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The evolving role of adiponectin as an additive biomarker in HFrEF

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Abstract

Heart failure (HF) is a growing health problem. Despite improved management and outcome, the number of patients with HF is expected to keep rising in the following years. In recent research, adiponectin was shown to exert beneficial effects in the cardiovascular system, but the protein was also implicated in the development and progression of HF. The objective of this review is to provide an overview of current knowledge on the role of adiponectin in HF with reduced ejection fraction (HFrEF). We discuss the cardioprotective and (anti-) inflammatory actions of adiponectin, and its potential use in clinical diagnosis and prognosis.

Keywords

Heart failure; adiponectin; cardioprotection; inflammation; biomarker

Introduction

Heart failure (HF) continues to be a growing problem, its incidence and prevalence is rising worldwide, mostly because of the increase in average life expectancy and the improved survival of patients with coronary heart disease (CHD) [1]. It is now well-established that among HF patients, about half of the patients display a reduced ejection fraction (HFrEF) [2]. HFrEF currently affects about 26 million people and is the most common diagnosis among patients who are 65 years of age and older [3]. Despite improvements in therapy, many patients with HFrEF still face poor prognosis. The overall five-year survival rate is only 30-40% [3]. Moreover, in the last two decades, a paradigm shift in the pathophysiology of HFrEF has taken place. HFrEF is no longer considered as a single organ disease but is now seen as a complex multisystem syndrome involving diverse hemodynamic, neuro-hormonal and metabolic alterations [4].

In this setting, adiponectin turned up to be a specific protein of interest. Low levels of adiponectin are in general associated with increased prevalence of cardiovascular disease, including coronary artery disease (CAD) and peripheral artery disease [5,6]. In addition, in experimental animal and *in vitro* studies, adiponectin was shown to accomplish a variety of myocardial and vascular protective effects [7-10]. However, in patients with acute decompensated and chronic HFrEF, increased blood levels of adiponectin have been linked to poor outcome. Several recent studies uncovered that the elevation of serum adiponectin levels is an independent predictor of mortality and morbidity in HFrEF patients [11-14]. Therefore, the aim of this review is to outline current knowledge on adiponectin in HFrEF and to discuss its use as an additive biomarker.

Adiponectin and its accompanying receptors

Structure

Adiponectin was first described in 1995 by Scherer et al. [15]. These authors discovered a novel adipocyte complement-related protein of 30 kDa, alternately named Acrp30, by cDNA cloning from 3T3-L1 adipocytes. Adiponectin, mapped to chromosome 3q27, contains 244 amino acids (247 amino acids for mouse orthologous) composed of four distinct domains: an amino-terminal signal sequence, a non-conserved variable region, a collagen-like domain (cAd) and a C-terminal globular domain (gAd) [15]. The globular region is homologous to the complement 1q (C1q) family and shows a strong similarity with tumor necrosis factor-alpha (TNF-α), suggesting that there might be an evolutionary link between adiponectin and TNF-α [16]. Adiponectin is one of the most abundant proteins in human plasma [17,18]. Circulating levels of adiponectin range from 5 to 30 μg/ml in healthy individuals, accounting for approximately 0.05% of total blood proteins. In the circulation, the 30-kDa monomers of adiponectin assemble into several polymeric forms including trimeric low molecular weight (LMW; ~67 kDa), hexameric medium molecular weight (MMW; ~180 kDa) and oligomeric high molecular weight (HMW; ≥300 kDa, e.g.; dodecamers and octadecamers) forms [19]. The combination of these forms is often referred to as full-length adiponectin. LMW adiponectin is most predominant in circulation. Proteolytic cleavage of adiponectin may also occur, so that a smaller, globular fragment is found in plasma [20]. It remains controversial whether or not these different forms of adiponectin have different biological activities [21,22]. Ample data, however, do suggest that the HMW hexamer is of higher clinical significance, and that it has a more prominent role in cardioprotection [23-25].

Of note, adiponectin levels are generally two to three times higher in females than in males [15,26]. This sexual dimorphism has been attributed to the inhibiting effect of testosterone on the secretion of adiponectin and the higher body fat percentage observed in women [27,28]. However, although primarily secreted by adipocytes, adiponectin is also produced by non-adipose cell types such as hepatocytes, osteoblasts, cardiomyocytes and skeletal muscle cells [29-31].

