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REVIEW ARTICLE

Can Adiponectin Help us to Target Diastolic Dysfunction?

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Abstract Adiponectin is the most abundant adipokine and exhibits anti-inflammatory, antiatherogenic and antidiabetic properties. Unlike other adipokines, it inversely correlates with body weight and obesity-linked cardiovascular complications. Diastolic dysfunction is the main mechanism responsible for approximately half of all heart failure cases, the so-called heart failure with preserved ejection fraction (HFpEF), but therapeutic strategies specifically directed towards these patients are still lacking. In the last years, a link between adiponectin and diastolic dysfunction has been suggested. There are several mechanisms through which adiponectin may prevent most of the pathophysiologic mechanisms underlying diastolic dysfunction and HFpEF, including the prevention of myocardial hypertrophy, cardiac fibrosis, nitrative and oxidative stress, atherosclerosis and inflammation, while promoting angiogenesis. Thus, understanding the mechanisms underlying adiponectin-mediated improvement of diastolic function has become an exciting field of research, making adiponectin a promising therapeutic target. In this review, we explore the relevance of adiponectin signaling for the prevention of diastolic dysfunction and identify prospective therapeutic targets aiming at the treatment of this clinical condition.

Keywords Adiponectin · Adipokine · Obesity · Diastolic dysfunction · Heart failure with preserved ejection fraction

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Introduction

The prevalence of obesity has reached epidemic proportions worldwide. This epidemic poses important health concerns due to the association between overweight and obesity and adverse health effects such as cardiovascular diseases [1, 2]. Actually, it has been shown that obesity predisposes to changes in cardiac morphology and ventricular function, contributing to diastolic dysfunction and heart failure (HF) [3, 4], particularly the phenotype with preserved ejection fraction (HFpEF). HFpEF is characterized by abnormal relaxation and increased passive stiffness that manifests as prolonged isometric relaxation, slow left ventricle filling and increased diastolic stiffness [5]. It is a heterogeneous syndrome with several underlying etiologic and pathophysiologic factors [6]. It comprises a diversity of phenotypes and is initiated by comorbidities and inflammatory mediators with extracardiac manifestations and cardiac abnormalities. In fact, HFpEF affects not only the myocardium, but also other organs such as lungs, skeletal muscles and kidneys [7]. Although it represents approximately fifty percent of all HF cases, currently no effective therapeutic strategies are available [8].

Adipose tissue is no more considered as an inert storage depot for triglycerides, but rather as an important endocrine organ, participating in the regulation of energy homeostasis of many physiological systems, including the cardiovascular system. Indeed, adipocytes secrete a number of biologically active adipokines such as adiponectin, leptin, resistin, tumor necrosis factor-α (TNF-α), interleukins and plasminogen-activator inhibitor type 1 (PAI-1) [9].

Adiponectin is the most abundant protein secreted by white adipose tissue. It accounts for approximately 0.01 % of total

plasma protein, circulating at high concentrations ranging from 5 to 30 mg/L in healthy lean individuals [10].

In contrast to other adipokines, whose levels increase with fat mass, adiponectin levels are inversely associated with body weight, being decreased in obese individuals. Adiponectin is also known for its antiatherogenic [11], anti-inflammatory [12], antioxidative [13] and insulin sensitizing features. In addition, adiponectin is inversely correlated with cardiovascular risk factors such as hypertension [14], atherosclerosis [11], dyslipidaemia [15] and hyperglycemia [16] and may represent a potential target in diastolic dysfunction [17].

This review emphasizes some molecular characteristics of adiponectin and explores the effects and underlying mechanisms of this adipokine in the myocardium, specifically addressing its potential role in the prevention and treatment of diastolic dysfunction.

Molecular Characteristics of Adiponectin

Structure

Adiponectin is a 244 amino acid protein of 28 kDa and belongs to the complement 1q family. It is also known as GBP-28, apM1, AdipoQ and Acrp30 [18].

