

Review

Advanced glycation end-products (AGEs) and heart failure: Pathophysiology and clinical implications

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Abstract

Advanced glycation end-products (AGEs) are molecules formed during a non-enzymatic reaction between proteins and sugar residues, called the Maillard reaction. AGEs accumulate in the human body with age, and accumulation is accelerated in the presence of diabetes mellitus. In patients with diabetes, AGE accumulation is associated with the development of cardiac dysfunction. Enhanced AGE accumulation is not restricted to patients with diabetes, but can also occur in renal failure, enhanced states of oxidative stress, and by an increased intake of AGEs. Several lines of evidence suggest that AGEs are related to the development and progression of heart failure in non-diabetic patients as well. Preliminary small intervention studies with AGE cross-link breakers in heart failure patients have shown promising results. In this review, the role of AGEs in the development of heart failure and the role of AGE intervention as a possible treatment for heart failure are discussed. © 2007 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.

Keywords: Heart failure; Advanced glycation end-products; Atherosclerosis; Oxidative stress; Cross-linking

1. Introduction

Advanced glycation end-products (AGEs) were first identified in cooked food as end-products from a non-enzymatic reaction between sugars and proteins called the Maillard reaction [1]. Since the discovery that this reaction also occurs in vivo, it has been suggested that AGEs may play a role in the pathophysiology of several different diseases [2]. AGEs accumulate in the human body with age, and enhanced AGE accumulation has been reported in patients with diabetes. Consequently, the primary interest of AGE-related research has focussed on diabetes.

In patients with diabetes, enhanced AGE accumulation is associated with the development of diabetic sequelae and adverse outcome [3,4]. One of the diabetic complications

associated with AGE accumulation is the development of cardiac dysfunction [5]. The first manifestation is asymptomatic diastolic dysfunction, which later progresses to systolic dysfunction. In the presence of other substrates for heart failure (e.g. hypertension, coronary artery disease) this can accelerate the progression of heart failure.

Enhanced AGE accumulation is not just restricted to patients with diabetes, but can also occur in renal failure, enhanced states of oxidative stress, and as a result of an increased intake of AGEs. Therefore, AGEs may be involved in the development of heart failure in non-diabetic patients as well. Although this has been recognised by several authors, the current literature lacks a comprehensive review on the role of AGEs in heart failure [5–8]. This review will discuss basic AGE physiology, and the pathophysiological role that AGEs may play in the development and progression of heart failure. In addition, human and animal studies of the role of AGEs in heart failure will be reviewed. Finally, the possible

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clinical implications of AGE intervention in heart failure will be discussed.

2. Basic AGE chemistry and physiology

In the first step of the Maillard reaction, a sugar adduct such as glucose, reacts with a protein amino (NH_2) group, to form a Schiff-base (Fig. 1). This reaction occurs fast, and is reversible, depending on substrate concentrations. The Schiff-base then converts into a more stable Amadori product (e.g. HbA1c). The subsequent re-arrangement of Amadori products leads to the formation of stable and irreversible AGE compounds [1]. The final step of the Maillard reaction is driven by oxidative stress, defined as a high steady state level of reactive oxygen species (ROS). AGEs accelerate oxidation, and therefore favour their own production [1]. These pathways are especially important in diabetes. In addition to carbohydrate-driven reactions, other pathways have been identified. Important intermediates in these pathways are radicalized sugar and lipid adducts, the so-called reactive carbonyl compounds. Reactive carbonyl compounds are produced from lipids or carbohydrates reacting with ROS. These carbonyl compounds subsequently react with proteins to form AGEs [1].

AGEs have traditionally been detected using their fluorescence properties [9]. Recently, several mass spectrometry methods have been developed for the determination of AGE levels in both tissue and blood samples. These include gas chromatography mass spectrometry (GC–MS), and liquid chromatography mass spectrometry (LC–MS) [10]. The latter is considered to be the most accurate technique available at the moment. Other methods that have been used to measure AGE levels include high performance liquid chromatography (HPLC), enzyme-linked immunosorbent assay (ELISA),

several immunohistochemical techniques, and techniques based upon the fluorescence properties of AGEs [10,11]. However, there are some problems associated with these techniques. HPLC although relatively accurate, is time-consuming [10] and there are difficulties associated with standardization of ELISA [10]. In addition, fluorescent techniques previously required invasive tissue sampling. Recently, these techniques have been adapted to enable their use in a clinical setting [11]. In addition to biochemical assays and fluorescent techniques, there are several immunohistochemical techniques which can be used to assess AGE levels [12]. However, these methods are not suitable for routine clinical use. Differences in the accuracy of the techniques used, should be taken into consideration when interpreting data on AGE levels.

AGE accumulation in vivo occurs throughout the body, including the skin, neural, vascular, renal, and cardiac tissue [13,14]. Accumulation may occur within the cells or in the extra-cellular compartments. In patients with diabetes, accelerated AGE accumulation occurs mainly as a consequence of high glucose levels [15]. Renal failure also contributes to enhanced AGE accumulation through decreased clearance of AGE degradation products combined with increased exposure to oxidative stress [11,16]. Cigarette smoke and heated, cooked or roasted food products are other possible sources of increased AGE accumulation [17,18].