Function

Adiponectin is able to exert insulin-sensitizing, anti-atherogenic, anti-diabetic, anti-ischemic and anti-inflammatory properties [7,32-35]. Adiponectin also promotes endothelial function and modulates a wide range of metabolic processes, thereby regulating energy homeostasis [36,37]. Adiponectin mainly performs its actions through interaction with AdipoR1 and AdipoR2, which were cloned for the first time in 2003 by Yamauchi et al. [32,38,39]. These receptors share a significant molecular homology, with an internal N-terminus and an external C-terminus, but differ in the root-mean square deviations (i.e.; bond lengths and angles). They contain seven transmembrane domains, similar to the G-protein-coupled cell surface receptors (GPCRs), are capable of binding globular and full-length adiponectin and therein, will stimulate the main downstream effector adenosine monophosphate activated protein kinase (AMPK) [38,40] [41]. The high-affinity receptor AdipoR1 is ubiquitously expressed in endothelial cells and skeletal muscle fibers where it regulates glucose and lipid metabolism through AMPK, whereas AdipoR2, which serves as a moderate-affinity receptor, is mainly expressed in the liver and is involved in activation of peroxisome proliferator-activated receptor alpha (PPARα), leading to increased insulin sensitivity [32,39]. Further, AdipoR1 has been postulated to play an important role in adiponectin signalling of macrophages [42]. Activated AdipoR1 and AdipoR2 improve fatty acid oxidation (FAO) and glucose uptake, increase mitochondrial biogenesis and lactate production, reduce hepatic gluconeogenesis and suppress oxidative stress, inflammation and several important metabolic risk factors (e.g.; diabetes mellitus type 2) for HF [43,44]. AdipoR1 and AdipoR2 interact directly with adaptor protein containing a pleckstrin homology domain, a phosphotyrosine binding domain and a leucine zipper motif 1 (APPL1) [45,46]. APPL1 mediates the adiponectin-signaling cascade, transmitting signals from both adiponectin receptors to their downstream targets by interacting with the N-terminal intracellular region. Signaling via APPL1 is necessary for adiponectin to exerts its anti-inflammatory and cytoprotective effects on endothelial cells [47]. Apart from AdipoR1 and AdipoR2, a third adiponectin receptor, T-cadherin has been identified. T-cadherin exclusively binds with HMW adiponectin and acts as a co-receptor to facilitate adiponectin signaling [48]. T-cadherin is highly expressed in the heart and the vasculature, and to a lesser extent in skeletal muscle and liver [49].

Biological actions of adiponectin in the heart and vasculature

Adiponectin is able to induce a wide range of myocardial and vascular protective effects [7,10,18,50-53]. Experimental studies using adiponectin knock-out (KO) mice subjected to transverse aortic constriction (TAC) to induce pressure overload have demonstrated a protective role for adiponectin against cardiac hypertrophy, adverse LV remodeling and systolic dysfunction [54-57]. In addition, treatment of apolipoprotein E–deficient ($apoE^{-/-}$) mice with recombinant adenovirus expressing human adiponectin could suppress the development of atherosclerotic lesions [58]. Also, adiponectin deficiency in mice resulted into enhanced thrombus formation and

platelet aggregation upon carotid arterial injury, whereas adenovirus-mediated over-expression of adiponectin attenuated these processes [59]. Moreover, in preclinical pig and mouse models of ischemia/reperfusion injury, adiponectin treatment reduced infarct size and improved cardiac function, [60,61]. However, from these preclinical (animal and *in vitro*) studies it became increasingly evident that the signaling effects of adiponectin diverge with its sites of action.

In the vasculature, adiponectin exerts anti-atherosclerotic effects by inhibiting vascular smooth muscle cell proliferation and migration, suppressing macrophage to foam cell formation, contributing to plaque stability and by reducing inflammation [35,58,62-65]. In endothelial cells, adiponectin diminishes the generation of reactive oxygen species (ROS), stimulates the formation of nitric oxide (NO) and limits the production of pro-inflammatory cytokines and chemokines, including TNF-α and interleukin (IL)-8 [8,9]. Its anti-oxidant activity and effects on endothelial function (e.g.; vasodilatation, increasing NO bioavailability) occur to be mediated by AMPK and cAMP-dependent protein kinase A (PKA) [8,9]. Studies have further demonstrated that adiponectin is able to promote endothelial repair and angiogenesis [66]. In the myocardium, adiponectin reduces apoptosis, fibrosis, and oxidative stress but also promotes cell survival by attenuating the expression of inducible NO synthase (iNOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [10,32]. In addition, *in vitro* and animal experiments demonstrated that not only elevated circulatory levels of adiponectin, but also locally produced adiponectin protects against ischemia-reperfusion injury via AMPK and cyclooxigenase (COX)-2-dependent mechanisms [67]. AdipoR1 and AdipoR2 are both expressed in the myocardium. Yet, an experimental study in rats suggested that binding to T-cadherin is *de facto* critical for adiponectin-mediated cardioprotection [49]. In particular, in mice deficient in T-cadherin adiponectin failed to interact with cardiac tissue, leading to increased hypertrophy and worsening of ischemia-reperfusion injury [49]. In this regard, Joshi et al demonstrated how T-cadherin is essential for the protection of vascular endothelial cells against apoptosis resulting from oxidative stress [68].