It is composed of an amino-terminal signal peptide, a short non-helical variable region, a collagenous domain and a globular domain at the carboxyl-terminal with homology for the subunits of C1q and the collagen types VIII and X globular domains [19] (Fig. 1). Adiponectin is present in the circulation at different molecular weight forms (Fig. 1), such as trimers and hexamers, which constitute the low-molecular weight oligomers (LMW), and multimers collectively called high-molecular weight complexes (HMW) [9, 20] and which have been shown to be the major contributors for the adipokine metabolic actions.

Although adiponectin can circulate as full-length or as a smaller globular fragment, the principal fraction in plasma appears to be the full-length form [20].

Regulation of Adiponectin Expression and Secretion

There is no consensus regarding the place of production of adiponectin. It seems clear that the main site of synthesis is the adipose tissue, although it is controversial if the majority of the hormone is produced in the visceral or in the subcutaneous depot [21].

Despite being produced in the adipose tissue, adiponectin plasma concentration is inversely correlated with body mass index [9] and studies established an inverse relation between adiponectin expression and obesity [22].

Recently, other authors identified adiponectin secretion in various non-adipose cells, such as bone marrow, bone-forming cells, fetal tissue, myocytes, cardiomyocytes [23] and liver [21], although the regulating mechanisms seem to be different of those in the adipose tissue [21].

Research has been carried out in order to understand hormonal and environmental influences in adiponectin levels. These studies found that adiponectin circulating levels are not under acute regulation per se, except for fasting and refeeding acute regulation [24].

Adiponectin circulating levels show also a sexual dimorphism, presenting higher levels in females than in males. Curiously, there is also sexual dimorphism in the oligomeric complex distribution in the serum, as males have a reduced proportion of HMW multimers compared to females [25].

Receptors and Related Signaling Pathways

Three different adiponectin receptors have been described: two G-protein-coupled seven-transmembrane-domain receptors, AdipoR1 and AdipoR2, and a glycosylphosphatidylinositol-anchored extracellular protein, T-cadherin [9] (Fig. 2). AdipoR1 is essentially expressed in skeletal muscle, playing an important role in promoting lipid oxidation via AMPK activation [9, 21]. On the other hand, AdipoR2 is highly expressed in the liver, enhancing insulin sensitivity and reducing steatosis via AMPK activation and increased peroxisome-proliferator-activated receptor α (PPAR-α) ligand activity (Fig. 3) [21]. T-cadherin is present in muscle, cardiovascular and nervous systems [9], having preference for HMW adiponectin multimers [9, 21].

Adiponectin and Diastolic Dysfunction – Physiological and Pathophysiological Mechanisms

Diastolic dysfunction refers to a disturbance in ventricular relaxation, distensibility or filling. In its pathogenesis are implicated intrinsic factors, including determinants as myocardial relaxation and passive properties of ventricular wall, and extrinsic factors, like structures surrounding the ventricle, the left atrium, pulmonary veins and mitral valve [26].

Recently, adiponectin has been shown to be involved in preventing the pathogenesis of diastolic dysfunction [22]. Indeed, in myocardium, adiponectin-mediated protection is linked to the prevention of myocardial hypertrophy, cardiac fibrosis, atherosclerosis, inflammation, nitrative and oxidative stress and to the promotion of angiogenesis (Fig. 4), all representing HFpEF pathophysiological mechanisms that will be addressed in the next sections.

