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Review Article

The Influence of Regular Physical Exercise on the Advanced Glycated End Products

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ABSTRACT

Advanced Glycated End-products (AGEs) are heterogeneous glycated metabolites of protein, lipid, or nucleic acid. They are products of a chain of chemical reactions endogenously or diet and tobacco smoking exogenously. They exert significant pathological effects on many body tissues, leading to chronic disease complications such as diabetes, cardiovascular diseases, Alzheimer's disease, etc. This narrative review shows that there are no agreed management options to reduce AGEs level. However, regular Physical Exercise (PE) has a positive impact on the serum AGEs level through multiple additive metabolic effects associated with weight management, reduction in insulin sensitivity, decrease in receptors of AGEs, oxidative stress, and an overall improvement in the AGEs hemostasis. Evidence supports the synergistic effect of changing lifestyle, including regular PE on the progression of AGEs. Nevertheless, the literature needs further clinical evidence to address the required PE prescription that would be sufficient to reduce AGEs level.

Keywords: Advanced glycated end-products; Physical exercise; Chronic disease; Diabetes mellitus; Aging

Abbreviations

ADL: Activities of Daily Living; AGEs: Advanced Glycated End-Products; BMI: Body Mass Index; CML: Carboxymethyl-Lysine; CRP: C-reactive Protein; CVD: Cardiovascular Disease; DNA: Deoxyribonucleic Acid; DM: Diabetes Mellitus; HbA_1c: Glycated Hemoglobin A_1c; NF-κB: Nuclear Factor-kappa Beta; PE: Physical Exercise; RAGE: Receptors Advanced Glycated End Products; TNF-α: Tumor Necrosis Factor-α

Introduction

Advanced Glycated End-products (AGEs) are the outcome of prolonged exposure to sugar, thus called glycated. They could be proteins or lipids or nucleic acid in origin and are considered essential biomarkers for many chronic diseases, including Diabetes Mellitus (DM), Cardiovascular Disease (CVD), chronic renal, and Alzheimer's disease. Further, they are significantly linked to aging [1,2].

They are categorized widely into endogenous types and exogenous derived AGEs. Endogenous ones metabolically occur in DM; the best example is Glycated Hemoglobin A_1c (HbA_1c), which is used for clinical diagnosis and monitoring of DM. Exogenously are usually food derivatives mainly from animals. The best examples are red meat and butter [3,4].

Accumulated knowledge pointed to the role of AGEs for aging and aggravation of the age-related diseases. They are involved through complicated intracellular mechanisms that lead to cellular damage and subsequent vascular complications. The complications result from three primary AGEs damaging mechanisms; of impaired protein structure, cross-linkage of collagen, and cellular activation [5].

There is no international agreement on effective management to minimize the impact of AGEs. Nevertheless, evidence highlighted the preventive influence of some vitamins, supplements, and certain medications on the AGEs level as one of the most useful approaches [6,7,8]. Regular physical exercise is another potential area for study to prevent DM, CVD, some chronic diseases, and the accumulation of AGEs [9]. This narrative review attempts to explore the AGEs from metabolic aspects and to highlight the role and mechanism of regular PE on their progression.

Definition of advanced glycated end-products

Advanced glycated end-products are altered compounds, originally proteins, lipids, or nucleic acids, which are nonenzymatically glycated and oxidized following exposure to aldose sugars. They are accumulated in different body tissues during the normal aging process. Additionally, they are linked to many vascular and neurodegenerative manifestations in many chronic diseases. Advanced glycated end-products are responsible for various pathophysiological changes in DM, CVD, renal, cataract, Alzheimer's disease, and other neurodegenerative disorders [10].

Source of advanced glycated end-products

Advanced glycated end products can be originated endogenously, mainly in the aging process and during some pathological conditions, or exogenously from food intake or smoking and referred to as glycotoxins. Endogenously, proteins, lipids, and nucleic acids get glycated either in hyperglycemic or oxidative stress [11]. This is carried out through different metabolic pathways when reducing sugar interreacts by a non-enzymatic way with either amino acids in proteins, lipids, or Deoxyribonucleic Acid (DNA). These glycolytic intermediates generate reactive aldehydes and, eventually, AGEs due to further oxidation and glycation [12,13]. Exogenously, AGEs are acquired through the consumption of high heat processed diet and modern western diets [14,15].

