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Etiology and Pathophysiology

Adiponectin: from obesity to cardiovascular disease

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Summary

Adiponectin is an adipokine whose biosynthesis is deranged in obesity and diabetes mellitus, predisposing to atherosclerosis. Evidence suggests that adiponectin has anti-atherogenic properties by improving endothelial function and having anti-inflammatory effects in the vascular wall. In addition, adiponectin modifies vascular intracellular redox signalling and exerts indirect antioxidant effects on human myocardium. However, its clinical role in cardiovascular disease is obscure. Adiponectin's positive prognostic value in coronary artery disease had been widely supported over the last years, but this view has been questioned recently. High adiponectin levels are paradoxically associated with poorer prognosis in heart failure syndrome. These controversial findings seem surprising as adiponectin has been viewed overall as an anti-atherogenic molecule. Therefore, any certain conclusion about adiponectin's role in cardiovascular disease seems premature. Despite the rapidly accumulating literature on this adipokine, it is still unclear whether adiponectin is a key mediator or a bystander in cardiovascular disease. It is still uncertain whether adiponectin levels have any clinical significance for risk stratification in cardiovascular disease or they just reflect the activation of complex and opposing underlying mechanisms. Circulating adiponectin levels should be interpreted with caution, as they may have completely different prognostic value, depending on the underlying disease state.

Keywords: Adipocytes, adiponectin, cardiovascular disease, obesity.

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Introduction

The view of the adipose tissue as a site of pure energy storage has dramatically changed over the last years. Adipose tissue is now considered to be a large endocrine gland that takes part in the regulation of diverse biological functions (1). The communication between adipose tissue and other biological systems is accomplished through the expression of a large number of bioactive mediators that are collectively called 'adipokines' (1). Adiponectin is distinguished as one of the most important adipokines involved in multiple biological processes in the human body.

Adiponectin was first noticed as an adipose-tissue peptide being dysregulated in obesity (2). Not long after, its potential as an anti-atherogenic factor was recognized by its ability to modulate the expression of endothelial adhesion molecules (3) and to affect key mechanisms involved in atherogenesis. Since then, several experimental and clinical studies extensively examined the role of adiponectin in vascular homeostasis and its potential value as a clinical biomarker in cardiovascular disease, providing rather contradictory results.

In this review article, we performed a Medline (PubMed) search, to identify articles published during the last 10 years (with special focus on papers published during the last 3 years), examining the role of adiponectin in cardiovascular disease. We systematically present the mechanisms by which adiponectin affects cardiovascular system, and we discuss the clinical importance of this adipokine. Special attention was paid to the inclusion of large-scale clinical

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studies examining the effect of adiponectin on outcome of subjects at different disease stages. Finally, we briefly discuss the various therapeutic strategies targeting adiponectin's bioavailability in humans.

Biosynthesis of adiponectin

Adiponectin is synthesized by adipocytes and exerts its biological effects mainly through its receptors, AdipoR1 and AdipoR2 (4). Adiponectin's gene has been mapped at chromosome 3q27, but the mechanisms regulating its expression are still under investigation.