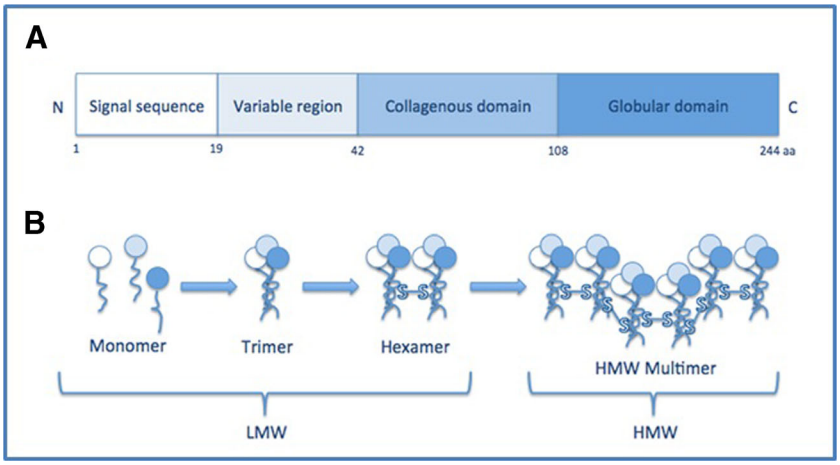

Fig. 1 Structure of human adiponectin and adiponectin multimerization. **a**. Adiponectin contains an amino-terminal signal sequence, a short variable region, a collagenous domain involved in collagen-triple helix formation and a globular head at the carboxyl-terminal. N: amino-terminal; C: carboxyl-terminal. **b**. Adiponectin circulates in serum in a number of complexes which include monomers, trimers and hexamers, collectively described as low-molecular weight (LMW) oligomers, and high-molecular weight (HMW) multimers

Myocardial Hypertrophy

An overload-induced increase in left ventricular mass, as in systemic hypertension, is considered an adaptive response to mechanical stress and a mechanism to preserve cardiac function [27]. Although cardiac hypertrophy is initially a compensatory response of the myocardium to increased mechanical load, this continuous effect becomes deleterious, leading to cardiac dysfunction and to heart failure. Hypertension represents a major risk factor for several heart diseases and an important contributor to HFpEF, showing a prevalence of 55–86 % in HFpEF patients [28]. Indeed, adiponectin restrains hypertrophy and is closely linked to diastolic dysfunction prevention. Several studies established a relationship between hypoadiponectinemia and hypertrophy exacerbation. Sam et al. [29] showed an increase in total wall thickness in adiponectin-deficient (APNKO) mice with aldosterone-induced diastolic hypertension, concluding that adiponectin has an essential role in preventing ventricular mass increase and that lack of adiponectin exacerbates myocardial hypertrophy and leads to diastolic dysfunction. McManaus et al. [30], based on observational studies in humans, also found this relation, suggesting a cardioprotective effect of adiponectin by concluding that higher levels of adiponectin are associated with lower left ventricular mass.

Adiponectin inhibition of myocardial hypertrophy appears to be mediated by AMPK signaling activation (Fig. 3) [31]. AMPK is activated by phosphorylation, which is only stimulated by the trimer form of adiponectin. AMPK is a protein involved in energy regulation and metabolic homeostasis and is increased in acute and chronic stresses such as hypoxia, ischemia and cardiac hypertrophy. Its activation modulates

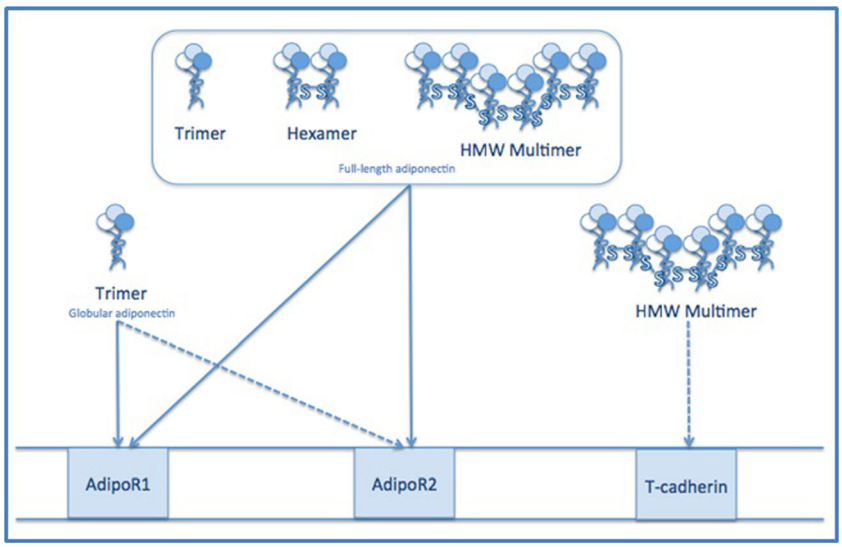

Fig. 2 Adiponectin and adiponectin receptors. Globular adiponectin exists as a trimer, whereas full-length adiponectin comprises 3 species of multimers: a trimer, an hexamer and a HMW multimer. The lines represent the affinity of each type of adiponectin for the different receptors. The *dotted line* reflects the low-affinity between adiponectin isoforms and the respective receptor