3. Pathophysiological effects of AGEs that may cause or accelerate heart failure

Heart failure is characterised by a structural or functional cardiac disorder that results in an inability of the heart to fill with or pump out blood, combined with symptoms of dyspnoea or fatigue. AGEs may contribute to the

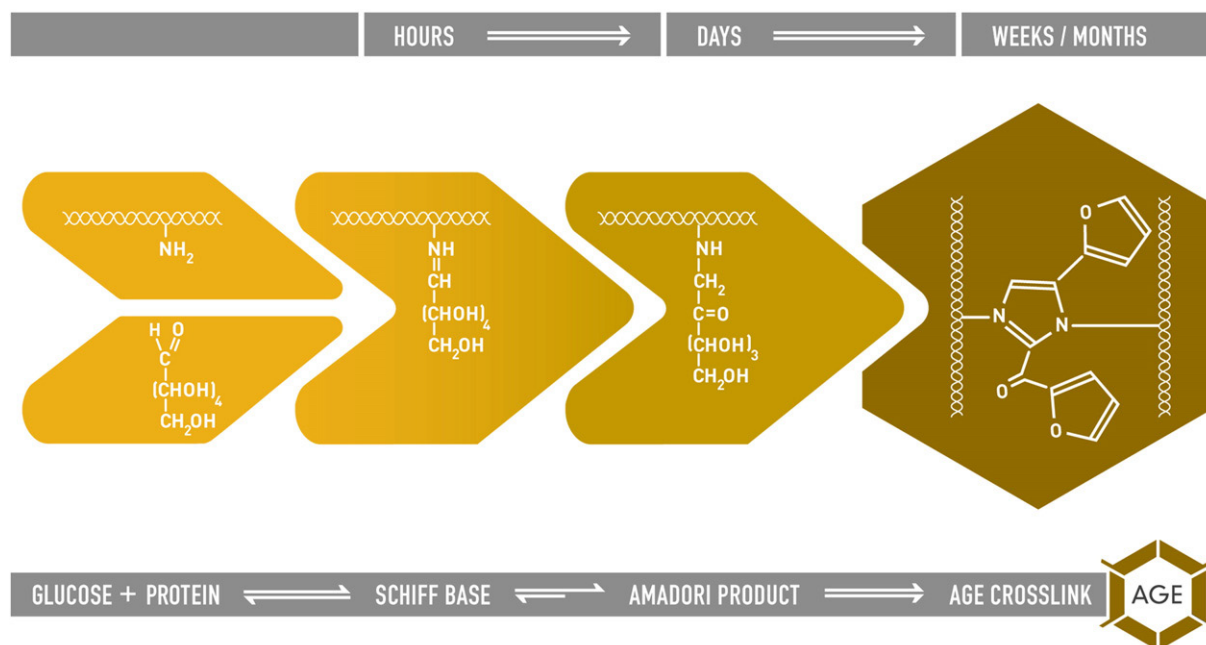


Fig. 1. The Maillard reaction. Abbreviations: AGE: advanced glycation end-product.

development of heart failure via two pathways. Firstly, AGEs affect the physiological properties of proteins in the extracellular matrix by creating cross-links. Secondly, AGEs cause multiple vascular and myocardial changes via the interaction with AGE receptors. AGEs may induce diastolic, systolic and vascular dysfunction through these pathways. Subsequently, these abnormalities may result in the development and progression of heart failure. A summary of these pathways is presented in Fig. 2.

3.1. AGEs and diastolic dysfunction

Cross-linking of extracellular matrix proteins is essentially a physiological phenomenon. It strengthens tissues ensuring tissue integrity, without compromising flexibility. AGEs, however, can covalently bind other AGEs, and form additional cross-links between matrix proteins like collagen, laminin, and elastin [2]. Excessive cross-linking caused by AGE accumulation undermines the flexibility of matrix proteins (Fig. 3a). This increased rigidity may induce diastolic dysfunction in the heart. Another pathway by which AGEs may contribute to the development of diastolic dysfunction is via the activation of AGE receptors, which have been identified on several cell-types (Fig. 3b) [19]. The most important AGE receptor is the Receptor for AGE

(RAGE). One of the receptor mediated effects of AGEs is the induction of fibrosis via the upregulation of transforming growth factor- β (TGF- β) [20]. AGE-receptor activation also seems to influence calcium metabolism in cardiac myocytes. Petrova et al. [21] created transgenic mice that over-expressed human RAGE in the heart and analyzed the calcium transients in cardiac myocytes in reaction to AGE exposure. RAGE over-expression was found to reduce the systolic and diastolic intra-cellular calcium concentration. Exposure to AGE caused a significant delay in calcium re-uptake. As a consequence, the duration of the re-polarisation phase of the cardiac contraction may increase, subsequently causing diastolic dysfunction.