Adiponectin expression seems to be regulated by distinct signalling pathways, involving different transcriptional factors. Studies on 3T3-L1 adipocytes have shown that oxidative stress (5), sympathetic nervous system activity (6) and pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin (IL)-6 (7), suppress adiponectin expression. Adiponectin levels have been associated with age, gender (lower in men, possibly as a result of androgens effect) (8) and smoking status, while Mediterranean diet and exercise increase its circulating levels (9–11). Hypoadiponectinemia has been closely associated with obesity, metabolic syndrome, type 2 diabetes mellitus (12), dyslipidemia (13) and essential hypertension (14). Moreover, genetic determinants seem to affect adiponectin levels (9). From a total number of 10 frequent single-nucleotide polymorphisms in adiponectin gene studied in many cross-sectional studies, two common single-nucleotide polymorphisms (+45T>G and +476G>T) have been proposed as determinants of circulating adiponectin levels (9). Notably, the findings are not always consistent, possibly because of the different ethnic groups studied and the presence of confounders, such as the type of diet and exercise. Therefore, the existing studies have been unable so far to fully address the role of gene–environment interaction (9). Despite being a hormone secreted mainly by adipose tissue, adiponectin levels are paradoxically inversely correlated with body weight, or body mass index (15). It appears that a negative feedback loop exists between adiponectin and adipose tissue. Adiponectin is decreased in obesity, while evidence suggests that adiponectin levels are increased after substantial weight loss (15). Regarding the effect of insulin on adiponectin expression, existing data are controversial. Some *in vitro* studies suggest that insulin decreases adiponectin expression (16), but at a clinical level, long-term insulin administration to diabetic patients had no impact on adiponectin levels (17). Importantly, in studies of type B insulin resistance, where insulin levels are particularly high, adiponectin levels are also extremely high (18). This hypothesis was also supported by *in vitro* data, indicating that insulin induces a twofold rise in adiponectin gene expression in adipocytes. Therefore, the controversial results of the clinical and experimental studies fail to provide a definite conclusion regarding the effect of insulin on adiponectin expression in humans (19).

Adiponectin and cardiovascular system: mechanistic insights

Circulating adiponectin exists in human plasma as monomeric, oligomeric and multimeric, high-molecular-weight (HMW) forms (Fig. 1) (20), but the biological importance of each one of these isoforms is still unclear. Nevertheless, recent data suggest that HMW adiponectin might be particularly important, as via its effects on AdipoR1 and

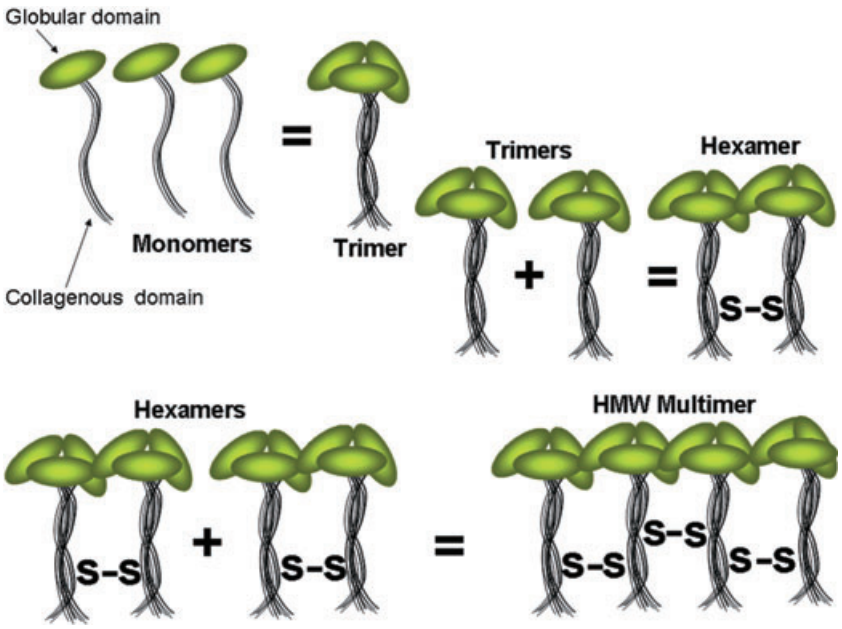

Figure 1 Adiponectin multimerization: Three monomers are bound together to form a trimer. This is achieved through association between their C-terminal globular domains and stabilized by the triple helix formation of the collagenous domains. Two trimers are then bound together via disulphide bond (Cys39 residue) to form a hexamer. High-molecular-weight (HMW) multimers are formed by non-covalent higher-order interactions between hexamers.

AdipoR2 receptors (21) it has insulin-sensitizing and vaso-protective effects (20). It is now well established that adiponectin improves insulin-mediated glucose uptake by skeletal muscles and suppression of hepatic glucose production (22). Additionally, by promoting fat oxidation adiponectin reduces tissue triglyceride content in skeletal muscles and ameliorates insulin resistance (22,23).

