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LETTER TO THE EDITOR

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Reply to letter to the editor: "Advanced glycation end-products and their receptors: Exercise effects"

Dear Editor,

We would like to thank Kotani and Gugliucci[1] for their positive feedback and interest in our recent review.[2] We believe their letter brings light to an interesting discussion on how lifestyle interventions, specifically physical activity, can impact on advanced glycation end products (AGEs) and its receptors concentrations. Given that AGEs can have a detrimental effect on human health, understanding which and how lifestyle factors can play a role in preventing/reducing such effects is of interest to the scientific community and public health.[3]

In their letter, Kotani and Gugliucci searched and compiled data from interventional studies in which the effects of physical exercise on AGEs and soluble AGEs receptors (sRAGE) were evaluated.[4–10] Based on those studies, the authors concluded that the practice of physical exercise could reduce serum AGEs and, seemingly contradictory, it also reduces sRAGE concentrations.[1] However, we would advert caution before drawing these conclusions. AGEs and sRAGE concentrations can be affected by a wide range of factors, including age, smoking, dietary intake, medications, metabolic status, and occurrence of diseases.[11,12] Hence, there are a few methodological points we would like to address regarding the studies discussed in that letter.

First, there is considerable heterogeneity among the mentioned studies, both regarding the studies design (lengths of interventions, types and intensity of exercise, the presence or lack of control groups) and the population samples (age groups, nutritional and metabolic status, presence of diseases). Although Kotani and Gugliucci mentioned adopting adult participants as one of the inclusion criteria for the literature search,[1] the mean age of the studies population ranged from 24 to 65 years, and one study included only elderly individuals.[7] AGEs can have long-lasting effects on metabolic memory, and especially in older individuals, their accumulation seem to play a role in frailty and reduced muscle and physical function, in addition to vascular dysfunction.[13–16] Moreover, three studies included participants with type 1[9] and type 2[8] diabetes and patients living with human immunodeficiency virus.[10] Both hyperglycemia and elevated oxidative stress are complications related to these diseases and, in turn, can increase endogenous AGEs formation.[17]

Second, medication use may also affect AGEs and sRAGE concentrations.[18] Yet, current medication use was mentioned as exclusion criteria in only two out of the seven studies[6,7] mentioned by Kotani and Gugliucci.[1] Exogenous AGEs from smoking[19,20] and dietary intake[21,22] are major contributors to the body pool of AGEs. Conversely, in two papers, there is no mention about participants smoking status,[5,10] and dietary AGEs intake were only quantified in two studies.[4,5] In the study conducted by Walter et al, the intervention consisted of 11-week physical activity programme and dietary counselling.[5] Dietary AGEs intake was assessed before and after the intervention, based on a 7-day food record. Besides the reduction in serum AGEs, the authors also observed a lower dietary AGEs intake.[5] In a randomized controlled parallel trial, 43 healthy overweight or obese men were assigned to one of three groups: low-AGE diet, exercise with habitual dietary intake, or exercise plus low AGE diet.[4] Interestingly, in the exercise with habitual dietary intake group, concentrations of AGEs remained unchanged after the intervention period. Whereas, in both groups following a low-AGEs diet, serum AGEs decreased.[4]

Additionally, we also searched for original articles that investigated the effects of exercise on serum AGEs and its soluble receptor concentrations, in both adults and elderly individuals, published up to March 2020, on MEDLINE (PubMed, www.pubmed.com). The used search strategy was AGEs OR soluble receptor AGEs AND exercise OR physical activity. We identified four more studies in which the sRAGE was evaluated in response to an exercise intervention (Table 1).[23–26] Among the acute studies, sRAGE concentrations remained unchanged after the inventions.[23,26] Nevertheless, the exercise intervention increased serum sRAGE in chronic studies.[24,25] Although study duration may play a role on sRAGE concentrations, the results from these studies demonstrate that the effect of exercise on sRAGE serum concentrations is inconsistent, similar to what we observed in our systematic review in response to weight management interventions (diet and bariatric surgery).[2] Therefore, further research is warranted to understand the potential modulator effect of exercise on AGEs and its receptors concentrations.

Finally, we believe the review letter from Kotani and Gugliucci[1] raises an important discussion on the role of exercise in preventing complications related to AGEs accumulation in the body. However, it is not possible yet to conclude whether and how exercise affects AGEs and sRAGE concentrations in humans based on the available studies. Future well-designed studies are required to investigate the possible beneficial effects of exercise on these glycation markers, considering other factors that can influence its concentrations.

KEYWORDS

advanced glycation end product, chronic diseases, physical activity, sRAGE

TABLE 1 Characteristics of the additional studies in which the response of soluble receptor for advanced glycation end products to exercise interventions was assessed

Reference	Samples	Intervention	Duration	Main results	Major comments
Danzig et al, 2010[23]	21 elderly with CAD (18 male) and 22 healthy adults (17 male) Age: Elderly: 65 ± 7 years Adults: 30 ± 5 years	Groups: 1 Exercise in healthy adults (*n* = 22): Bicycle performed up to the maximal tolerated effort 2 Exercise in elderly with CAD (*n* = 21): Bicycle performed up to the maximal tolerated effort	1 day	Exercise had no effect on sRAGE in both elderly with CAD and healthy adults	Acute Study. All CAD patients were in therapy including ACE inhibitors, statins, and low-dose (100 mg) acetylsalicylic acid. All patients were invited to withdraw all antianginal treatment (calcium channel blockers, beta-blockers, long- acting nitrates) at least 24 h before the test.
Choi et al, 2012[24]	75 women with T2DM Age: 54.4 ± 6.6 years	Groups: 1 Control group (*n* = 37): No exercise 2 60 min of aerobic exercise at moderate intensity 5×/week (*n* = 38)	12 weeks	Exercise group: ↑ sRAGE	Medical history for medications at baseline was well matched between the control and exercise groups and was not changed during the intervention period. Level of physical activity was not monitored during the study, especially in the control group.
Sponder et al, 2018[25]	98 adults and elderly with at least one cardiovascular risk (60 males) Age: 30-65 years	At least 75 min/week of vigorous or 150 min/week of moderate intensity endurance training within the calculated training pulse Groups: Initially nonsportive 1 Performance gain ≤ 4.9% 2 Performance gain > 5% Initially sportive 3 Performance gain ≤ 4.9% 4 Performance gain > 5%	8 months	↑ sRAGE (up to 22%) both among initially sportive and noninitially sportive subjects with a performance gain >5% when compared with a gain ≤4.9%	Subjects had at least one classic cardiovascular risk factor: Excess body weight, hypertension with antihypertensive medication, hyper/dyslipidemia with statin therapy, diabetes mellitus with medication, smoker, and known chronic heart disease.
Fuller et al, 2018[26]	12 healthy men Age: 26.6 ± 3.8 years	Groups: 1 High fat diet (*n* = 12) 2 High fat diet + cycle ergometer for 45 mins at 65% VO_2 peak (*n* = 12)	1 day	No effect of exercise on sRAGE, esRAGE, and cRAGE	Acute study. No record of medication use, habitual dietary intake, neither level of physical activity from subjects.

Abbreviations: CAD: coronary artery disease; ACE: angiotensin-converting enzyme;T2DM: Type 2 Diabetes Mellitus; sRAGE: soluble receptor of advanced glycation end products; esRAGE: endogenous secretory receptor for advanced glycation end products; cRAGE: cleaved receptor for advanced glycation end products; ↓: reduced; ↑: increased.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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