muscle strength (grip strength) and muscle mass (AMSI), but not with gait speed (Wu et al., 2021). The study defined sarcopenia using the updated AWGS definition (Chen et al., 2020) and found a significant association between confirmed sarcopenia (low muscle mass and either low muscle strength or gait speed), but not with possible sarcopenia (having one sarcopenia component) or severe sarcopenia (having all three components) (Wu et al., 2021). Sex-stratified analyses revealed stronger associations between higher levels of sRAGE and lower grip strength, muscle mass, and sarcopenia in women, and gait speed in men after adjustment for age, smoking and chronic diseases (including diabetes, cardiovascular and pulmonary diseases) (Wu et al., 2021). Because of large confidence intervals, the results should be interpreted with caution.

High uCML was significantly associated with lower grip strength in 104 Taiwanese older women (aged ≥ 65 years) adjusted for age, body fat, serum creatinine, and blood urea nitrogen levels, but no associations were observed in men, or with any other muscle-related outcome (walking speed, TUG) (Yang et al., 2019). In this study sarcopenia was assessed by the AWGS definition, but only a combination of higher uCML levels and poor physical functioning (TUG) was associated with an increased risk of sarcopenia in all participants. The association needs to be interpreted with caution because of large confidence intervals and small sample size in the study (Yang et al., 2019). In the Good Ageing and Intervention Against Nursing Care and Activity Decline study (GAINA; Hino, Japan) of 254 middle-aged and older adults, u-pentosidine was a significant predictor of lower grip strength in both men and women after adjusting for age, anthropometry, and blood-based biomarkers, including BMI, glycated hemoglobin, and serum vitamin D (Moriwaki et al., 2021). No associations were found between u-pentosidine and SMI (Moriwaki et al., 2021).

3.5.2. Physical functioning and related outcomes

Five studies included some measure of physical functioning in relation to circulating AGEs in blood and urine (Ebert et al., 2019; Moriwaki et al., 2021; Semb et al., 2010a; Sun et al., 2012; Yang et al., 2019), of which only one was a prospective longitudinal study (Sun et al., 2012). In Italian study of 944 older adults, those in the highest quartile of plasma CML had greater odds of slow walking speed independent of lifestyle factors and chronic diseases (Semb et al., 2010a). However, in 1770 German adults aged ≥ 43 years higher levels of total plasma fluorescent AGEs were associated with lower physical functioning (SF-12) in women but not in men after adjustment for BMI, lifestyle factors, diabetes mellitus, and CVD medication (Ebert et al., 2019). Similar associations were observed for higher AGE-sRAGE ratio and lower physical functioning, but not for sRAGE alone (Ebert et al., 2019). A prospective analysis of serum CML and walking disability in 394 older women with disability in at least two domains (e.g., mobility and higher functional tasks) revealed an increased risk of incident severe walking disability (walking speed <0.4 m/s or unable to walk) independent of cardiometabolic diseases and renal insufficiency (Sun et al., 2012). Urinary pentosidine was a significant predictor of slow gait speed in 254 men and women from the GAINA study after adjusting for several covariates (age, anthropometry, blood-based biomarkers) (Moriwaki et al., 2021).

3.6. Multiple AGEs and muscle-related outcomes

Only one cross-sectional study assessed multiple AGEs (SAF by the AGE Reader, and pentosidine in serum and urine by ELISA) in association with SMI and low appendicular SMI (here termed sarcopenia) in 70 older women (Eguchi et al., 2021). Only serum pentosidine was negatively correlated with SMI, and serum pentosidine was the only AGE to differ between those with low (<5.75 kg/m²) and normal appendicular SMI showing a medium ES (Table 1). Other biomarkers examined (urinary pentosidine, SAF, serum homocysteine and vitamin D) were similar across the groups.

3.7. Summary of findings

Table 2 gives an overview of the main findings.