Effects on inflammatory mechanisms

Further to its central role in the metabolism of carbohydrates, lipids and general energy homeostasis (1), adiponectin seems to play an important role in human vascular homestasis. Evidence suggests that adiponectin affects important inflammatory mechanisms involved in cardiovascular disease and especially in atherogenesis. Ouchi *et al.* (3) have demonstrated that adiponectin interferes with nuclear factor kappa-B (NF-κB) intracellular signalling pathways, suppressing the expression of adhesion molecules. Additionally, TNF-α, a molecule that initiates and organizes inflammatory changes in vascular tissue and whose expression is controlled by NF-κB, seems to have a reciprocal relationship with adiponectin. Adiponectin knockout mice show high levels of TNF-α mRNA in adipose tissue and TNF-α plasma levels (24). Furthermore, adiponectin has the ability to negatively regulate IL-2-induced natural killers cell activation and inhibit the synthesis of endothelium-derived inflammatory cytokines (25). Adiponectin induces the production of the anti-inflammatory mediators IL-10 and IL-1RA in human inflammatory cells and impairs interferon-γ production, another target gene of NF-κB (25).

However, opposing data also exist. Globular adiponectin has also been shown to be capable of activating NF-κB transcriptional pathways in vascular endothelial cells, promoting inflammation (26). In the large KORA S4 study, it was recently suggested that hypoadiponectinemia and pro-inflammatory state are largely independent from each other (27). Therefore, the true impact of adiponectin on inflammatory mechanisms is still controversial. It is likely that the underlying disease state is a key determinant of the association between adiponectin and inflammation, as it will be discussed later in this article.

Effects on vascular endothelium

In vitro studies have shown that adiponectin directly stimulates the production of nitric oxide (NO) by endothelial cells, via PI3-dependent pathways, which enhance endothelial NO synthase (eNOS) activity by triggering its AMPK-induced phosphorylation (28). Other cell culture studies have illustrated adiponectin's ability to decrease TNF-α-induced production of asymmetric dimethylarginine (29), an L-arginine analogue that inhibits NO formation and thereby can impair vascular function. This activation and up-regulation of eNOS could explain some of the observed vaso-protective properties of adiponectin. Apart from its beneficial effects on eNOS, adiponectin improves endothelium redox state by suppressing NADPH oxidase-derived superoxide generation (30). Evidence also suggests that HMW adiponectin suppresses endothelial cell apoptosis (31) and promotes vascular healing and angiogenesis (32).

Anti-atherogenic effects

The first direct evidence for adiponectin's potential role in preventing atherosclerosis was provided by experiments on mice. It was noticed that adiponectin knockout mice show increased neo-intimal proliferation in response to vascular injury (33). The primary hypothesis was further confirmed by the finding that adiponectin prevents atherosclerosis in apolipoprotein-E-deficient mice (34). In addition, *in vitro* studies have revealed some specific anti-atherogenic actions of adiponectin. Studies on human aortic endothelial cells have proved that adiponectin suppresses TNF-α-induced expression of adhesion molecules (2). Furthermore, adiponectin prevents macrophage's transformation into foam cells, a crucial step in atherogenesis (35). Arita *et al.* (36) also showed that adiponectin suppresses proliferation of human aortic smooth muscle cells, suggesting a possible interference in vascular remodelling. Besides, as above-mentioned, it has been shown that hypoadiponectinemia is associated with coronary artery disease (CAD) (37). Moreover, adiponectin plasma levels correlate with various atherosclerotic risk factors, such as low-density lipoproteins, particle size and triglycerides (13). Therefore, it is generally believed that by acting as an anti-inflammatory, antioxidant and vasodilator agent, adiponectin prevents endothelial dysfunction and the progression of atherosclerosis.