Metabolism of advanced glycated end-products

Formation of AGEs can be through three main metabolic pathways; Maillard reaction, oxidation & peroxidation, and through Polyol pathway as in Figure 1. The Maillard reaction occurs between reactive carbonyls in reducing sugar and their metabolites, such as methylglyoxal or deoxyglucosone, with amino groups from the Schiff base and Amadori products set of chemical rearrangement; (the byproducts from the glycation of protein, DNA, or lipids). The second pathway is through oxidative stress, where autoxidation of glucose or peroxidation of lipids occurs. These result in many dicarbonyl derivatives like glyoxal, methylglyoxal (MG), and 3-deoxyglucosone, collectively known as α-oxaldehydes. These chemicals interact with the amino acids and produce AGEs. The third mean that leads to the production of AGE is the polyol pathway. Glucose is reduced to sorbitol via aldose reductase, which is reduced further by sorbitol

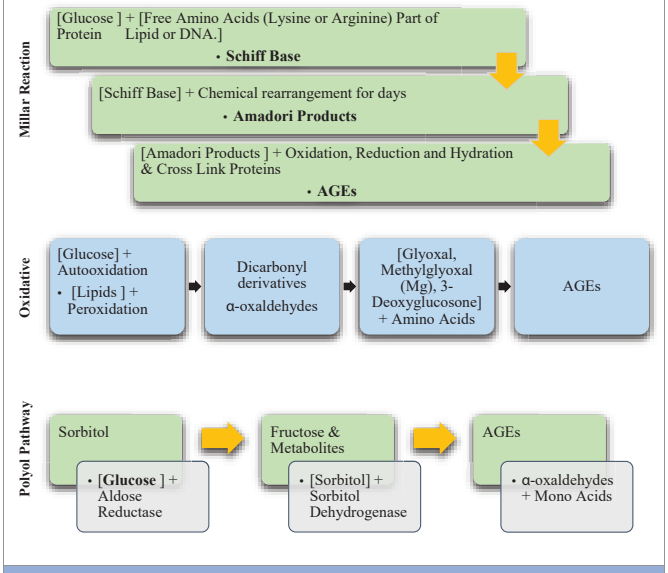

Figure 1: Metabolic formation of endogenous advanced glycated end products the Oxidative part.

dehydrogenase to fructose. Fructose metabolites also undergo chemical reactions to yield α-oxaldehydes, which finally interact with monoacids to produce AGEs [16,17,18,19].

All AGEs are stable heterogeneous chemicals, have some fluorescent properties, cross-linked, and accumulate either inside or outside cells, resulting in significant interference with protein functions. Among the commonest are carboxymethyl-lysine (CML), pentosidine, pyrrolidine, and methylglyoxal (α-oxaldehyde) biomarkers for AGEs [20].

Exogenously, AGEs can be acquired by consuming certain food items like custard, burned carbs, caramel, coffee roasting, and bread baking, especially after they are exposed to heat. Heat is well known to stimulate Maillard's reaction and add more safety and taste in the food industry [21]. In addition to food intake, tobacco smoke inhalation and air pollution are other exogenous sources of AGEs [22].

Pathophysiological effect of advanced glycated end-products

Advanced glycated end products may exert their pathological effect through two mechanisms, extracellularly and intracellularly, leading to significant pro-oxidant & inflammatory actions and protein structure damage [23].

Extracellularly, the impact is achieved by two means. Firstly, forming cross-links between critical molecules in the cellular basement membrane, cellular structure, characteristics, and function eventually results in permanent changes. Secondly, through the interaction of AGEs with Receptors Advanced Glycated End products (RAGE) that change the cellular function and leads to the intracellular effect [24].

Intracellularly, the interaction of AGEs with RAGE, a member of the immunoglobulin superfamily of receptors, which is highly expressed in many cells, leads to many intracellular chemical changes. These changes finally activate Nuclear Factor-kappa beta (NF-κB) in the cellular nucleus causing higher production of proinflammatory cytokines, adhesion molecules, and RAGE receptors as well. Subsequently, inflammatory mediators get activated, mainly Tumor

Necrosis Factor-α (TNF-α), interleukin-6, and C-reactive protein (CRP) [25].

This inflammatory status is associated with many pathological conditions, co-existed in diseases with high AGEs such as DM and its complications, including diabetic nephropathy, peripheral neuropathy, retinopathy, cataracts, and other degenerative ophthalmic diseases. Common medical conditions exhibit high AGEs levels like CVD, Alzheimer's, sarcopenia, renal diseases, rheumatoid arthritis, Parkinson's disease, vascular dementia, and other chronic diseases [26,27,28].

The serum level of AGEs is under the control of many factors that include endogenous production, external dietary intake, and renal & enzymatic clearance. The detoxification of AGEs is done by enzymes, e.g., glyoxalase I, II, and carbonyl reductase. This mechanism is thought to slow down with advancement in age. This explains why the AGEs levels are higher in the elderly. When chronic diseases and aging co-exists, further accumulation and development of long-term complications may become accelerated [29,30].

