

Advanced glycation end-products, a pathophysiological pathway in the cardiorenal syndrome

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Abstract The prevalence of heart failure (HF) is increasing. A distinction is made between diastolic HF (preserved left ventricular ejection fraction (LVEF)) and systolic HF (reduced LVEF). Advanced glycation end-products (AGEs) are crystallized proteins that accumulate during ageing, but are particularly increased in patients with diabetes mellitus and in patients with renal failure. Through the formation of collagen crosslinks, and by interaction with the AGE-receptor, which impairs calcium handling and increases fibrosis, AGE-accumulation has pathophysiologically been associated with the development of diastolic and renal dysfunction. Interestingly, diastolic dysfunction is a frequent finding in elderly patients, diabetic patients and in patients with renal failure. Taken together, this suggests that AGEs are related to the development and progression of diastolic HF and renal failure. In this review, the role of AGEs as a possible pathophysiological factor that link the development and progression of heart and renal failure, is discussed. Finally, the role of AGE intervention as a possible treatment in HF patients will be discussed.

Keywords Heart failure · Advanced glycation end-products · Diastolic dysfunction · Renal failure · Cardiorenal syndrome

Introduction

The prevalence of chronic heart failure (HF) increases fast due to a population of increasing age and an increasing prevalence of diabetes, resulting in a prevalence of HF of 10–20% in 70–80 year old people [1, 2]. Chronic HF may occur in the presence of a preserved (diastolic HF) or depressed (systolic HF) left ventricular ejection fraction (LVEF), both having a similar (poor) prognosis [1, 3–5]. The prevalence of diabetes in systolic HF is estimated at 23% [6, 7] and in diastolic HF at 25–33% [8–11]. A possible mechanism underlying diastolic HF may be an increase in advanced glycation end-products (AGEs). AGEs are formed during a non-enzymatic reaction between proteins and sugar residues [12, 13]. AGEs accumulate in the body with age and are increased in patients with chronic systolic and diastolic HF, diabetic complications and renal dysfunction [12, 14]. In diabetic HF patients tissue AGEs are more increased compared with HF patients without diabetes [14]. Whether a difference in accumulation of AGEs in diabetic patients between systolic and diastolic HF is present, remains to be established. AGEs can also activate the receptor for AGE (RAGE) and thereby induce cardiovascular dysfunction [12]. In cardiovascular disease, renal dysfunction often exists and is frequently referred to as the cardiorenal syndrome [15]. The cardiorenal syndrome is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other and vice versa [16]. Interestingly, patients with renal dysfunction often have diastolic dysfunction, and have an increased prevalence of HF, in particular diastolic HF [17–20]. In addition, the risk factors for developing renal dysfunction have an overlap with the risk factors for the accumulation of AGEs.

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Cardiorenal syndrome

In patients with chronic HF the co-existence of renal dysfunction is common, and renal failure is among the strongest predictor of mortality in patients with HF [21]. This co-existence has often been referred to as “cardiorenal syndrome”, in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ [16, 22]. The pathophysiology of the cardiorenal syndrome is multifactorial and involves decreased renal perfusion, atherosclerosis and inflammation, endothelial dysfunction and neurohormonal activation [23, 24].

Advanced glycation end-products

Advanced glycation end-products (AGEs) are a heterogeneous group of compounds, formed by oxidative and non-oxidative reactions between proteins and sugar residues, called the Maillard reaction [12, 13]. The Maillard reaction is a slow reaction and initiates when protein amino groups are exposed to sugar adducts, and proceeds from reversible Schiff base adducts to more stable, slowly reversible Amadori products (e.g. HbA1c). It further proceeds through the re-arrangement of Amadori products to the formation of stable and irreversible AGE compounds, for example N^ε-(carboxymethyl)lysine (CML), N^ε-(carboxyethyl)lysine (CEL), and pentosidine [12, 13]. The final step is catalyzed by oxidative stress, defined as a high steady state level of reactive oxygen species (ROS), which causes an increase in AGEs [12]. This increase in AGEs causes acceleration of oxidation, creating a vicious circle. Rapid formation of AGEs occurs via another pathway involving reactive carbonyl compounds (RCC) during oxidative stress [25]. RCCs are produced from lipids or carbohydrates reacting with ROS. AGE accumulation in vivo occurs throughout the body, including the skin, neural, vascular and renal tissue [26, 27]. Smoking cigarettes, heated, cooked or roasted food products are possible sources of increased AGE accumulation [12, 28, 29]. AGE degradation products are excreted via the kidney [25].