Effects on myocardium

Adiponectin is synthesized and secreted by human cardiomyocytes as reported before, while AdipoRs exist in cardiac muscle. As in other energy-consuming tissues, adiponectin also regulates energy homeostasis in cardiac muscle, increasing cardiac oxidation of fatty-acids (Fig. 2) (1). However, recent data suggest that adiponectin exerts also a direct cardio-protective action. Two recently published studies demonstrated that adiponectin accumulates in myocardial tissue that has been damaged by ischaemia/reperfusion injury (38) and protects myocardium by inhibiting inducible NOS and NADPH-oxidase expression and resultant oxidative stress (39), while it may protect against myocardial ischaemia/reperfusion injury through AMPK- and COX-2-dependent mechanisms (40). Even more importantly, adiponectin seems to be involved in coronary plaque vulnerability as that is characterized by angiographic lesion

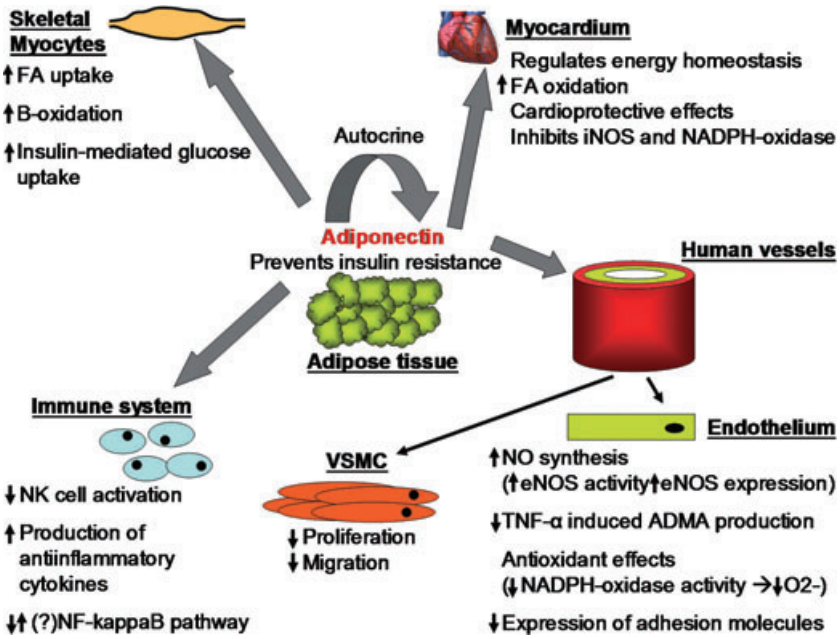

Figure 2 Cardiovascular system-related actions of adiponectin. Adiponectin is synthesized mainly in adipose tissue, where it acts in a paracrine way, while it also exerts multiple actions in vascular wall, immune system, skeletal and myocardial myocytes and other tissue types. ADMA, asymmetrical dimethylarginine; eNOS, endothelial nitric oxide synthase; FA, fatty acid; iNOS, inducible nitric oxide synthase; O2-, superoxide radicals; TNF-α, tumour necrosis factor alpha.

complexity (41). In view of this evidence, it seems reasonable enough to claim that adiponectin at least takes part in the pathophysiology of ischaemic heart disease if not altering its course and outcome.

Overall, adiponectin seems to be a key player in cardiovascular homeostasis. However, most of the mechanistic data currently available are based on observations from cell culture and animal models, and extrapolations to humans should be made with caution.

Clinical implications

Adiponectin and atherosclerosis

Despite the strong evidence provided by experimental studies, the role of adiponectin in human atherosclerosis and its association with cardiovascular mortality remain unclear. Indeed, evidence suggests that adiponectin expression in epicardial adipose tissue is decreased in patients with CAD (42). However, plasma adiponectin has been negatively associated with common carotid intima media thickness, but not with the presence of atherosclerotic plaques (43). Therefore, hypoadiponectinemia may have a clinical value at the early stages of atherogenesis, but its role as a meaningful biomarker is questioned at more advanced disease stages. The role of plasma adiponectin in the evaluation of CAD progression is controversial, as reviewed in Table 1. Recent clinical studies (Table 1) have demonstrated that adiponectin may have a predictive value for the development of CAD, but not in high-risk groups (Table 1). Although adiponectin can poorly explain the association between metabolic syndrome and cardiovascular mortality (44), it is an independent inverse predictor of cardiovascular risk in patients with diabetes mellitus (45), CAD (46) or recent acute myocardial infarction (47). However, conflicting data also supported that adiponectin cannot be effectively used for cardiovascular risk stratification among healthy individuals, after 20 years of follow-up (Table 1) (48).