Evidence of the regular physical exercise effect on advanced glycated end-products

The effect of regular PE on body physiology and metabolic hemostasis was highlighted recurrently in the medical literature. The health benefits at both the macro and microlevel of the regular PE is an emerging field of interest for many researchers as it is a cost-effective and preventive management option, particularly for chronic diseases [31,32,33,34].

There is an agreement that PE's effect is dose-related, accumulative, and inclusive, where it involves all body systems synergistically with complicity and complexity acutely and chronically [35,36]. Physical exercise is defined as a planned movement of a muscle or group of muscles in a repetitive manner aiming to achieve health-related or/ and skill-related benefits. Health-related benefits are body components improvement, cardiopulmonary fitness, flexibility, and both muscular strength & endurance. The skilled related benefits are usually more advanced ones, including balance, power, coordination, agility, reaction time, and speed [37,38].

The recommended daily PE for maintaining weight, prevention from chronic diseases, and general health benefits is (150) minutes per week of moderate activity, preferably a mix of both cardio and resistant exercises. For weight management and another part of many chronic disease plans, it could reach up to (300) minutes per week between cardio and resistant PE. Some medical conditions have specific considerations or precautions on the PE prescription [39].

T Yoshikawa and his team highlighted the favorable impact of healthy lifestyle modification on the level of serum AGEs during a controlled clinical trial in (2009). All eligible participants underwent (12) weeks of a healthy diet and a structured, supervised mixed PE program of cardio and resistance exercises. The study showed a noticeable change in anthropometric measurements, lipid profile, and serum AGEs level. Although the participants' age group was between (37- 70) years and all recruited participants were healthy females, mixing the intervention between dietary and PE made it hard to relate the effect to one of them [40].

Similar findings were identified by K Kotani *et al.* on both genders but non-diabetic elder age group with a longer only PE program of (6) months. Both Body Mass Index (BMI) and serum AGEs and even soluble receptor for AGEs were reduced [41].

Quite some equivalent results reported in the literature support the effect of regular PE on reducing AGEs among DM patients. Russell *et al.,* demonstrated improvement in glycemic control, BMI, and post-intervention microvascular adaptation among type II DM patients of both genders [42]. B Farinha (2018) established similarly improved AGEs level and other glycemic control parameters following (6) weeks program of both resistance training and high-intensity intermittent training among type I DM patients [43].

Some studies revealed that even patients with chronic diseases showed a marked reduction in AGEs serum level following PE. KL Rodrigues *et al.* reported improved AGEs serum level among physically inactive HIV-patients following three supervised PE programs [44]. Furthermore, Sheikholeslami-Vatani illustrated a significant reduction in AGEs level among postmenopausal women with type II DM after conducting eight weeks of supervised resistant PE three times a week [45].

Many authors pointed to regular PE on reducing AGEs serum levels in different chronic diseases, including CVD, obesity, and various complications of type II DM like peripheral neuropathy and erectile dysfunction [46,47,48,49,50,51]. Furthermore, low physical activity is significantly associated with higher serum levels of AGEs. Hans Drenth *et al.* addressed this inverse association, following his cross-sectional data analysis of about (5624) elderly client's skin autofluorescence AGEs levels compared to physical activity days and physical function. Results showed that higher levels of AGEs might be a contributing factor & a biomarker for low physical activity, and low functionality. However, the recruited sample in his study was the elderly, where AGEs are also a substantial contributing factor for aging. However, the finding is crucial, as even the elderly population engaged in regular PE showed reduced AGEs levels [52]. Similarly, Semba and his team reached similar findings when they compared the walking speed with the AGE levels that are also confirmed with low functionality by Sun and his colleagues [53,54].

Such parallel confirmation was described by Whitson HE and his team when they assessed the quality of life of a group of older adults by evaluating their ability to perform Activities of Daily Living (ADL). The more disabled with low ADL scores, the higher the serum AGEs levels [55].

Repeated correlation supports the effect of PE on AGEs levels from muscular outcome perspectives, where the more the muscular disability and weakness, the higher the level of AGEs as reported by Shah KM *et al.* in studying the upper arms, or by Dalal and her colleagues when they assessed the muscle power of the hands in elderly females [56,57,58].

High AGEs level was correlated positively with increased weight, which is reflected more in sedentary individuals, as described by Maria *et al.* On the contrary, the muscle mass was negatively correlated with the AGEs level, as Tanaka illustrated, which is seen as more physically active [59,60].