AGE accumulation can be measured in blood and in tissue. In blood, the preferred technique for determination of CML and CEL is stable-isotope-dilution liquid chromatography tandem mass spectrometry (LC–MS/MS) [30]. For determination of pentosidine in blood, a rapid and sensitive high-performance liquid chromatography (HPLC) method is considered the preferred technique [31]. In skin tissue, AGE accumulation can be measured at the volar side of the lower arm, more simple and non-invasively with a skin auto-fluorescence (AF) reader (AGE-reader) [32].

Advanced glycation end-products in diabetes mellitus

Accumulation of AGEs depends on both sugar concentration and the rate of protein turnover [33]. Diabetic patients have a higher sugar concentration and therefore a higher amount of AGEs compared to healthy controls. The rate of formation of Amadori products is directly proportional to the glucose concentration [33]. It has also been shown that diabetes is a risk factor for the development of a more impaired diastolic function, independent of age [34–36]. Furthermore, diabetes is not only increasing the risk of developing HF, but also accelerates its occurrence [37]. This could be partly explained by a higher amount of AGEs, which also occurs in HF patients [35]. Interestingly, diabetics also have a more impaired diastolic function compared with non-diabetics [34, 36]. We recently provided evidence for an association between tissue AGEs and diastolic dysfunction (measured with mean E'), suggesting that AGEs might explain diastolic dysfunction in diabetic HF patients [14].

The RAGE axis

AGEs can also bind to the receptor of AGE (RAGE) and thereby induce cardiovascular dysfunction [12]. RAGE is a multi-ligand member of the immunoglobulin superfamily of cell surface molecules that is expressed in a variety of cell lines [38]. RAGE has a C-truncated secretory isoform, soluble RAGE (sRAGE) that circulates in plasma [39]. sRAGE has been proposed to have an atherosclerotic-protective function, in particular by acting as a decoy for AGE [39–41]. AGE-accumulation can cause upregulation of RAGE [42]. When AGE is interacting with RAGE, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is activated, causing activation and inflammation of NF-kappaB, which induces further inflammation and can increase AGE-accumulation, creating a vicious cycle [42].

Advanced glycation end-products in heart failure; pathophysiology

Patients with diastolic HF have decreased ventricular relaxation, abnormal active relaxation, and/or an increase in ventricular and arterial stiffness [5, 43, 44]. The degree of diastolic dysfunction is correlated with the severity of myocardial fibrosis [45]. Several other mechanisms underlying diastolic HF have been proposed [12, 46–49]. One possible mechanism could be an increase in AGEs. AGEs may induce diastolic dysfunction in the heart through three different pathways (Fig. 1). First, AGE accumulation causes excessive cross-linking, which increases rigidity, thereby