On the other hand, hyperadiponectinemia appears to be an independent predictor of cardiovascular mortality in patients with end-stage renal failure (49) (Table 1), while it predicts the progression from macroalbuminuria to end-stage renal failure in type 1 diabetic patients (50). This could be due to malnutrition and hyper-catabolic state observed in these patients, conditions associated with both increased adiponectin levels and the severity of the disease (51).

The contradictory results regarding the use of plasma adiponectin as a biomarker in cardiovascular disease could be explained by the different disease stage of the various populations included into the clinical studies so far. Decreased circulating adiponectin in healthy populations seems to be predictive for the development of atherosclerosis. However, after the establishment of atheromatous disease, this association becomes weaker, especially in the presence of conditions inducing a hyper-catabolic state (such as heart or renal failure), which are associated with increased plasma adiponectin, accelerated progression of atherosclerosis and worse clinical outcome.

Adiponectin and heart failure: a clinical paradox

Despite the well-established role of pro-inflammatory cytokines and especially TNF-α and IL-6 in heart failure

Table 1 The clinical impact of adiponectin in cardiovascular disease

Study	Population	Design	Findings
Iglseder *et al.* (43)	1515 healthy white subjects	Cross-sectional design	Adiponectin levels are negatively associated with common carotid artery IMT
Langenberg *et al.* (44)	2118 subjects with several components of metabolic syndrome	Prospective follow-up (20 years) End point: CHD mortality	Adiponectin explains little to the association between the metabolic syndrome and CHD mortality
Kanaya *et al.* (71)	3045 older black and white adults	Prospective follow-up (6 years) End points: MI, death	High adiponectin is associated with higher risk of CHD in older blacks
Laughlin *et al.* (48)	1513 community members	Prospective follow-up (20 years) End points: CHD events, MI, cardiovascular death	Higher adiponectin is associated with reduced risk of nonfatal MI in men only; adiponectin is not associated with CHD mortality in either sex
Zoccali *et al.* (72)	227 patients with end-stage renal disease	Prospective follow-up (mean 31 months) End point: cardiovascular events	Plasma adiponectin is an inverse predictor of cardiovascular outcomes in patients with ESRD
Schulze *et al.* (45)	745 type 2 diabetic men	Prospective follow-up (5 years) End point: CAD	Increased adiponectin levels are associated with a moderately decreased CHD risk in diabetic men
Menon *et al.* (49)	820 patients with chronic renal disease	Prospective follow-up (10 years)	High adiponectin is associated with increased mortality in patients with chronic renal disease
In patients with CAD			
Pilz *et al.*,(73)	273 control subjects, 367 subjects with silent CAD, 608 patients with stable angina, and 378 patients with unstable angina		Low adiponectin is an independent predictor for stable and unstable angina. There was no significant differences of adiponectin levels between stable and unstable angina group, nor between any classes of angina according to the Canadian Cardiovascular Society Angina Score for stable angina
Dieplinger *et al.* (74)	433 patients with symptomatic PAD and 433 controls	Cross-sectional	Hypoadiponectinemia is associated with symptomatic atherosclerotic PAD
Kumada *et al.* (37)	225 male CAD patients with CAD and 225 controls	Cross-sectional	Hypoadiponetinemia is significantly correlated with CAD
Shioji *et al.* (75)	431 patients with CAD (ACS excluded)	Cross-sectional design	Adiponectin levels are positively associated with the severity of CAD (number of afflicted vessels), but not with common carotid artery IMT
Hara *et al.* (76)	104 patients with CAD	Cross-sectional design	Plasma adiponectin predicts the severity of coronary atherosclerosis (assessed by Gensini score system)