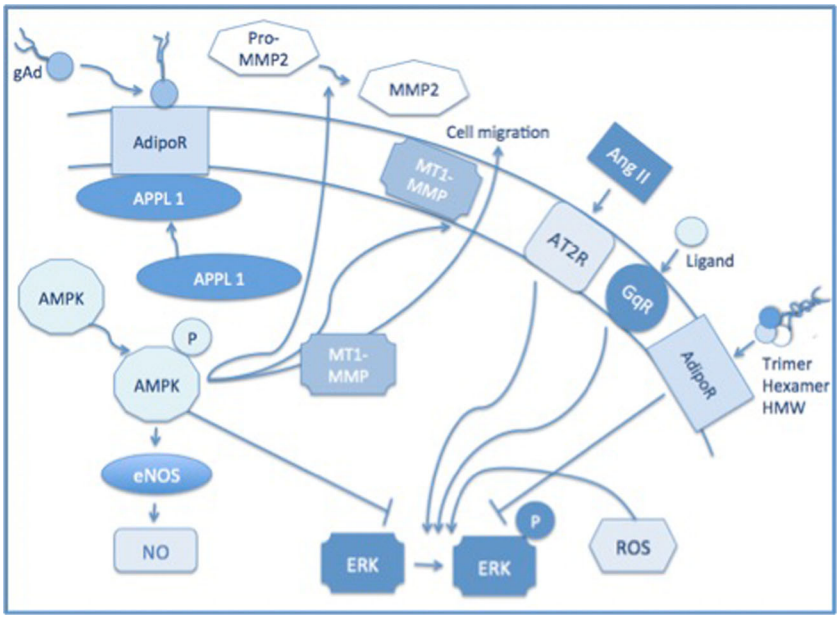

Fig. 3 Simplified model of adiponectin-mediated signaling pathways. Adiponectin binds to its receptor (AdipoR), adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif (APPL 1) binds to AdipoR and activates 5′ AMP-activated protein kinase (AMPK). Matrix metalloproteinases (MMP) isoforms are translocated to the cell membrane (MT1-MMP) or secreted (MMP2) and the inactive MMP zymogen secreted is activated by MT1-MMP on the cell surface and facilitates cell migration. Extracellular-regulated kinase (ERK) phosphorylation is stimulated by α-adrenergic ligands, angiotensin-II (AngII) and reactive oxygen species (ROS). Trimer, hexamer and HMW adiponectin forms bind to theirs receptors and suppress the activation of ERK. AMPK also suppresses ERK phosphorylation. AMPK activates endothelial nitric-oxide sintase (eNOS) and increases nitric-oxide (NO) production. *gAd* globular adiponectin and *GqR* Gq-coupled receptor

rapid activation of energy-generating metabolic pathways by enhancing glucose uptake and glycolysis and stimulating fatty acid oxidation, leading to inhibition of cardiomyocyte hypertrophy [32].

Adiponectin suppression of ERK phosphorylation is another important mechanism that prevents cardiomyocyte hypertrophy. ERK phosphorylation is stimulated by α-adrenergic receptors and angiotensin-II and is responsible for myocyte hypertrophy [33]. The trimer form of adiponectin and, in a lesser extent, the hexamer or HMW forms suppress the activation of ERK and play an important role in preventing the increase of myocyte size [31]. Adiponectin has also an indirect effect in the suppression of ERK phosphorylation, as its activation of AMPK has been shown to also suppress ERK phosphorylation (Fig. 3) [33].