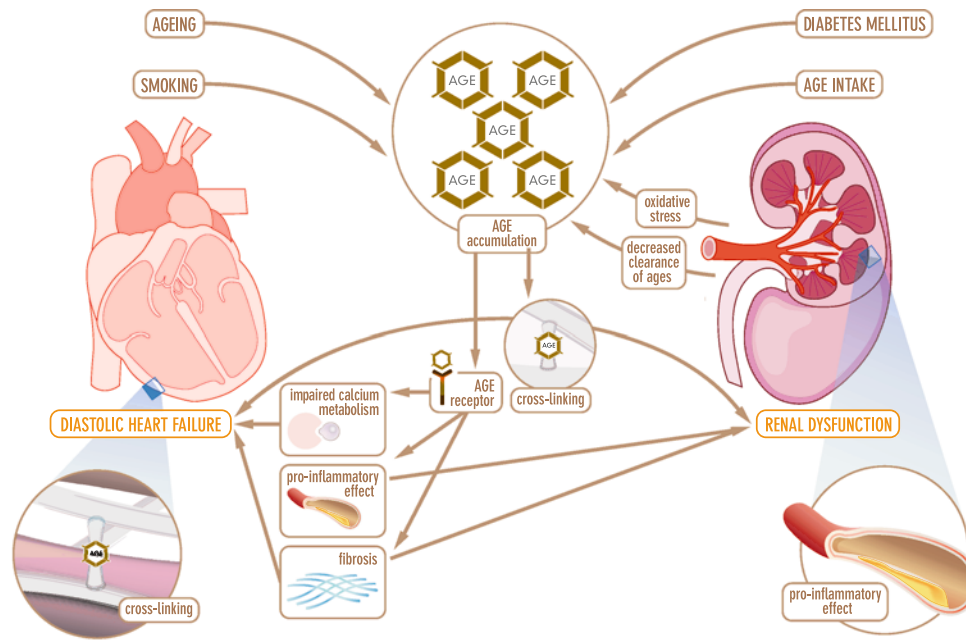


Fig. 1 Schematic representation of the pathophysiological pathways by which advanced glycation end-products causes diastolic heart failure and renal dysfunction

causing diastolic dysfunction as well as renal dysfunction. Second, when AGEs interact with the AGE receptor, the receptor is activated. Activation of AGE receptors (most important receptor is Receptor for AGE (RAGE)) causes increased fibrosis via the upregulation of transforming growth factor- β (TGF- β). Third, when the AGE receptor is exposed to AGEs, it causes a significant delay in calcium reuptake. As a consequence, the duration of the repolarisation phase of the cardiac contraction may increase, subsequently causing diastolic dysfunction. Based on these data it can be hypothesized that AGEs are a causal factor in diastolic HF.

Advanced glycation end-products in heart failure; evidence

Evidence for a role of AGEs in HF patients comes from experimental work and increasing number of clinical studies. In diabetic obese rats diastolic function measured by cardiac catheterization has been shown to correlate with levels of CML [50]. AGE receptor activation influences calcium metabolism and thereby induces diastolic dysfunction. In transgenic mice that over expressed human RAGE in the heart, diastolic and systolic intracellular calcium concentration was reduced [51]. We recently showed that tissue AGEs are related to diastolic function in dialysis patients [18]. In another clinical study, we found an association between tissue AGEs and diastolic function (measured with mean E') [14].

The overall prevalence of HF is increasing. Furthermore, roughly 50% of patients die in 4 years [1]. Several factors have been established as independent predictors for survival in HF patients, among which are LVEF, New York Heart Association (NYHA) functional class, anemia and renal function [46, 52–54]. Four studies investigated the prognostic role of AGEs in HF patients. We have previously shown that plasma AGE CML was related to the severity and prognosis of 102 HF patients, but after correction for renal function this relation subsided [46]. In a second study in 141 HF patients, pentosidine was related to severity of HF and it was an independent risk factor to predict adverse clinical outcome [55]. However, the authors did not adjust their findings for all known risk factors for mortality, such as hemoglobin and gender. Furthermore, they may have introduced a possible co-linearity problem by simultaneously introducing creatinine levels and estimated glomerular filtration rate (GFR) in the multivariable model. A third study showed that pentosidine was an independent predictor for cardiac events in 160 HF patients [56]. Cardiac events were defined as a composite end point of cardiac death and rehospitalization.