Table 1 *Continued*

Study	Population	Design	Findings
Maahs *et al.* (77)	306 type 1 diabetic and non-diabetic patients with CAD	Prospective follow-up (mean 2.6 years)	Low plasma adiponectin levels predict progression of coronary artery calcification
Costacou *et al.* (78)	Type 1 diabetic patients (28 with CAD and 34 controls)	Prospective follow-up	Adiponectin concentration is positively associated with a lower risk of CAD in type 1 diabetic patients
Kojima *et al.* (47)	156 patients with AMI	Prospective follow-up End points: major adverse cardiac events	Plasma adiponectin concentrations can be used to predict future adverse cardiac events in AMI patients
Cavusoglu *et al.* (79)	325 males with chest pain undergoing angiography	Prospective follow-up (2 years) End points: MI, death	High plasma adiponectin independently predicts risk of death and MI in men presenting with chest pain
Shimada *et al.* (80)	127 patients undergoing elective coronary stenting	Prospective follow-up End point: restenosis (>50% stenosis)	Adiponectin cannot predict angiographic restenosis after elective coronary stenting
Pilz *et al.* (81)	2473 subjects with and 673 subjects without angiographic CAD	Prospective follow-up (mean 5.45 years)	High plasma adiponectin independently predicts all-cause, cardiovascular and non-cardiovascular mortality in individuals with CAD
Dekker *et al.* (82)	2325 individuals with and without CVD	Prospective follow-up End point: all-cause and CVD mortality and morbidity	High levels of adiponectin predict mortality, particularly in patients with prevalent CVD.
In patients with heart failure			
McEntegart *et al.* (53)	30 patients with HF (20 with cachexia), 10 with CAD/no HF and 7 healthy controls	Cross sectional	Adiponectin levels are increased only in patients with HF and cachexia
Nakamura *et al.* (54)	90 patients with CHF and 20 controls	Cross sectional	Hyperadiponectinemia is associated with the severity of ventricular dysfunction in CHF
Tamura *et al.* (55)	54 (24 ischaemic and 30 non-ischaemic) CHF patients and 55 controls	Cross sectional / Prospective follow-up	Adiponectin levels are increased in CHF; Higher adiponectin is associated with higher mortality especially in the ischemic CHF patients
George *et al.* (56)	175 patients with CHF	Prospective follow-up (2 years) End points: death, CHF hospitalizations	Adiponectin is increased in CHF patients and predicts mortality and morbidity

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CRF, chronic renal failure; CVD, cardiovascular disease; ESRD, end-stage renal disease; HF, heart failure; IMT, intima media thickness; MI, myocardial infarction; PAD, peripheral artery disease.

(HF) (52), the potential impact of adiponectin on the pathophysiology of HF is largely controversial. Very recently, published data suggest that adiponectin levels are paradoxically increased in chronic HF (Table 1) (53–55). Indeed, adiponectin levels are positively correlated with brain natriuretic peptide levels and the severity of ventricular dysfunction as estimated by New York Heart Association Classification (54). Furthermore, it has been suggested that adiponectin predicts mortality and morbidity in HF patients (Table 1) (56). Given the vaso- and cardioprotective properties of adiponectin, these findings cannot be easily explained, and cachexia seems to be the connective link: the reduction in body mass may up-regulate adiponectin's synthesis. As it has been suggested, adiponectin raised levels may just reflect the hyper-catabolic state in severe HF (51). Indeed, McEntegart *et al.* (53) have recently shown that adiponectin levels are increased in HF only in the presence of cachexia; patients with HF but no cachexia had similar adiponectin levels matched individuals without normal left ventricular function. Nevertheless, it remains to be clarified whether hyperadiponectinemia *per se* is involved in the pathogenesis of HF or whether it simply reflects the degree of cachexia in these patients.