In summary, adiponectin inhibits myocardial hypertrophy via AMPK and ERK signaling pathways, which may result in the improvement of diastolic function. However, further research is needed to understand the importance of myocardial hypertrophy to the development of HFpEF as, although it may

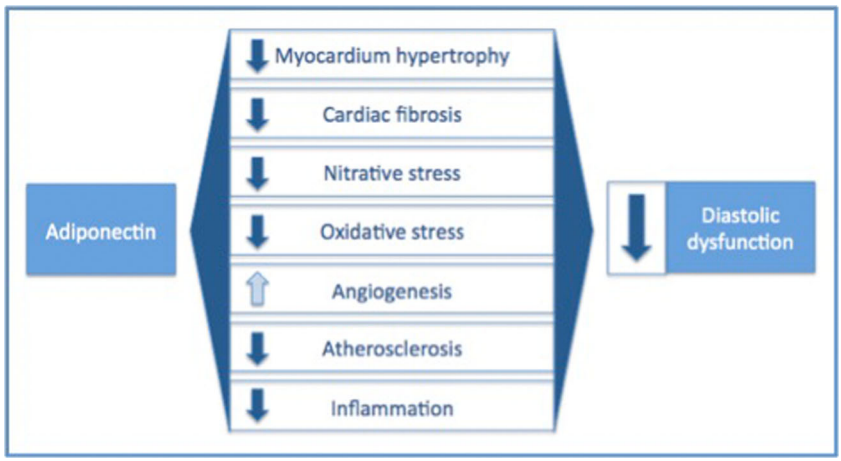

Fig. 4 Main effects of adiponectin on diastolic dysfunction. Adiponectin is implicated in the prevention of myocardium hypertrophy, cardiac fibrosis, nitrative and oxidative stress, atherosclerosis and inflammation and is involved in the potentiation of angiogenesis, avoiding the pathogenesis of diastolic dysfunction

contribute to diastolic dysfunction, less than 50 % of HFpEF patients have ventricular hypertrophy [34].

Cardiac Fibrosis

Acute and chronic stressors have been shown to induce necrotic cell death and the loss of cardiomyocytes. As a result, the structural integrity of the myocardium is ensured by cardiac fibroblasts, which mount a healing process [35]. This response can initially aid contractile function but renewal of matrix with inadequately structured collagen increases myocardial stiffness and contributes to diastolic dysfunction.

Evidence indicates that effector hormones of the renin-angiotensin-aldosterone system (RAAS) are key features of cardiac fibrosis [35]. Angiotensin-II (Ang-II)-induced cardiac fibrosis is mediated by AMPK-dependent PPAR-α suppression, a pathway activated by adiponectin, which plays an important role in protecting against cardiac fibrosis.

Indeed, Fujita et al. found that APNKO presented severe Ang-II-induced fibrosis and that AMPK activation partly inhibited Ang-II-dependent ERK1/2 signaling, whereas blockage of Ang-II-induced ERK1/2 activation resulted in AMPK activation [36].

Cardiac fibroblasts regulate ECM dynamics through a tight balance between matrix metalloproteinases (MMPs), which degrade structural proteins, and their tissue inhibitors (TIMPs) [37]. Adiponectin has been shown to have an important effect on principal MMP isoforms. This cytokine seems to increase cell surface MT1-MMP levels and MMP2 activity in extracellular media, contributing to a cardioprotective role by promoting fibroblast migration to damaged areas and matrix degradation, an initial favourable response to cardiac injury. This response is mediated by adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif (APPL 1), a protein that plays an essential role in activation of AMPK by adiponectin [38].

In conclusion, via interaction with the RAAS and inflammatory system reactions, adiponectin inhibits cardiac fibrosis, limiting myocardial stiffness and improving diastolic dysfunction.

Nitrative Stress

Nitric oxide (NO) is a known modulator of cardiac relaxation. Adiponectin can regulate NO production by both endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS), although in an opposite way. Under pathological conditions, when iNOS is induced, adiponectin inhibits iNOS expression, preventing excessive NO secretion [39]. Under physiological conditions, adiponectin stimulates NO production via AMPK-mediated eNOS phosphorylation [40], contributing to vasodilator, anti-inflammatory and cardioprotective effects.

On the other hand, in hypoadiponectinemia, reduced NO levels [41, 42] may lead to phospholamban changes [43]. Phospholamban is a phosphoprotein that regulates Ca^{2+} reuptake via Ca^{2+}-ATPase (SERCA2) to the sarcoplasmic reticulum and thus cardiac relaxation and contractility. Phospholamban dephosphorylated form inhibits SERCA2 and its phosphorylated form reverses this inhibition, leading to improved relaxation and contractility [44]. Thus, phospholamban changes can result in increased cytosolic calcium, impaired myocardial relaxation and diastolic dysfunction [22]. Although there is no direct evidence of the link between calcium signaling and adiponectin, this relation may explain the effects of hypoadiponectinemia in diastolic dysfunction, thus opening avenues for further research.