Further details on the cardiac effects and inflammatory actions of adiponectin are provided in table 1.

Adiponectin and heart failure with reduced ejection fraction

Since 2005, adiponectin has been extensively studied in the setting of chronic HFrEF (Table 2). Elevated serum levels of total adiponectin were repeatedly reported in these patients [69-75]. Baldasseroni et al. demonstrated that patients with CAD and overt HFrEF have marked increased circulating levels of total adiponectin compared to patients with CAD and no HF symptoms [76]. Also, patients with acute HFrEF were shown to have elevated levels of circulating adiponectin (Table 2). A cohort study by Ohara et al. reported increased plasma levels of total and HMW adiponectin in patients with acute HFrEF (non-ischemic, non-valvular origin) compared to patients with supraventricular arrhythmia without HF [77]. In chronic HFrEF, high levels of total adiponectin were shown to confer poor prognosis and predict all-cause mortality, independent of cardiovascular risk factors including age, systolic blood pressure, LVEF <25%, HF duration and creatinine clearance [71]. This association between high total adiponectin and mortality risk was more pronounced in elderly patients suffering from HFrEF having a normal body mass index (BMI; 21–25 kg/m^2) than in aged HFrEF patients with a BMI value that is too low or too high (<21 or >25 kg/m^2) [71,72]. Moreover, in a large, cross-sectional community based study of elderly patients (>70 years of age, n= 954), and by using an in-house time resolved immunofluorometric assay, adiponectin concentrations were inversely associated with LVEF in men, but not in women [78]. In addition,

total adiponectin in circulation has been associated with the severity of HF, as assessed by NYHA class [12-14,75,79]. Further, in a community-based and cross-sectional (n=1414) study of Lee et al., total serum adiponectin concentration was negatively associated with left ventricular (LV) mass index in subjects at low risk of LV hypertrophy, but a positive association was shown in subjects who were at a high risk of developing hypertrophy [80]. These results indicate that the relationship of LV mass index with adiponectin may vary with the risk and the severity of LV hypertrophy. Moreover, in patients with chronic HFrEF, elevated levels of total adiponectin were associated with higher cardiovascular mortality and morbidity [80,81]. Increased levels of adiponectin in chronic HFrEF thus seem to parallel a worsening prognosis (Table 2). In addition, with regard to acute HFrEF, a high value of the HMW to total adiponectin ratio at hospital admission, and also a larger decrease in this ratio from admission to discharge, has been related to improved prognosis [77]. Total and HMW levels of adiponectin had no significant impact on patient prognosis in acute HF. Hence, because adiponectin is credited with multiple beneficial effects on cardiac hypertrophy and failure, its negative impact on the survival of patients with chronic HFrEF has been designated as '*the adiponectin paradox'*. To date, the underlying pathophysiologic mechanisms that account for the negative connotation of increased adiponectin concentrations in chronic HFrEF patients remain unclear.

Adiponectin: dual role in heart failure?

Recent experimental data has overturned the dogma that the actions of adiponectin are exclusively cardioprotective and anti-inflammatory during chronic HFrEF [82,83]. These findings will be discussed in the next paragraphs. A detailed overview is also provided in table 1.