Advanced glycation end-products and renal failure; pathophysiology

Several mechanisms underlying renal dysfunction have been proposed, for example decreased renal perfusion, atherosclerosis and inflammation, endothelial dysfunction

and neurohormonal activation [24, 57–59]. Another possible mechanism could be an increase in AGEs. AGE-accumulation in patients with renal dysfunction can occur through two different pathways (Fig. 1). First, increased AGE accumulation is caused by decreased clearance of AGE degradation products. After modification or degradation in proximal tubuli, AGEs are eventually cleared in the urine [60–62]. Patients with renal dysfunction have a decreased clearance and thereby accumulation of AGEs occurs. Second, oxidative stress is enhanced in patients with renal dysfunction, which also causes an increase in AGE formation [63]. An increase in AGEs causes acceleration of oxidation, regenerating another increase in AGEs.

When endothelial cells in the kidney are stimulated by AGEs, they release the pro-inflammatory mediators vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 [61, 64, 65]. This may lead to tissue damage in the kidney. In summary, it can be hypothesized that AGEs are a possible mechanism underlying renal dysfunction.

Advanced glycation end-products and renal failure; evidence

Evidence for a role of AGEs in patients with renal failure comes from experimental and clinical studies. In 50 healthy male Sprague-Dawley rats AGEs were increased by adding AGE-modified albumin. This resulted in structural changes in the glomerulus [66]. In healthy nondiabetic rats and rabbits administering AGE-modified albumin led to an increase in vascular permeability and inflammation in the vasculature [66]. In clinical studies, AGEs accumulate during renal failure and dialysis [61, 67]. In patients with renal failure plasma AGEs are elevated [67, 68]. In patients on dialysis, tissue AGEs are even more increased compared to patients with renal failure without dialysis [69]. After renal transplantation AGE accumulation is lower than during hemodialysis, but remains elevated [69].

Renal dysfunction is strongly associated with a poor clinical outcome in HF patients [54, 70–72]. In addition, AGEs are related to the severity of HF and its clinical outcome as well. The prognostic role of AGEs in end-stage renal disease has however been inconsistent [73–76]. Two studies reported that high level of CML were associated with an increased mortality, but a third study showed an association with a decreased mortality. However, AGEs are a heterogenous group of compounds. Several different AGEs exist; some show cross-linking properties (pentosidine), whereas others do not (CML and CEL). All three studies only measured accumulation of the non-cross-linking AGE CML. The cross-linking AGE pentosidine was not measured. Furthermore CML was not measured with LC-MS/MS, which is the preferred technique with

highest specificity. Another study reported that tissue AGE was an independent predictor of mortality and associated with cardiovascular disease in hemodialysis patients [77]. Further research is warranted to provide more insight into the prognostic role of AGEs in patients with renal dysfunction.