Although low NO levels lead to impaired relaxation and diastolic dysfunction, at very high concentrations, NO can also compromise diastolic function. Actually, NO itself does not cause tissue injury, but reacting with superoxide, it generates peroxynitrite, a product that causes nitrative stress and tissue injury, which can lead to diastolic dysfunction [45]. In this context, iNOS inhibition induced by adiponectin plays an important role in ischemic-reperfused cardiomyocytes, exerting anti-ischemic and cardioprotective effects via inhibition of peroxynitrite-induced nitrative stress. In fact, experiments demonstrated that, after ischemia-reperfusion, APNKO mice presented enhanced NO production and intensified peroxynitrite formation [46].

In summary, the lack of adiponectin may contribute to diastolic dysfunction by both reducing NO levels and inducing phospholamban changes, and enhancing NO concentration, facilitating nitrative stress.

Oxidative Stress

Oxidative stress is an imbalance between antioxidant defenses and excessive reactive oxygen species (ROS), and modulates intracellular signaling pathways that are important in HFpEF [47]. Increased levels of ROS may promote changes in Ca^{2+} handling proteins and increase Ca^{2+} sensitivity of myofilaments inducing diastolic dysfunction [48]. Oxidative stress also decreases NO bioavailability which may contribute to increased myocardial stiffness, impaired relaxation and myocardial hypertrophy [49].

Adiponectin protects cardiomyocytes against oxidative stress via both positive and negative regulation of AMPK and ERK signaling, respectively, and downstream regulation of NF-kB activity [13].

ROS can have different effects in cardiac myocytes depending on their concentration. At lower but physiological concentrations, ROS, including hydrogen peroxide (H_2O_2), induce hypertrophy [50]. At higher levels, ROS induce cell death and enhance reactive radicals that lead to cardiac remodeling [51], namely hypertrophy via activation of MAPK and

NF-kB. As described in previous sections, ERK and AMPK signaling pathways are involved in mechanisms related to hypertrophy [32, 33], and ROS are able to activate ERK, p38 kinase, and JNK members of MAPK signaling cascades. Adiponectin has been shown to have an inhibitory effect on ERK activity in cardiomyocytes by preventing ROS-induced ERK phosphorylation. Furthermore, adiponectin is responsible for AMPK phosphorylation [31], enhancing its activity and inhibiting hypertrophy.

NF-kB activation is also involved in the development of hypertrophy. ROS has a dual effect on NF-kB pathway, either enhancing or reducing its activity. At high concentrations, H_2O_2 seems to inhibit NK-kB, but at physiological concentrations, H_2O_2 leads to its activation, an effect that has been shown to be attenuated by adiponectin [52].

Moreover, oxidative stress induces MMP activity, and it has been shown that adiponectin modulates H_2O_2-induced MMP-9 and MMP-2 activity [13, 53], protecting against the development of fibrosis as referred above.

In conclusion, adiponectin protects against effects induced by accumulation of ROS, such as cardiomyocyte hypertrophy and myocardial fibrosis, interacting with AMPK/ERK/NF-kB signaling axis and being involved in the inhibition of MMP expression, respectively.

Angiogenesis

Cardiac hypertrophy increases oxygen demand and promotes myocardial angiogenesis in order to minimize the hypoxic situation and maintain cardiac function [54]. In this regard, in physiological cardiac hypertrophy, an increase in the number of myocardial capillaries is often observed, whereas in pathological hypertrophy, reduced capillary density triggers myocardial hypoxia and cardiac dysfunction [55–57].

Adiponectin is known to have proangiogenic and antiapoptotic functions, protecting against the development of diastolic dysfunction by preventing capillary loss. These effects are specifically mediated by the HMW form of adiponectin and involve AMPK signaling [58].