An apparently cardioprotective hormone

For a long time, adiponectin was believed to be a true cardioprotective hormone in patients with diverse metabolic and cardiovascular disorders. On one hand, diminished plasma levels of total adiponectin were found in the presence of obesity, diabetes mellitus (type 1 and 2), hypertension, insulin resistance, myocardial infarction and CAD, and associated with adverse outcomes [76,84-88]. On the other hand, elevated adiponectin levels were shown to improve NO production, apoptosis, insulin sensitivity and LV systolic dysfunction [89,90]. Moreover, in a nested case-control study among 18 225 male participants (40 to 75 years) of the Health Professionals Follow-up Study, free of diagnosed cardiovascular disease, men with high total circulating adiponectin concentrations were are at a lower risk of myocardial infarction compared to men with medium-to low adiponectin levels [91]. This relationship was independent of inflammation and glycemic status but possibly related to differences in blood lipids. Also, in the Uppsala Longitudinal Study of Adult Men (ULSAM study, 832 healthy men, 70 years of age) a high concentration of total adiponectin was independently associated with a lower risk for CHD [11]. A reduction in adiponectin level was further related with the presence and severity of IHD caused by systemic atherosclerosis [92]. Hence, several studies have demonstrated a significant inverse relationship between total adiponectin and risk factors of HF [85,88,91,93]. Furthermore, adiponectin deficiency in early mouse HF models (i.e.; adiponectin KO mice subjected to TAC) caused greater LV remodelling, LV hypertrophy, systolic and diastolic dysfunction and mitochondrial oxidative capacity [54-57]. Shibata et al. further demonstrated that adenovirus-mediated over-expression of adiponectin can attenuate LV dysfunction in

mice following permanent LAD-ligation induced myocardial infarction, and thus that adiponectin is protective against the development of HFrEF [94] (Table 1).

However, when it comes to chronic HFrEF, several studies have questioned the cardioprotective properties of adiponectin. As mentioned before, higher concentrations of total adiponectin in chronic HFrEF patients have been associated with poor prognosis and all-cause mortality (Table 1). In addition, a U-shaped relation between adiponectin and all-cause mortality was recently reported [95]. This U-shaped relationship reconciles the *adiponectin paradox*, meaning that the association of adiponectin with all-cause and cardiovascular mortality is less favorable with increasing cardiovascular risk [95-97]. However, on the assumption that adiponectin is a true cardio-protective hormone, adiponectin levels might rise in an attempt to mitigate the robust activation of neuro-hormonal and pro-inflammatory responses and metabolic impairment in HFrEF. It is possible that the beneficial actions of adiponectin are insufficient to counteract these adverse processes, even at high levels, which could offer an explanation for its association with a worsening prognosis in established HF. Furthermore, in patients with acute non-ischemic and non-valvular HF, a higher ratio of HMW to total adiponectin level was associated with a better prognosis in multivariate survival analysis. The total and HMW-adiponectin levels at the time of hospital admission or discharge had no significant impact on the prognosis [77]. Yet, in a paper by Dieplinger et al. a higher total adiponectin level in patients with acute HF was associated with worse prognosis. These conflicting results between studies may relate to differences in the underlying etiology of acute HF (e.g.; dilated cardiomyopathy versus hypertension) or the adiponectin isoform being measured (total versus HMW adiponectin). Still, in the Cardiovascular Health study, a strong correlation had been found between total and HMW adiponectin. In addition, a non-linear relationship between HMW and total adiponectin with incident diabetes type 2 (a major risk factor for HF) was documented [95,98]. Hence, the role of adiponectin in HFrEF is to be interpreted with caution, and the underlying conditions and diseases have to be taken into account. At present, it seems that elevated levels of adiponectin exert a predominant cardioprotective effect and act as a favourable prognostic indicator in early HF, whereas in chronic disease (at least for HFrEF), high circulating adiponectin concentrations are associated with adverse LV remodelling and accelerated progression toward end-stage HF [80,93,99]. Therefore, it looks like adiponectin balances on a tight rope between protective and harmful in HFrEF.

A hidden pro-inflammatory nature?

Most adipokines are pro-inflammatory. Several *in vitro* studies, however, support a role for adiponectin in attenuating inflammation in various cells types and tissues including cardiomyocytes, adipocytes, endothelial cells, macrophages, and adipose tissue [33,58,100-103]. Adiponectin, for instance, reduces the synthesis and secretion of C-reactive protein (CRP) from human aortic endothelial cells and rat primary hepatocytes under hyperglycemia via upregulation of AMPK and downregulation of NF-κB [104]. In addition, adiponectin is able to reduce the expression of vascular cell adhesion protein (VCAM)-1, intracellular adhesion molecule (ICAM)-1 and E-selectin in human endothelial cells, and therefore monocyte attachment [100]. Findings also indicate that adiponectin combats cellular inflammation by affecting sphingolipid metabolism [105]. Moreover, adiponectin can suppress oxidative stress-mediated autophagic-induced cardiomyocyte death, and is thus endowed with anti-oxidative potential [106]. Park et al. has shown that adiponectin prevents hypoxia/reoxygenation induced DNA