3.2. AGEs and systolic dysfunction

AGE accumulation may be involved in the development of systolic dysfunction by accelerating the progression of coronary artery disease. AGE-receptor interaction may induce atherosclerosis, thrombosis, and vasoconstriction (Fig. 3b). By negatively influencing LDL-metabolism, AGEs may further increase the risk of developing atherosclerosis and subsequent myocardial infarction [22–24]. Small soluble AGE peptides can form cross-links with low-density lipoprotein (LDL), rendering LDL particles more atherogenic and less susceptible

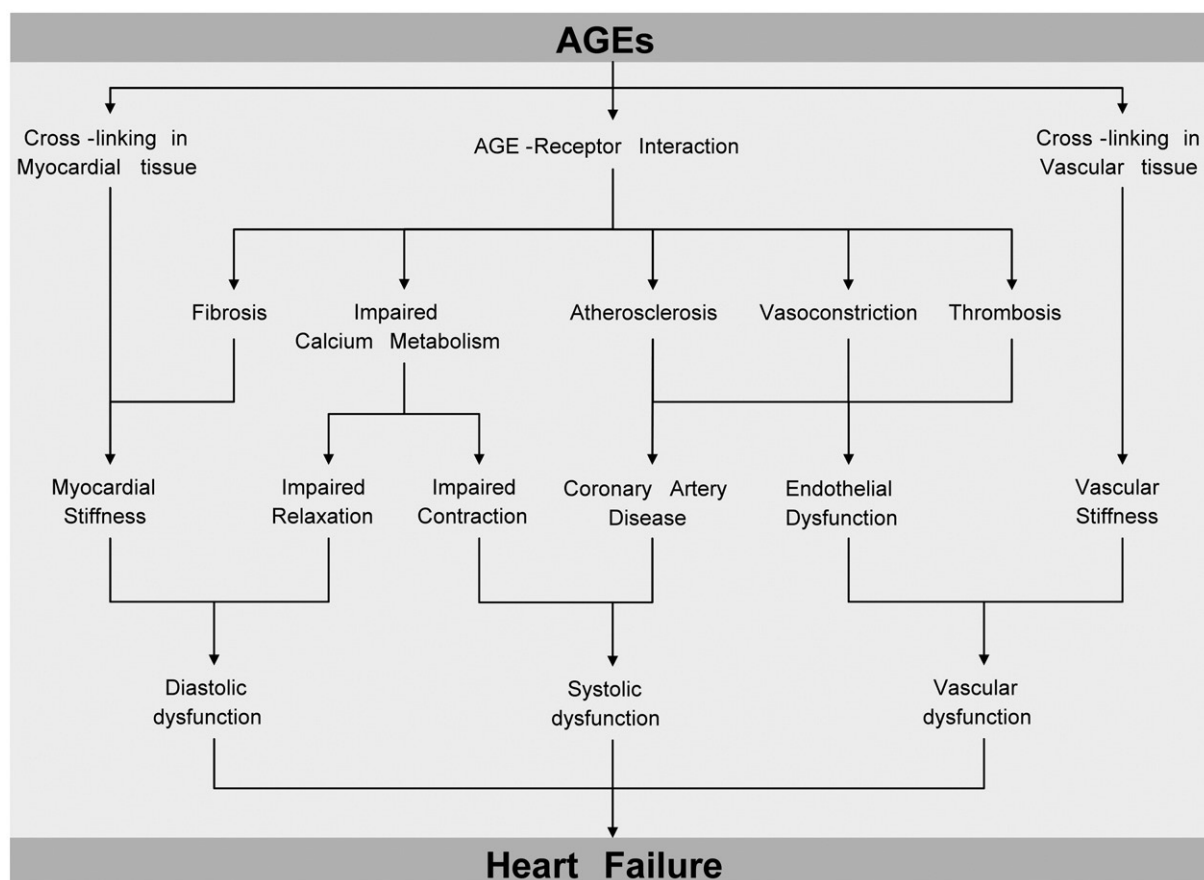


Fig. 2. Summary of the pathways via which AGEs may cause heart failure. Abbreviations: AGE: advanced glycation end-product.

to LDL-receptor uptake and subsequent clearance [22]. In addition, AGE modified LDL is more susceptible to macrophage uptake by AGE receptors, creating foam cells [23,24]. If AGEs play a role in the development of atherosclerosis, one would expect AGE-lowering treatments to reduce atherosclerosis and possibly even myocardial infarction. Indeed, the use of AGE breakers and AGE-formation inhibitors in diabetic animal models reverses atherosclerosis [25]. Whether or not myocardial infarction can be prevented by AGE-lowering treatments remains to be investigated. Additionally, the reduced levels of intra-cellular calcium induced by AGEs, as discussed above, may induce systolic dysfunction due to decreased myocardial contractility [21].