3.7.1. SAF and muscle

Studies using SAF as a surrogate measure for total autofluorescent AGEs (measured by the AGE Reader or the AGE sensor RQ-AG01) showed negative associations with several muscle-related outcomes in the general and older adult populations. In adjusted cross-sectional analyses, higher levels of SAF were associated with reduced muscle strength (grip strength, leg extension strength, hip flexion/adduction strength) (Momma et al., 2011; Tabara et al., 2019; Waqas et al., 2022), muscle mass (SMI) (Kato et al., 2017; Tabara et al., 2019; Waqas et al., 2022), worse physical functioning, related measures (Drenth et al., 2018), and sarcopenia (Waqas et al., 2022). These associations were independent of one or more cardiometabolic and renal factor or diseases reported to be linked to higher levels of SAF (Rajaseelina et al., 2015; Viramontes Horner, Taal, 2019). The studies adjusted for CVD (Drenth et al., 2018), diabetes mellitus (Drenth et al., 2018; Momma et al., 2011; Waqas et al., 2022), fasting blood sugar (Kato et al., 2017; Drenth et al., 2018), insulin resistance (Tabara et al., 2019), renal function (Tabara
et al., 2019; Waqas et al., 2022), and kidney disease (Momma et al., 2011). Only one study investigated the role of SAF in sarcopenia (EWGSP2) and reported increased risk of sarcopenia with higher levels of SAF (Waqa et al., 2022). Prospective longitudinal studies investigating the relationship between SAF and muscle health and function are lacking in both younger and older adult populations.

3.7.2. Circulating AGEs and muscle

CML in blood measured by ELISA was the most common AGE investigated in relation to muscle health. Negative associations between CML (blood and urine), muscle strength (Ebert et al., 2019; Moriwaki et al., 2021; Semb et al., 2010a; Yang et al., 2019), and physical functioning (Moriwaki et al., 2021; Semb et al., 2010a; Sun et al., 2012) were the most consistent findings in univariable and multivariable analyses, of which only one used prospective data (Sun et al., 2012). Similar to SAF studies, higher odds of poor muscle-related outcomes with higher levels of circulating AGEs were independent of cardiovascular disease (Waqa et al., 2022). Prospective longitudinal studies investigating sarcopenia as an outcome with validated definition (Wu et al., 2021; Yang et al., 2019), and their results should be interpreted with caution. Only one provided solid evidence for the role of circulating AGEs/sRAGE in muscle strength, function or sarcopenia (Ebert et al., 2019; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019), of which three observed negative associations in women only (Ebert et al., 2019; Wu et al., 2021; Yang et al., 2019). Sex differences were attributed to genetic differences between the sexes, hormones (loss of estrogen), residual confounding (arthritis in women), and sex-specific survival bias in older cohorts.

Taken together, these observational findings support the hypothesis that AGEs are associated with worse muscle-related outcomes. However, the associations were moderate and could be reported only narratively with higher levels of circulating AGEs were independent of cardiovascular disease (Waqa et al., 2022). Prospective longitudinal studies investigating the relationship between SAF and muscle health and function are lacking in both younger and older adult populations.

4. Discussion

This systematic review synthesised a considerable body of research about the role of tissue-bound and circulating AGEs in skeletal muscle health in community-dwelling adults aged ≥ 30 years from observational studies by updating the previous review (Drenth et al., 2016) and doubling the number of studies. This allowed for the inclusion of several populations (younger and older adults from Europe, Asia and North America) and the summary of consistent findings (circulating CML and SAF in relation to muscle health). We found a lack of prospective longitudinal studies, studies examining multiple AGEs, and those with sarcopenia as an outcome. Only seven studies were conducted in older adults (aged ≥ 65 years) (Dalal et al., 2009; Drenth et al., 2018; Semb et al., 2010a; Sun et al., 2012; Whitson et al., 2014; Wu et al., 2021; Yang et al., 2019), and studies varied markedly by participant characteristics (sex, age range, type AGEs, and muscle health outcomes).

Although the evidence presented here supports the hypothesis that AGEs may play an important role in muscle health starting from mid-adulthood, this is largely based on cross-sectional studies. To confirm a robust relationship between AGEs and muscle health and sarcopenia, well-designed prospective studies are needed with a view to developing interventions for this potentially modifiable target (Prasad and Tiwari, 2017; Rowan et al., 2018).