The overall findings stated that the AGEs level is high, with physically inactive candidates and markedly reduced in regular PE. Further, this negative correlation is evident by weight, muscle mass, and physical function [61].

Mechanism of regular physical exercise on the pathophysiology of advanced glycated end-products

The mechanism of reducing the level of AGEs by the PE is still not fully explored. However, some authors suggested many probable explanations that reflected the PE effect's complexity on metabolic hemostasis. All proposed mechanisms are listed in Figure 2.

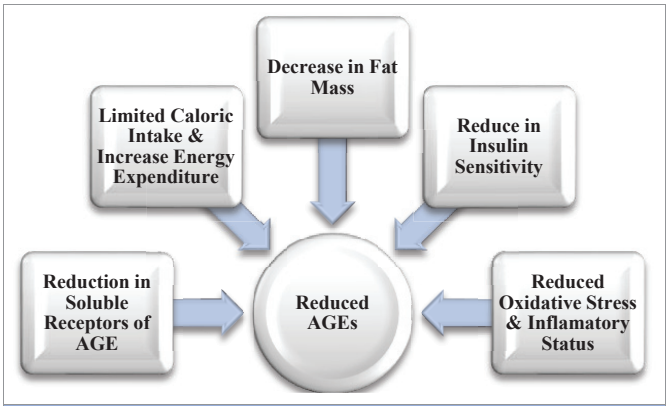

Figure 2: Physical exercise mechanisms contributed to a decrease in advanced glycated end products.

One quite frequent explanation reported in the literature is by reducing the associated AGEs soluble receptors. [41] Tavares *et al.* reported a reduction in overall AGEs soluble receptors. However, he involved many studies focusing on weight management with bariatric surgery and other lifestyle modifications [62]. Nevertheless, even with limited studies that used PE exclusively as an intervention, reduced AGEs are related to an overall reduction of caloric intake associated with PE programs. Reduction in the overall energy intake will reduce the high glucose environment on the body and, subsequently, substrates of AGEs [63,64].

Another likely mechanism is related to the loss of fat mass among those who regularly do PE. A proposed idea is that most of the AGEs are available in the adipose tissues and lost following regular PE with fat mass loss. An inverse correlation between fat mass and serum level of AGEs and receptors of AGEs was proposed as a possible explanatory mechanism [65,66,67,68].

Some researchers suggested that PE could decrease in the soluble receptor for AGEs due to reduction of the insulin sensitivity and the associated reduction in fat mass [69,70,71]. Soluble receptors for AGEs also play a role in stopping interaction between AGEs and its assigned receptors [72].

Another explanation could be related to the improvement in glycemic control. The more controlled the serum glucose level, the fewer AGEs found in body tissues as these compounds are conditioned by glycemia levels, which is greatly influenced by regular PE [73,74]. Such effect is under the impact of a noticeable reduction on the peripheral resistance to insulin, which could attenuate the accumulation of AGEs [75,76,77].

Some authors link the level of AGEs in diabetics to the oxidative stress mechanism, which is also impaired and contributes to many chronic complications in diabetics [78]. The more physically active the individual, the less the level of oxidative stress, leading to increased anti-oxidation capacity, thus reducing AGEs levels [79].

Furthermore, a link was emphasized between reducing the AGEs level and reducing the inflammatory status in people with diabetes after regular PE. It is a bidirectional relation due to cross-linking between soluble AGEs receptors and subsequent monocytes and other inflammatory pathways [80]. Available evidence demonstrates that regular PE improves immune capacities and systemic anti-inflammation impact, like in DM [81,82,83,84].

Conclusion

Advanced glycated end products are the outcome of prolonged exposure to hyperglycemia, where proteins, lipids, and nucleic acids are glycated and yield intra and extracellular effects. In addition to healthy aging, they are considered responsible metabolites for long-term complications of DM, CVD, and Alzheimer's disease.

The serum level of AGEs is under hemostatic control and may result in pathological conditions of chronic course if disturbed. This made AGEs to be of great attention from the research community. There is no agreed management modality to manage AGEs serum level. However, PE showed a convincing supportive role in limiting their impact and control the disease status. Physical exercise is considered preventive for AGEs accumulation and slows down chronic disease sequels' progression, especially if combined with other options that stabilize the medical condition.

The role of regular PE could be explained by a decrease in fat mass, insulin sensitivity, overall inflammatory status, RAGEs expression, and general body physiology.

Future directions must give space for further assessing which exercise type is superior in affecting the AGEs level and whether PE alone is as effective as dietary or medication management.

Conflict of interest

Authors have no financial interest, arrangement, or affiliation with anyone concerning this narrative review that could be perceived as a real or apparent conflict of interest in the context of the subject of this study.

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