3.3. AGEs and vascular dysfunction

Endothelial dysfunction is an important predictor of adverse cardiac events, hospitalization for heart failure, and death [26]. Together with vascular compliance, endothelial dysfunction closely relates to the functional capacity of chronic heart failure patients [27]. AGEs are able to impair vascular function by influencing both endothelial function and vascular compliance (Fig. 3a and b). AGEs may induce endothelial dysfunction by reducing the availability of the vasodilator nitric oxide (NO) [28,29]. Furthermore, AGEs can enhance the production of endothelin-1, a potent vasoconstrictor [28,29]. Vascular compliance is influenced by AGE cross-linking in a similar fashion as in myocardial tissue. In humans, levels of circulating AGEs correlate with arterial compliance [30]. Moreover, treatment with AGE breaking medication (ALT-711) improves arterial compliance in patients with vascular stiffening [31].

4. Results from animal and human studies

4.1. Diastolic heart failure

The results of studies investigating the adverse effects of AGEs on cardiac function are summarized in Table 1. In rats, diastolic function measured by cardiac catheterisation has been shown to correlate with levels of carboxymethyllysine (CML), a well-known AGE [32]. Similar results were obtained in patients with type 1 diabetes mellitus [33]. Norton and colleagues [34] were the first to examine the role of AGEs in the development of diastolic dysfunction in an animal intervention study. In their experiment, the induction of diabetes in rats led to decreased compliance of the left ventricle measured with cardiac catheterisation. The authors also investigated whether captopril or the AGE-formation inhibitor aminoguanidine, could improve diastolic function. AGEs were determined by measuring myocardial collagen fluorescence. It was reported that aminoguanidine improved myocardial compliance, whereas no improvement was observed in captopril treated animals. The improvement with aminoguanidine was paralleled by a decrease in myocardial collagen fluorescence. Avendano et al. [35] confirmed these findings for

aminoguanidine in a similar experiment. However, they also reported a treatment effect of ACE inhibition (using enalapril) on diastolic dysfunction and AGE accumulation.

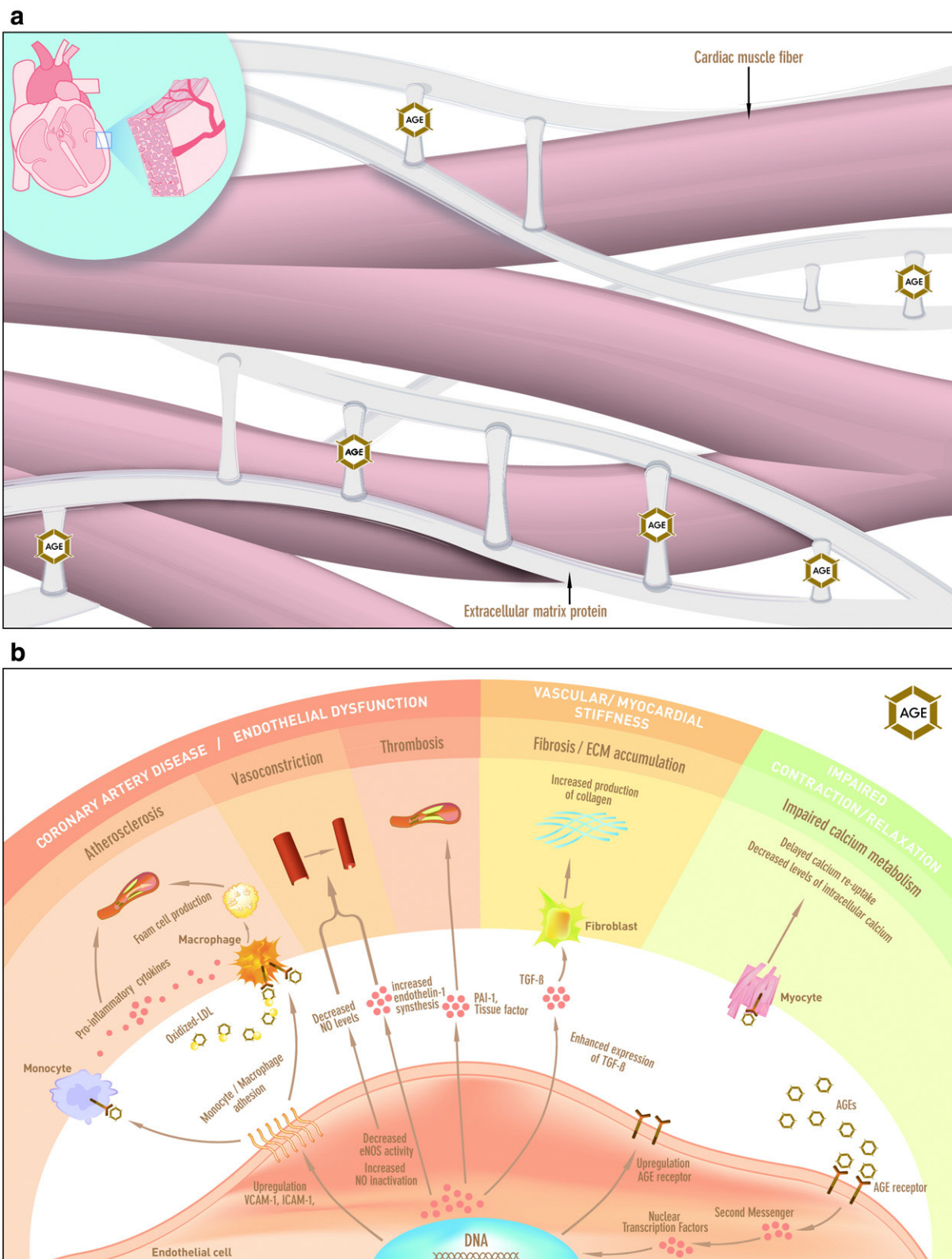
To date there are no published studies of the role of aminoguanidine on diastolic function in humans. Development was discontinued due to safety issues regarding the toxicity of aminoguanidine [36]. Another disadvantage of aminoguanidine is that it inhibits production of nitric oxide (NO). A well-known alternative for aminoguanidine is the AGE-breaker alagebrium (ALT-711). Using ALT-711, Asif et al. [37] studied the effect of AGE lowering on left ventricular stiffness in aged dogs. They observed a significant reduction in age-related left ventricular stiffness measured by cardiac catheterisation after a 4-week treatment with ALT-711. These results were confirmed by Vaitkevicius et al. [38] in a similar experiment. The effect of ALT-711 on diastolic dysfunction has also been studied in humans. In the DIAMOND trial, Little et al. [39] treated 23 patients with stable diastolic heart failure with ALT-711. After 16 weeks, left ventricular mass (measured by MRI) was reduced and diastolic function (measured by tissue Doppler) had improved. Furthermore, the drug was well-tolerated and had a positive effect on patients' quality of life. The results, however, should be interpreted with caution due to the open-label study design. The PEDESTAL trial is an open-label study to investigate the effects of ALT-711 on diastolic function and left ventricular mass in patients with systolic heart failure and diastolic dysfunction. Preliminary results confirm the findings of the DIAMOND trial [40].