Several recent narrative reviews have provided critical mechanistic insights from cellular, animal, and human studies about AGEs/RAGE involvement in muscle health and sarcopenia, including the potential for treatment and prevention (Chen et al., 2018; Daussin et al., 2021; Olson et al., 2021; Riuzzi et al., 2018; Suzuki et al., 2022). How AGEs may contribute to pathogenesis of declining muscle health and sarcopenia remains to be fully determined but may involve several pathways. Non-enzymatic crosslinking by AGEs of muscle connective tissue (e.g., endomysial and other collagen in the extracellular matrix) may contribute to muscle stiffness and decreased muscle function (Haus et al., 2007; Olson et al., 2021). AGEs-induced structural changes in the cellular proteins may lead to functional impairments of key cellular structures such as mitochondria (Daussin et al., 2021; Olson et al., 2021; Rowan et al., 2018). Furthermore, AGEs may amplify ‘inflamaging’ by contributing to the increased production of pro-inflammatory cytokines and reactive oxygen species (Ott et al., 2014; Reynaert et al., 2016; Rowan et al., 2018) via RAGE signalling cascade (Daussin et al., 2021; Ott et al., 2014; Reynaert et al., 2016; Riuzzi et al., 2018; Rowan et al., 2018). Both inflammation and oxidative stress have been implicated in the pathogenesis of sarcopenia (Mankhong et al., 2020). Although the results of the studies examining the association between soluble forms of RAGE and muscle-related outcomes were inconclusive (Ebert et al., 2019; Dalal et al., 2009; Kim et al., 2018; Moriwaki et al., 2021), these may act as scavengers of circulating AGEs, thus inhibiting the AGE-RAGE binding and the activation of pro-inflammatory pathway (Chaudhuri et al., 2018; Daussin et al., 2021; Riuzzi et al., 2018). AGEs may affect other components of the musculoskeletal system (bone, cartilage, tendons, and ligaments) and nervous system (motor neurons), resulting in similar structural and functional changes in the target cells reviewed in (Bailey, 2001; Gautieri et al., 2017; Suzuki et al., 2022).

The most consistent negative associations were obtained for muscle strength (grip strength) and AGEs (tissue-bound and circulating), which were reported in eight studies (Dalal et al., 2009; Ebert et al., 2019; Momma et al., 2011; Moriwaki et al., 2021; Semb et al., 2010a; Sun et al., 2012; Tabara et al., 2019; Waqa et al., 2022). Low muscle strength, the primary component of sarcopenia for diagnostic purposes and the most reliable measure of muscle function (Cruz-Jentoft and Sayer, 2019), has been linked to a range of adverse health outcomes in older adults (Bohannon, 2015), and proposed as a biomarker of ageing (Sayer and Kirkwood, 2015). Establishing stronger evidence for the AGEs involvement in the complex mechanisms that lead to muscle strength decline with ageing will be essential in designing future therapies and interventions for sarcopenia.

This review found limited evidence for a direct relationship between higher levels of AGEs/RAGE and sarcopenia (Waqa et al., 2022; Wu et al., 2021; Yang et al., 2019). Two studies had large confidence intervals (Wu et al., 2021; Yang et al., 2019), and their results should be interpreted with caution. Only one provided solid evidence for the relationship between SAF and sarcopenia (Waqa et al., 2022), and no large population-based studies investigating the prospective association between AGEs and sarcopenia could be found, warranting further investigations.

The varying results and negative findings across the studies may be affected by the type of AGE and measurement methodology employed for their quantification. AGEs are heterogenous and biochemically diverse molecules produced endogenously (Chaudhuri et al., 2018) but also acquired exogenously from the environment (Chaudhuri et al., 2018). This diversity poses various methodological challenges and the need for standardised protocols for their detection and quantification (e.g., fluorometric, immunological, spectroscopy, mass spectrometry) (Chaudhuri et al., 2018; Suzuki et al., 2022).

Although SAF measurement (by the AGE Reader (Meerwaldt et al., 2004)) is easy to use, non-invasive procedures to implement in the research and clinical settings, there are several limitations related to SAF to be considered. SAF serves as a surrogate measure of cross-linking
fluorescent AGEs in the skin, thus it is both non-specific and does not capture the total burden of AGE in the body. Equally, other non-AGE fluorescent substances in the skin can interfere with the accuracy of fluorometric method (Suzuki et al., 2022). Although SAF measurement by the AGE Reader follows an established protocol, the florescence intensity is affected by the presence of blood vessels (veins) and skin pigments (melanin) (Meerwaldt et al., 2004; Suzuki et al., 2022).