Indeed, adiponectin affects endothelial cell survival and stimulates vascularization, maintaining myocardial capillary density and preserving myocardial relaxation function. It also diminishes myocardial apoptosis, resulting in the direct pro-survival effects of adiponectin on myocytes. Studies demonstrated that APNKO mice present reduced capillary density and impaired angiogenic repair capacity, whereas treatment with adiponectin stimulated blood vessel growth [59]. In contrast, other studies have demonstrated a potent inhibition of endothelial angiogenic events like migration and proliferation by adiponectin, involving MAPK and cAMP-PKA pathways [60, 61].

These discrepancies seem to be due to the differences in the forms of adiponectin used. Adya et al. [62], in a study to investigate the effect of globular adiponectin (gAd) and full-length adiponectin (fAd) on endothelial cell proliferation, and in vitro migration and angiogenesis, found that gAd was implicated in endothelial proliferation, migration and angiogenesis, whereas fAd was only related with endothelial cell proliferation, and concluded that the beneficial or detrimental effect of adiponectin in angiogenesis remained unclear and could depend on the different isoforms of adiponectin.

Atherosclerosis

Several studies demonstrated an association between atherosclerotic disease and diastolic function. Jaroch et al. [63] described a significant correlation between arterial stiffness indices and diastolic dysfunction parameters in untreated hypertensive patients. Akintunde et al. [64] also found a correlation between right ventricular diastolic dysfunction and carotid atherosclerosis, in a group of hypertensive patients.

Atherosclerosis is characterized by chronic systemic inflammation. The first change preceding the formation of lesions of atherosclerosis is endothelial injury, which is mediated by inflammatory stimuli such as TNF-α. Subsequently, monocytes adhere to the endothelium, migrate to arterial wall and transform into macrophages, which modify LDL and transform into foam cells [65].

Adiponectin has been suggested to have anti-atherosclerotic properties. Its action can be resumed in three major effects: (i) modulation of inflammatory response of endothelial cells, by inhibiting TNF-α induced monocyte adhesion and endothelial expression of endothelial-leukocyte adhesion molecule-1 (E-selectin), vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1), and, via inhibition of endothelial NF-kB signaling through the activation of cAMP, protein kinase A; (ii) suppression of macrophage to foam cell formation through the inhibition of class A macrophage scavenger receptor (SR-A); (iii) inhibition of proliferation and migration of smooth muscle cells induced by platelet-derived growth factor BB (PDGF-BB) by directly binding with PDGF-BB and by inhibiting ERK phosphorylation in PDGF-BB-stimulated smooth muscle cells [66].

Therefore, adiponectin seems to have an important role in preventing atherosclerosis, which may contribute to the prevention of diastolic heart failure.

On the other hand, one study showed that, in preclinical rodent models, adiponectin levels did not correlate with atherosclerosis, suggesting that adiponectin may not be involved in advanced plaque progression in mice [67] and revealing the complex and multifaceted actions of adiponectin in the cardiovascular system.

Inflammation

A systemic pro-inflammatory state is a main characteristic of HFpEF. It not only contributes to the development of a

diversity of comorbidities such as obesity, diabetes [68], chronic pulmonary disease [69] and renal dysfunction [70], but also contributes to endothelial dysfunction and direct detrimental myocardial effects [71]. In fact, elevated levels of pro-inflammatory cytokines may play an important role in the pathophysiology of HFpEF, as they act locally on immune activation, cause skeletal muscle wasting, reduce myocardial contractility and induce myocardial hypertrophy [72].

Hypoadiponectinemia may contribute to an increased inflammatory response, but the mechanisms underlying this association are yet poorly known. This inconsistency is further supported by the fact that not all forms of adiponectin seem to prevent the inflammatory response [73]. Literature indicates that adiponectin isoforms may differ in their biological activity and in their role in inflammation. In fact, although both LMW and HMW isoforms induce apoptosis, reduce macrophage scavenger receptor mRNA expression and stimulate phosphorylation of AMPK, only LMW isoform displays anti-inflammatory properties by reducing lipopolysaccharide-induced IL-6 secretion [74].