4.2. Systolic heart failure

The majority of data gathered on the role of AGEs in systolic dysfunction originates from studies in diastolic dysfunction (see Table 1). In studies where left ventricular systolic function was normal, AGE-lowering treatment had no effect on systolic function [35,39,41]. Interestingly, AGE-lowering therapy appears to improve systolic function in animals with systolic dysfunction. Liu et al. [42] examined the effect of ALT-711 on haemodynamic changes occurring with age in diabetic dogs which had developed marked left ventricular systolic dysfunction and aortic stiffness. ALT-711 restored left ventricular systolic function, and reduced aortic stiffness and left ventricle mass. Vaitkevicius et al. [38] previously reported a similar effect of ALT-711 in aged monkeys with a reduced left ventricular systolic function. Cheng et al. [43] investigated the effect of the novel AGE-breaker C16 and ALT-711 on diabetes induced cardiac dysfunction in rats. Four weeks of treatment with either C16 or ALT-711 both significantly improved cardiac output, reduced total peripheral resistance, and increased systemic arterial compliance. Heidland et al. [44] were the first to measure plasma AGE levels in patients with severe systolic heart failure, heart transplant recipients, and normal controls. In contrast to expectations, the authors found lower levels of plasma CML and AGE-fluorescence in patients with systolic heart failure when compared to controls. Heart transplant recipients had higher

levels of AGEs than controls. Possible biases, however, were hypervolaemia, lower concentration of plasma protein and decreased dietary intake of AGEs in patients with systolic heart failure. Recently, we showed that plasma levels of carbox-

ymethyllysine (CML), a well-known AGE, correlate with NT-pro-BNP and NYHA functional class and predicted outcome in patients with systolic heart failure. Koyama et al. [45] also evaluated the prognostic value of serum AGEs in CHF. They



found that serum pentosidine levels were a significant predictor of cardiac death and re-hospitalization, independent of other known risk factors in CHF, like BNP, renal function, age, and NYHA functional class. The influence of AGE-lowering treatments in systolic dysfunction in humans are limited to the results of the PEDESTAL trial, as discussed previously, in which a trend towards an improvement in echocardiographic left ventricular systolic function was observed [40].

5. Discussion and clinical implications

The data presented in this review suggest that AGEs may be involved in the development of both diastolic and systolic heart failure. Evidence for a role of AGEs in diastolic heart failure is much stronger, but there is an overlap between the underlying pathophysiology of diastolic and systolic dysfunction. Diastolic dysfunction often precedes and/or accompanies systolic dysfunction. Over 90% of patients with systolic dysfunction have diastolic dysfunction as well [unpublished data]. One of the hallmarks of diastolic dysfunction is an increased left ventricle end diastolic pressure, which creates an enhanced susceptibility to develop pulmonary congestion and symptoms of dyspnoea. Indeed, in patients with systolic heart failure, diastolic function and not systolic function was related to NYHA functional class and predicted exercise intolerance measured with cardiopulmonary exercise testing [46]. Therefore, we believe that the effects of AGE accumulation on diastolic function may also have an impact on patients with systolic heart failure.

As discussed earlier, vascular function is an important determinant of morbidity and mortality in patients with heart failure. In this respect, patients with an increased afterload due to vascular dysfunction seem to be more likely to exhibit symptoms of reduced organ perfusion given a certain left ventricular ejection fraction. Although AGEs have been shown to have a marked effect on vascular function; whether improving vascular function by AGE intervention reduces morbidity and mortality in patients with heart failure remains to be investigated.