AGEs as a pathophysiological factor in cardiorenal syndrome

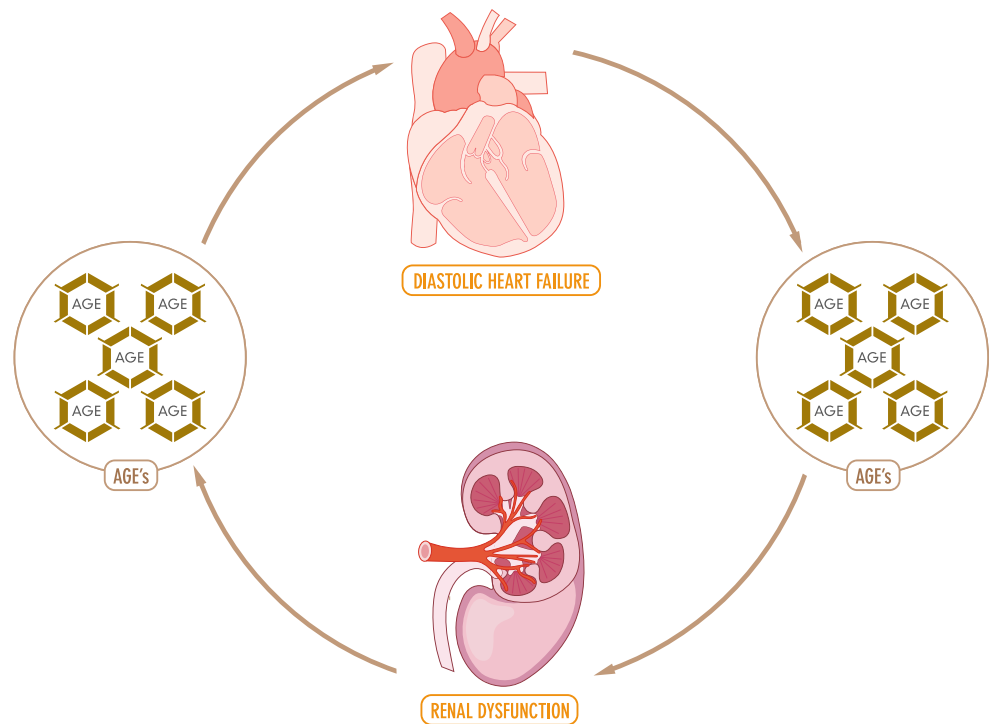
The data presented in this review suggests that AGEs may be involved as a pathophysiological factor in cardiorenal syndrome (Fig. 1 and 2). AGE-accumulation is not restricted to specific patient groups and accumulates in the body with age. With ageing, diastolic function impairs, while systolic function remains unchanged [1]. Diastolic dysfunction can be caused by AGEs through increasing rigidity and by causing a delay in calcium reuptake [12]. Patients with renal dysfunction are known to have increased AGE-accumulation and diastolic dysfunction is a frequent finding in these patients. The prevalence of diastolic dysfunction in dialysis patients varies from 25–87% depending on definitions used and patients included [17, 20]. Diastolic dysfunction predisposes to the development of HF, which causes a further decrease in renal function, creating a vicious circle (Fig. 1 and 2). [19]. Patients with diabetes mellitus are also known to have increased AGE-accumulation, independent of their age (Fig. 1). Accumulation of AGEs depends on both sugar concentration and the rate of protein turnover [33]. Furthermore, diabetic patients have a more impaired diastolic function compared to non-diabetics [34, 36]. Interestingly, the risk factors for developing renal dysfunction have a certain overlap with the risk factors for the accumulation of AGEs.

Taken together, diabetic patients and patients with renal dysfunction have an increased accumulation of AGEs, and an increased prevalence of diastolic dysfunction. In addition, patients with renal dysfunction and diabetes have higher tissue AGE levels compared to patients with renal dysfunction without diabetes [14, 25]. Whether this translates into a higher risk for new onset heart failure remains to be established. Together with its pathophysiology, where AGEs can be linked with diastolic dysfunction, we therefore suggest that increased amount of AGEs in heart and renal failure can be a common pathophysiological factor which causes both heart and renal failure (Fig. 2).

Interventions

AGE-accumulation was associated with a reduced survival in patients with diabetes, renal failure, and HF and may

Fig. 2 Advanced glycation end-products and cardiorenal syndrome



therefore be a target for intervention. The adverse effects of AGE-accumulation can be targeted in several ways.

In vitro and in vivo studies have shown that angiotensin II type 1 receptor blockers (ARBs) can reduce AGE formation [78–80]. ARBs prevent the production of reactive carbonyl and dicarbonyl compounds (RCOs), which are critical precursors of AGEs [78–81]. However, we recently showed that the angiotensin II type 1 receptor blocker eprosartan did not decrease levels of AGEs, within 6 months, in patients with hypertension and diastolic function [82].

AGE intake can also increase 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 [12, 28, 29].

Several AGE crosslink breakers, such as alagebrium and TRC4186, are currently under investigation for use in diabetic and non-diabetic patients. We recently conducted the BENEFICIAL study, the first prospective, randomized, double-blind, placebo controlled study to examine the effects of the AGE-breaker alagebrium on exercise capacity and cardiac function in patients with systolic HF [83].

Conclusion

There is a pathophysiological and epidemiological link between AGEs, renal dysfunction and heart failure. This suggests that AGEs are related to the development and progression of diastolic HF and renal failure. Therapies

targeted at reducing the effects of AGEs will have to provide further evidence for this hypothesis.

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