fragmentation, intracellular ROS generation and activation of the intrinsic apoptotic pathway via AdipoR1/APPL1 signaling and is endowed with an increased anti-oxidant potential [107]. Furthermore, Tsatsanis et al. provided evidence that adiponectin mediates its anti-inflammatory effects by the induction of macrophage tolerance: exposure of macrophages to high levels of globular adiponectin rendered the cells tolerant toward pro-inflammatory stimuli and adiponectin itself, whereas a decrease in globular adiponectin level and subsequent re-exposure to high doses made macrophages more sensitive to pro-inflammatory stimuli, including its own [108]. Adiponectin was also shown to facilitate the uptake of apoptotic cells by macrophages, and by that the inflammatory reaction and immune dysfunction induced by apoptotic bodies could be weakened [109,110].

In recent years, however, substantial evidences also emerged challenging the perspective of adiponectin as an exclusively anti-inflammatory cytokine. In contrast with a reduction in serum adiponectin in metabolic diseases, chronic inflammatory and immune-mediated pathologies such as diabetes type 1, rheumatoid arthritis and HFrEF, account for apparently paradoxically high levels of circulating adiponectin [111]. In these chronic inflammatory/immune conditions, adiponectin may exert pro-inflammatory rather than anti-inflammatory activities. Globular adiponectin induced the expression of VCAM-1, ICAM-1, E-selectin, IL-8 as well as superoxide dismutase 2 (SOD2) and plasminogen activator inhibitor-1 (PAI-1) in vascular endothelial cells [112]. In the context of arthritis, it has been shown that adiponectin induces the synthesis of IL-6 and matrix metalloproteinase inhibitor 1 (MMP-1) in fibroblasts [113]. In patients with diabetes type 1, high adiponectin levels have been positively correlated with increased levels of CRP, IL-6 and TNF-α [114]. In patients with chronic obstructive pulmonary disease (COPD), adiponectin is now considered a marker of low-grade systemic inflammation [115]. Experiments in mice also demonstrated that adiponectin mediates an important pro-inflammatory role in tobacco smoke-induced COPD [116].

These clinical and preclinical data suggest that the anti-inflammatory properties of adiponectin in several metabolic disorders cannot be applied to chronic inflammatory conditions, in which the levels of adiponectin are markedly elevated. In chronic HFrEF, elevation of circulating adiponectin occurs concomitantly with an increase in systemic inflammation (e.g.; rise in CRP, TNF-α and IL-6), the opposite of what is observed for metabolic diseases [12,13,69,117]. In view of this, and because of adiponectin's pro-inflammatory profile described above, it seems reasonable to assume that adiponectin at very high circulating levels adds to the chronic systemic inflammatory condition which is present in HFrEF. Hence, fluctuating plasma concentrations of adiponectin in HFrEF (with initially reduced levels of adiponectin in CAD or after myocardial infarction, followed by increased levels when HF is established), may weaken macrophage tolerance towards the constant pro-inflammatory cytokine storm, resulting in macrophage activation and thereon production of high levels of pro-inflammatory cytokines including TNF-α and IL-6; a hypothesis which has also been put forward by Tsatsanis et al in the context of obesity [108]. In this regard, it was also shown that adiponectin induces pro-inflammatory programs in macrophages, such as the release of various pro-inflammatory cytokines including TNF-α and IL-6 [118,119]. On the other hand, however, elevated circulating adiponectin may act as a compensatory mechanism for the increase in systemic inflammation, whereby adiponectin levels rise in an attempt to counterbalance the high levels of pro-inflammatory cytokines in chronic HFrEF. Up to now, the question remains open whether and/or when adiponectin serves as a pro-or anti-inflammatory cytokine in HF. *In*

vivo and *in vitro* studies on the pro- and anti-inflammatory actions of adiponectin in HFrEF are tabulated in table 1.

Adiponectin: A target in search of another BNP

Adiponectin has not been officially recognized as a biomarker in HFrEF. Several results from studies, though, suggest that adiponectin might be useful as a marker for monitoring treatment and predicting prognosis, or that adiponectin may act as a valuable adjunct to natriuretic peptides in the sub-classification of patients with HF. Some clinical studies, however, have also questioned the utility of adiponectin as a biomarker in HFrEF. Here, we discuss the current evidence available.