The adverse effects of AGE accumulation can be targeted in several ways. Two excellent reviews on this topic have been written by Peyroux et al. [47], and Monnier [48]. We have identified eight different AGE intervention strategies,

as illustrated in Fig. 4. The first step in the Maillard reaction is dependent on glucose levels, thus patients with high levels of glucose are more prone to AGE accumulation. Indeed, adequate glycaemic control in patients with diabetes mellitus can prevent increased AGE accumulation [3]. The final step in the Maillard reaction is catalyzed by oxidative stress. Therefore, anti-oxidants (e.g. benfotiamine, carnosine, and flavonoid) are possible candidates to inhibit this step. Other drugs that prevent the latter step in the Maillard reaction are known as AGE-formation inhibitors (e.g. aminoguanidine, and pyridoxamine). ACE inhibitors and angiotensin II receptor antagonists have shown inhibitory effects on AGE formation as well [49]. AGE breaking medication (e.g. ALT-711) has the capacity to break formed AGE cross-links. Thus, this group of drugs has the potential to repair tissue damage induced by AGEs [39,40]. AGE intake can also be modulated to prevent AGE accumulation. Both smoking and certain food products contain high levels of AGEs and AGE precursors. Smoking cessation and low-AGE diets have been shown to reduce AGE intake and thereby AGE levels in blood [17,18]. In addition, AGE-receptor interactions can be prevented in several ways. Firstly, by using a soluble form of the AGE receptor or an AGE lysozyme, AGEs and AGE precursors can be scavenged from the circulation [47,48]. Secondly, the consequences of AGEs can be prevented by blocking AGE receptors using antibodies [47,48]. Finally, intra-cellular signalling pathways upregulated by AGEs can be inhibited by AGE signal transduction inhibitors (e.g. incadronate disodium, cerivastatin, and curcumin) [47,48]. It should be noted that some of the drugs discussed above use more than one strategy to prevent AGE-related effects.

The cross-link breaker ALT-711 is currently being investigated for use in heart failure. ALT-711 (Alagebrium) or 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-thiazolium chloride, is the first of a new class of thiazolium derivatives which break established AGE cross-links between proteins. By cleaving AGE cross-links, ALT-711 has the ability to restore the compliance of aged and/or diabetic vascular tissue, and myocardium. The effects of ALT-711 are not restricted to vessel tissue and myocardium, but also occur for example in skin and renal tissue. Importantly, ALT-711 does not affect the natural carbohydrate modification to proteins, intra-

Fig. 3. a. An illustration of AGE cross-linking between matrix proteins surrounding the cardiac muscle fibres. Abbreviations: AGE: advanced glycation end-product. b. An illustration of the pathways involved in AGE-receptor interaction. AGE-receptor expression has been demonstrated on various cell-types, including endothelial cells, monocytes, macrophages, and cardiac myocytes [19]. The most important AGE receptor identified is the Receptor for AGE (RAGE). This is a multiligand receptor of the immunoglobulin superfamily. Although distinct families of ligands, among which are S100/calgranulins, amphoterin, and amyloid- β -peptide, can interact with RAGE, we will focus on the effects of AGE-ligands. Activation of RAGE stimulates second messenger pathways, among which the Ras pathway, Rac-Cdc42 pathway, Jac-Stat pathway, and the production of ROSs via the NADPH oxidase pathway [52,53]. In turn, these second messengers activate or prolong activation of nuclear transcription factors (e.g. nuclear factor- κ B), that subsequently upregulate the production of endothelin-1, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, plasminogen activator inhibitor-1 (PAI-1), tissue factor, and transforming growth factor- β (TGF- β) [52,53]. Activation of RAGE upregulates RAGE expression itself as well [54]. Via the pathways depicted in Fig. 3b, AGEs may contribute to the development of coronary artery disease, endothelial dysfunction, vascular and myocardial stiffness and impairment of cardiac contraction and relaxation. Abbreviations: AGE: advanced glycation end-product; LDL: low-density lipoprotein; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; PAI-1: plasminogen activator inhibitor-1; TGF- β : transforming growth factor- β ; NO: nitric oxide; eNOS: endothelial nitric oxide synthase; ECM: extracellular matrix.