Because of the biochemical diversity of circulating AGEs, several methodologies for their detection and quantification have been employed, each with their own limitations and disadvantages (reviewed in Suzuki et al., 2022). The most studied circulating AGE in the studies was CML (assessed by ELISA), a well-characterised and abundant AGE in human blood (Chen et al., 2016), but the comparability of the CML concentrations across the studies was difficult to evaluate. Although ELISA can quantify a specific AGE, sample pretreatment required by the ELISA protocol (heating, incubation), can lead to overestimation of pentosidine and CML (Suzuki et al., 2022). Because the epitopes of the antibodies for many AGEs are not known, cross-reactivity with similar proteins and structures cannot be excluded. State-wide levels of the AGEs in the circulation are affected by exogenous sources (e.g., diet), urinary clearance, and homeostatic processes of formation and breakdown, and may require repeated assessments (Rowan et al., 2018), thus explaining some of the null and inconclusive findings in the studies reviewed. Also, it is not known whether different AGE compounds affect muscle cells differently, and which type of AGEs and their associated pathological pathway (e.g., extracellular cross-linking, intracellular signal transduction) are the most detrimental for muscle, for which appropriate cellular and animal models are needed (Chaudhuri et al., 2018). Comparative studies evaluating different AGES in relation to muscle health in older adults are warranted (Eguchi et al., 2021).

Residual confounding and shared biological pathways between ageing, common age-related diseases and sarcopenia may present additional challenges in discerning the strength and direction of AGES-muscle relationship. Although most studies in this review have adjusted for a range of ageing diseases and factors linked to higher levels of AGES in the literature (e.g., cardiometabolic and renal factors and diseases (Heidari et al., 2020; Kizer et al., 2014; Rajaoabelina et al., 2015; Viramontes Hörner, Taal, 2019; Yubero-Serrano, Pérez-Martínez, 2020), significant associations should be interpreted with caution. The presence of multiple diseases with overlapping pathophysiology in older adults makes it difficult to examine to what extent AGES are byproducts of ageing and age-associated disease, including sarcopenia, and to what extent they actively contribute to disease development and progression (discussed in Chaudhuri et al., 2018; Gugliucci, 2017; Ramasamy et al., 2005; Rowan et al., 2018; Semba et al., 2010b).

4.1. Study strength and limitations

We used strict inclusion criteria and selected only 15 observational studies with community-dwelling adults that reported a relationship between the level of AGES and muscle-related outcomes, a combination of specific terms describing the elements of sarcopenia (Cruz-Jentoft et al., 2019) and broader (less specific) terms relating to muscle and physical function (Appendix 2). Associations in specific clinical populations (e.g., diabetes, renal disease, Alzheimer’s disease, osteoarthritis) and studies reporting the effect of AGES on the tissue level (i.e., muscle biopsies) without measures of muscle function were excluded. Limiting our search to sarcopenia and its components increased the internal validity of the findings, and including only community-dwelling adults enhanced the external validity of the analysis to those residing in the community, although limiting the generalisability to excluded populations. Not all studies had multivariable analyses, and for a limited number of those not reporting any association coefficients, we were able to calculate effect sizes. We included studies written in English, thus omitting possibly relevant information in other languages. Our conclusions were based largely on cross-sectional studies thus, no causality should be implied. Most studies included a range of confounding factors, but because of their observational nature, the possible effect of residual confounders should be considered when interpreting the results. We observed high heterogeneity across the studies (e.g., study population, outcome measures) possibly affecting the findings and precluding the conduction of meta-analysis. More detailed discussion of critical insights about the role of AGES/RAGE in skeletal muscle was outside the scope of this review and can be found elsewhere (Chen et al., 2018; Daussin et al., 2021; Olson et al., 2021; Riuatti et al., 2018; Suzuki et al., 2022).

5. Conclusions

Higher levels of AGES in the skin and circulation were associated with lower muscle strength, mass and function in community-dwelling adults aged ≥ 30 years in cross-sectional studies. This finding should be confirmed in well-designed prospective studies which include harmonised assessment of sarcopenia as AGES represent a potentially modifiable target for intervention as well as biomarkers of skeletal muscle health (Scharf and Heineke, 2012).

Declarations

Availability of data and materials. All data has been shared in the manuscript.

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Data availability

All data relevant for this systematic review is included within the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mad.2022.111744.

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