Therapeutic strategies

In spite of the existing opposing data regarding the use of adiponectin as a clinically relevant biomarker, this adipokine is an insulin-sensitizing and anti-atherogenic molecule. Therefore, therapeutic strategies targeting adiponectin's bioavailability may prove to have a significant beneficial effect in atherogenesis. These strategies should be focused either on up-regulation of adiponectin's expression (and/or its receptors), or on targeting adiponectin's receptors through the development of the right agonists.

The effect of insulin and insulin resistance on the adipose-tissue-specific inflammatory response is a growing field of research. The insulin sensitizers, thiazolidinediones, which are PPARγ agonists and are widely used in the treatment of type 2 diabetes mellitus, have been shown to increase circulating adiponectin levels in humans (57). Indeed, this effect is independent of their insulin-sensitizing ability (58), as it was observed not only in obese and diabetic patients, but also in healthy individuals (57). However, this beneficial effect is not linked in any way to increased expression of adiponectin receptors in human fat or muscle (59). It is likely that the anti-diabetic and anti-atherogenic effect that has lately been attributed to thiazolidinediones (60) may be partly explained by their ability to raise adiponectin levels.

Another interesting class of medications widely used in the field of cardiology and equally related with adiponectin is angiotensin type 1 receptor blockers (ARBs). It has been demonstrated that some agents of the ARB family, such as telmisartan and to a lesser extent candesartan, exert PPARγ ligand activities (61). As expected, ARBs induced adiponectin gene transcription in humans (62). ARBs may also ameliorate adipokine dysregulation by reducing oxidative stress in adipose tissue (63). Furthermore, the renin-angiotensin-aldosterone system has been identified to have a regulatory role in adiponectin expression *in vivo*; therefore, its blockade either with ARBs or angiotensin-converting enzyme inhibitors has been shown to induce an increase in plasma adiponectin (64).

Statin treatment is considered to be a major therapeutic strategy targeting inflammatory mechanisms in cardiovascular disease (65), but the exact mechanisms of their effects on adiponectin expression are still unclear. At a clinical level, simvastatin treatment reduced adiponectin's levels in non-diabetic individuals (66) while pravastatin showed no effect on circulating adiponectin levels in a similar population (67). On the other hand, atorvastatin administration for 12 weeks in subjects at high risk for CAD significantly increased adiponectin levels (68). These conflicting results indicate the need for further mechanistic studies examining the effects of statins on the expression of adiponectin in the various atherosclerotic disease states.

Other therapeutic strategies include the use of cannabinoid type 1 receptor antagonists, such as rimonabant and taranabant, which might be particularly useful in the treatment of obesity (69). Recent studies illustrate that cannabinoid type 1 receptor blockers, in addition to the improvement of cardiometabolic risk factors, also up-regulate adiponectin levels *in vivo* (69). However, the use of these drugs is largely limited by their serious side effects on central nervous system and their clinical value now being re-evaluated. Finally, up-regulation of adiponectin receptors and use of adiponectin receptor agonists might also prove of clinical value in the future (70).

Conclusions

Adiponectin is a key adipokine with multiple actions in the human body. Of the three soluble forms of adiponectin, the multimeric HMW adiponectin seems to have the most important biological role. At a cellular level, adiponectin increases endothelial NO bioavailability, and it has anti-inflammatory, anti-apoptotic and overall anti-atherogenic properties, while it seems to affect myocardial remodelling. However, despite the beneficial role of adiponectin in vascular homeostasis, many studies suggest that high circulating adiponectin is associated with increased cardiovascular mortality in CAD patients. Furthermore, hypoadiponectinemia has been paradoxically associated with better clinical outcome in patients with advanced HF, but this finding probably reflects adiponectin association with the increased hyper-catabolic state observed in these patients. Indeed, adiponectin cannot be

easily used as a reliable, universal clinical marker in coronary atherosclerosis, and the underlying disease state is a key feature determining its potential clinical value. Therefore, it is still premature to state that adiponectin can be used as a therapeutic target in cardiovascular disease, and further research is required to understand the complexity of the molecular mechanisms regulating its biosynthesis and the true contribution of this adipokine in cardiovascular homeostasis.

Conflict of Interest Statement

No conflict of interest was declared.

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