Table 1
Animal and human studies on the role of AGEs in CHF

Reference	Study population	Study design	Results		
			AGE accumulation	Diastolic function	Systolic function
<i>Animal studies</i>					
Norton et al. [34]	104 Rats; ST-DM; (<i>n</i> =58); C (<i>n</i> =46)	Prosp.; captopril vs. AG; 4 months	AG prevented increased AGE fluor. in DM rats, effect of captopril not reported	AG prevented DD in DM rats; captopril did not	–
Avendano et al. [35]	24 Male dogs; alloxan induced GI (<i>n</i> =16); C (<i>n</i> =8)	Prosp.; enalapril vs. AG; 6 months	AG and enalapril prevented AGE formation	AG and enalapril prevented DD	No differences in SF were found
Asif et al. [37]	20 Male dogs; young C (<i>n</i> =7); old ALT-711 (<i>n</i> =8); old C (<i>n</i> =5)	Prosp.; ALT-711 vs. C; 1 month	–	ALT-711 improved DF	ALT-711 increased CO; no changes in LVEF
Vaitkevicius et al. [38]	6 aged primates; ALT-711; baseline as C	Prosp.; ALT-711; 3-week treatment, 39 weeks follow-up	–	ALT-711 improved DF	ALT-711 improved SF
Liu et al. [42]	12 Dogs; alloxan-DM; ALT-711 (<i>n</i> =5); C (<i>n</i> =7)	Prosp.; ALT-711 vs. C; 1 months	–	ALT-711 reduced aortic stiffness; no data on DF	ALT-711 restored LVEF
Chang et al. [41]	21 Rats; young C (<i>n</i> =7); old AG treated (<i>n</i> =7); old C (<i>n</i> =7)	Prosp.; AG vs. C, 6 months	–	AG improved arterial function; no data on DF	No differences in CO were found
Cheng et al. [43]	32 rats; ST-DM; ALT-711 (<i>n</i> =8); C16 (<i>n</i> =16); C (<i>n</i> =8)	Prosp.; ALT-711; C16 vs. C; 4 weeks	ALT-711 and C16 decreased AGE accumulation	ALT-711 and C16 improved arterial function; no data on DF	ALT-711 and C16 improved CO
Schafer et al. [32]	11 Zucker diabetic rats; 11 non-obese; non-DM littermates	Cross-sectional	AGEs increased in serum and cardiac tissue in DM rats.	Impaired DF in DM rats; DF correlated with cardiac AGE	No correlations between SF and AGE parameters
<i>Human studies</i>					
Berg et al. [33]	52 Patients with type 1 DM	Cross-sectional	No controls	Serum AGE levels correlated with DF	No correlations between SF and AGE parameters
Heidland et al. [44]	22 Patients with advanced SHF; 30 HTX recipients; 20 C	Case-control	Lower AGEs in CHF vs. C; higher in HTX recipients	–	–
Little et al. [39]	23 Patients with DHF	Prosp.; open-label; ALT-711; 16 weeks	–	ALT-711 improved DF (echo); decreased LV mass (MRI)	No differences in SF were found
Thohan et al. [40]	22 Patients with SHF and DHF	Prosp.; open-label; ALT-711; 6 months	–	ALT-711 improved DF (echo); decreased LV mass (echo)	Trend to improved SF
Koyama et al. [45]	141 Patients with CHF and 18 C	Prosp.; cohort study; 479 days; endpoint: death/re-hospitalization	Pentosidine independently predicted endpoint	–	–
Hartog et al. [55]	102 Patients with SHF	Prospective	CML correlated with NYHA functional class and NT-pro-BNP and predicted outcome	–	No correlation was found between CML and LVEF

Note. Abbreviations: AG: aminoguanidine; ST: streptozotocin; DM: diabetes mellitus; C: control; Prosp: prospective; fluor: fluorescence; DF: diastolic function; SF: systolic function; DD: diastolic dysfunction; SD: systolic dysfunction; GI: glucose intolerance; LVF: left ventricular function; CO: cardiac output; LVEF: left ventricle ejection fraction; DHF: diastolic heart failure; SHF: systolic heart failure; CHF: chronic heart failure; HTX: heart transplant; LV: left ventricle; MRI: magnetic resonance imaging; CML: carboxymethyllysine; CEL: carboxyethyllysine; NYHA: New York Heart Association; NT-pro-BNP: N-terminal-pro-brain natriuretic peptide.

molecular cross-linking or peptide bonds that ensure the normal integrity of the collagen chain. Clinical experiences with ALT-711 have been favourable. Generally, ALT-711 has been reported to be safe and well-tolerated at doses up to 210 mg, administered once or twice daily. No differences in the incidence or type of adverse events have been reported to date, in patients treated with ALT-711 vs. placebo.

Despite encouraging results, both the DIAMOND and the PEDESTAL trials have an open-label design, which is not ideal. Especially since the clinical end-points in these studies such as NYHA functional class, Minnesota Living with Heart Failure score, and exercise testing, are subjectively assessed and this may introduce bias. Double-blind, randomised, placebo-controlled trials using ALT-711 are currently ongoing.