Of the myriad of biomarkers that have been studied in HFrEF, natriuretic peptides are the best characterized. BNP and NT-proBNP are the gold standard biomarkers in assessing the diagnosis and prognosis of HFrEF, but does adiponectin have additive biomarker value? Cavusoglu and colleagues demonstrated that high adiponectin is an independent predictor of LV systolic dysfunction in patients undergoing coronary angiography (n= 389) [120]. HFrEF patients with serum adiponectin concentrations above the 75th percentile were shown to be at an increased risk of death, irrespective of baseline clinical (e.g.; age, sex, diabetes, NYHA class) or laboratory findings (e.g.; serum TNF-α, IL-6, CRP) [69]. The rise in adiponectin level was proportional to the extent and worsening of HFrEF. Also, the number of risk factors was shown higher in HFrEF patients with the highest level of adiponectin [121]. In addition, in a study by Dieplinger et al. in patients with acute decompensated HFrEF (n=137), total adiponectin level was shown to act as a significant prognostic marker for 1 year all-cause mortality, and this independently of the presence of clinical confounders (e.g.; older age, renal dysfunction, arterial hypertension, low systolic blood pressure, NYHA class III/IV) CRP, BMI and BNP [122]. Accordingly, serum adiponectin may seem useful as an additive biomarker for monitoring patients with HFrEF and predicting their future disease course. Yet, this prognostic value of circulating adiponectin may not hold true after adjustment for other important clinical characteristics of patients like age, exercise capacity, type of HF, and medication use (i.e.; beta-blocker treatment) [123-126]. Moreover, interactions between risk factors including diabetes mellitus type 2 may also affect adiponectin concentration in patients with HFrEF, making it difficult to ascertain the role of circulating adiponectin in the development and progression of HFrEF. In addition, adiponectin was not reliable as a marker for the diagnosis of acute decompensated HFrEF in patients with shortness of breath [127]. The study of Fu and colleagues, however, examined whether total serum adiponectin is associated with onset of HF from hypertension through LV hypertrophy in spontaneously hypertensive rats, and puts adiponectin forward as a useful biomarker during the transition from diastolic to systolic dysfunction in HF [128]. The adiponectin level in rats decreased with increasing hypertension during the first three months, and continued to decline when diastolic dysfunction became overt, whereas at month 15, levels started to rise again prior to the appearance of systolic dysfunction at month 18 [128]. In this respect, adiponectin might turn out helpful for sub-classifying HF patients. However, the comparative prognostic and diagnostic significances of the different isoforms of adiponectin, its therapeutic meaning *(vide infra)* and potential to monitor the efficacy of HFrEF therapy are all still unclear. Consequently, more research is needed before adiponectin can be considered of additive value in the clinical management of HFrEF patients.

Toward end-stage HF

Patients with a more severe stage of HF have higher concentrations of adiponectin compared to HF patients with rather mild symptoms [69]. Although no study results are available yet, it is, therefore, not unlikely that in patients with end-stage HF adiponectin levels are utterly high. Progression to end-stage HF is associated with weight loss and wasting, long-term systemic inflammation and renal failure. Weight loss and renal failure have been correlated with high blood levels of adiponectin in patients with ischemic heart disease (IHD) [71,129,130]. In addition, patients with end-stage renal disease have been associated with a doubling of circulating adiponectin concentrations [131]. Therefore, it is conceivable that the co-morbid conditions which are present in end-stage HF contribute to an increase in circulating adiponectin. [121]. Consistent with this hypothesis, high body mass and hence rather low circulating adiponectin might favour outcome in these patients.

Concluding remarks

Current evidence from experimental and clinical studies indicates that adiponectin has favourable effects on cardiovascular health and reduces the risk of developing HFrEF. In early and acute HFrEF, moderately elevated levels of circulating adiponectin likely confer improvement in prognosis. In chronic HFrEF, however, adiponectin seems to lose its global cardio-protective and anti-inflammatory predominance. In these patients, high serum concentrations of adiponectin emerge as an independent risk factor of poor outcome.

Author Disclosures

The authors declare that there is no conflict of interest regarding the publication of this paper. All authors have read and approved the manuscript. Design and drafting of the manuscript: TS, VYH. Critically revising the manuscript: TS, AMVB, AG, CJV and VYH. TS, and VYH edited the revised version. All authors approved the final manuscript.

Ethical Standards

The study was approved by the local Ethics Committee of the Antwerp University Hospital (committee for medical ethics UZA - UAntwerp) and is in keeping with the principles of the Declaration of Helsinki. All participants provided written informed consent before enrolment.

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Tables

Table 1: Cardiac effects and inflammatory actions of adiponectin in animal and cell culture studies

Table 2. Circulating adiponectin concentrations in patients with HFrEF