An elevation of TNF-α and IL-6 plasma levels in patients with diastolic dysfunction and preserved systolic function has been observed [75]. The mechanism behind this association was suggested by Wu et al., who demonstrated that these cytokines down-regulate SERCA2 gene expression, decreasing diastolic calcium reuptake and causing cardiac diastolic dysfunction [76]. Treatment of cultured macrophages with adiponectin has been shown to reduce TNF-α production [77], which may be beneficial for the prevention of diastolic dysfunction.

In recent studies, the inflammatory marker C-reactive protein (CRP) was also related to left ventricular diastolic dysfunction [78], and adiponectin has been shown to be inversely correlated with CRP concentrations [12], suggesting that hypoadiponectinemia may contribute to an increased inflammatory response in diastolic dysfunction.

Clinical Relevance and Future Directions

Adiponectin seems to prevent most of the pathophysiologic mechanisms underlying HFpEF as it is linked to the prevention of myocardial hypertrophy, cardiac fibrosis, atherosclerosis, inflammation, nitrative and oxidative stress and to the promotion of angiogenesis. Considering these effects together with the beneficial effects of adiponectin on several animal models, adiponectin represents a potentially interesting therapeutic target in HFpEF. Actually, interventions that are associated with an increase of adiponectin levels, have been previously related to the prevention and treatment of diastolic dysfunction, including (i) exercise [79, 80], (ii) diet-induced weight-loss [81, 82] and (iii) weight-loss induced by bariatric surgery [83, 84], further highlighting the potential clinical relevance of adiponectin in the treatment of patients with HFpEF [81, 85]. On the other hand, one cannot ignore studies that found no relation between adiponectin levels and diastolic function [86, 87]. The contradictory results between studies may be related to the evaluation of different stages of HFpEF or to the study of different isoforms of adiponectin.

The peroxisome proliferator-activated receptor (PPAR)-γ is the main regulator of adipocyte differentiation and adipocyte gene expression [66], and PPAR-γ-dependent pathways are important targets to induce the expression of adiponectin [23]. PPAR-γ agonists, thiazolidinediones, have been shown to increase plasma adiponectin levels in humans [88], revealing its potential in improving diastolic function. However, despite the direct beneficial effects on adiponectin levels of thiazolidinediones, they are also known to induce fluid retention which may contribute to the development of heart failure [89]. At this moment, the available thiazolidinediones are not recommended for the treatment or prevention of HFpEF [90], however the development of PPAR-γ agonists with greater specificity for adipose tissue may represent an interesting therapeutic approach to increase adiponectin levels without the detrimental fluid retention. Likewise, the fibrates have been shown to increase adiponectin levels, partly mediated by PPAR-responsive element (PPRE) [91]. Treatment with angiotensin-converting enzyme inhibitors also triggers adiponectin levels elevation. The mechanisms by which RAAS inhibition leads to the increase of adiponectin concentration include enhancing insulin sensitivity, recruiting and promoting differentiation of preadipocytes and increasing transcription/translation of adiponectin [66].

Exogenous adiponectin has been used in several animal models [92–94]. However, adiponectin is a complex molecule that undergoes significant posttranslational modifications, making direct administration of adiponectin a particularly challenging and inconvenient treatment. On the other hand, the use of synthetic molecules that could activate adiponectin-related pathways is one of the more promising therapeutic weapons in this field. Recently, an orally active synthetic adiponectin receptor agonist (known as AdipoRon) was shown, not only to significantly improve insulin sensitivity and glucose tolerance in mice [95], but also to induce cardioprotective effects through both AMPK-mediated and AMPK-independent signaling in mice with myocardial ischemia [96]. More pharmacological and animal model studies are required before we move on to treating humans.

However, the prospect of adiponectin treatment is an exciting scenario for the treatment of many facets of diastolic dysfunction.

Conclusion

Hypoadiponectinemia may be a link between obesity and diastolic dysfunction. Indeed, decreased levels of plasma

adiponectin are present in obese individuals and are associated with cardiovascular disease such as diastolic dysfunction.

HFpEF is a condition with complex and incompletely known pathophysiology, and therapeutic options or consensual diagnostic criteria for these patients are still lacking. Due to its role in improving diastolic function, raising adiponectin levels may become a potential pharmacologic target in diastolic dysfunction.

Compliance with Ethical Standards

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Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interests The authors declare that there are no competing interests.

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