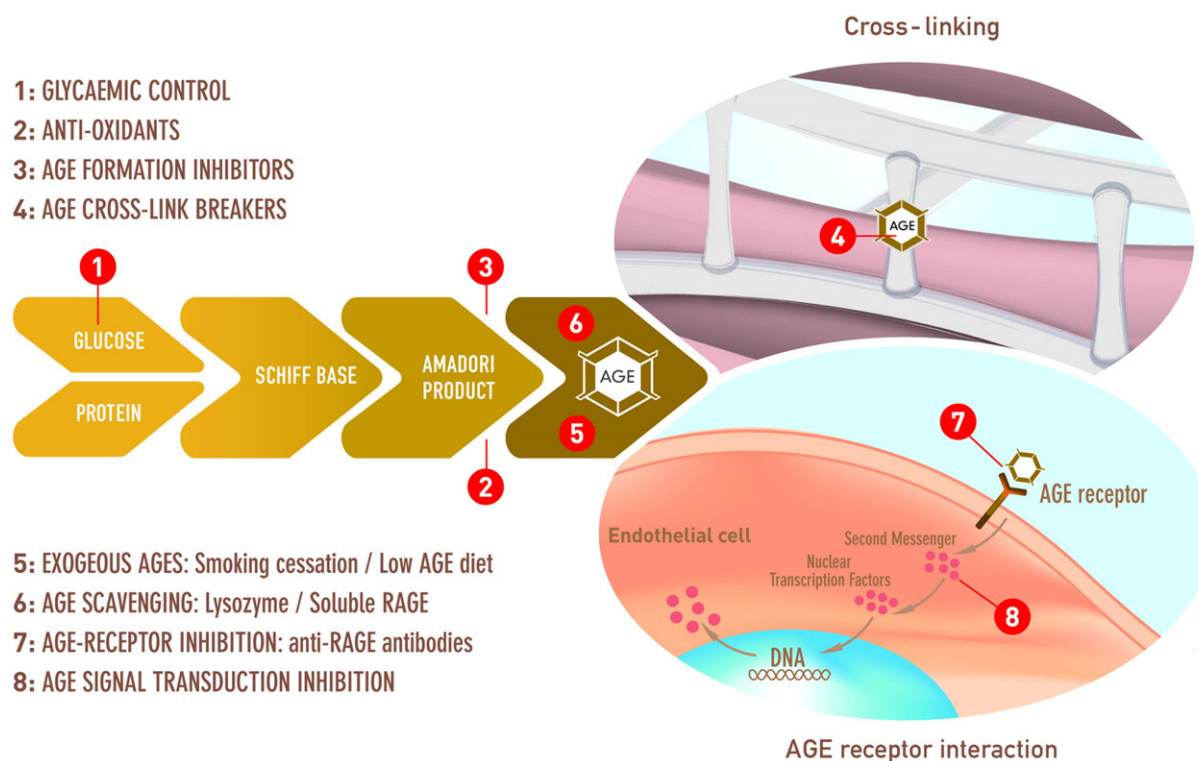


Fig. 4. An illustration showing eight possible strategies for prevention of the deleterious effects of AGE accumulation in heart failure. The Maillard reaction and subsequent processes of AGE cross-linking and AGE-receptor interaction, are shown. The numbers indicate the point of action: (1) Adequate glycaemic control in patients with diabetes mellitus reduces AGE accumulation; (2) anti-oxidants (e.g. benfotiamine) prevent the last step in the Maillard reaction as this step is catalyzed by oxidative stress; (3) AGE-formation inhibitors (e.g. aminoguanidine, ACE inhibitors, and angiotensin II receptor antagonists) also inhibit the latter step in the Maillard reaction; (4) AGE breaking medication (e.g. ALT-711) has the capacity to break already formed AGE cross-links; (5) exogenous AGE intake can be reduced by discontinuation of smoking or the initiation of low-AGE diets; (6) AGE scavenging using a soluble form of the AGE receptor or an AGE lysozyme can prevent AGEs interacting with AGE receptors; (7) AGE-receptor inhibition or modulation can be accomplished by the use of AGE-receptor antibodies; (8) AGE signal transduction inhibition can inhibit intra-cellular pathways induced by AGE-receptor interaction. Abbreviations: AGE: advanced glycation end-product.

ACE inhibitors, and angiotensin II receptor antagonists have also been shown to have inhibitory effects on AGE formation [49]. Although Norton et al. [34] did not detect a treatment effect of ACE inhibition with captopril on diastolic dysfunction in rats, Avendano et al. [35] reported an effect with enalapril in their experiments. The use of ACE inhibition in heart failure is widespread; however, the effect of ACE inhibition on AGE accumulation in patients with heart failure remains to be investigated. It is possible that these future investigations may identify ACE inhibitors or angiotensin II receptor antagonists that lead to decreased AGE accumulation, which may be associated with an additional beneficial effect on morbidity and mortality in heart failure patients. The other AGE intervention strategies outlined in Fig. 4 have not yet been investigated in heart failure.

AGE accumulation is not restricted to specific patient groups. However, diabetic patients and patients with renal failure are especially known to have increased AGE accumulation. Patients with these conditions also suffer from an increased prevalence of heart failure [50]. AGE accumulation has been shown to be associated with reduced survival in patients with diabetes mellitus and patients with renal failure

[4,51], and may possibly contribute to the increased prevalence of heart failure in these conditions. Therefore, patients with diabetes mellitus or renal failure may particularly benefit from AGE intervention.

6. Conclusion

This review, presents the current evidence for a role of advanced glycation end-products (AGEs) in the development of heart failure. AGEs seem to be a novel and interesting new target in the treatment of chronic heart failure. In particular, the development of AGE breaking medication such as ALT-711 might prove promising for the treatment of heart failure in the future.

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