Adiponectin: a key adipocytokine in metabolic syndrome

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ABSTRACT

The metabolic syndrome, a cluster of metabolic disorders often associated with visceral obesity, increases cardiovascular mortality and morbidity. As the body’s largest endocrine organ, adipose tissue not only stores excess body energy, but also secretes a variety of bioactive adipocytokines. Obese patients, particularly those with visceral fat accumulation, have reduced plasma levels of adiponectin, the most abundant and adipose-specific adipocytokine. Although the association of adiponectin with several diseases remains controversial, many clinical studies have demonstrated that low plasma concentrations of adiponectin (hypoadiponectinaemia) associate closely with obesity-related diseases, including atherosclerotic cardiovascular diseases, Type II diabetes mellitus, hypertension and dyslipidaemia. Accumulating experimental evidence indicates that adiponectin possesses anti-atherogenic, anti-inflammatory and anti-diabetic properties and may also participate importantly in the mechanism of metabolic syndrome and other diseases. Despite these associations, further clinical and experimental investigations will be needed to illuminate the in vivo pathophysiological significance of this protein. Although evaluation of adiponectin as a novel therapy will ultimately require clinical intervention studies, this mediator may represent a novel target for the prevention and treatment of visceral obesity metabolic syndrome.

INTRODUCTION

Obesity has become the most common nutritional disorder in industrialized countries. Indeed, two-thirds of all adults in the United States are currently obese or overweight [1]. A frequent companion of diabetes mellitus, dyslipidaemia, hypertension and other disorders linked to atherosclerotic cardiovascular disease and death, obesity generates an enormous economic burden which, in addition to its human costs, renders it one of the most urgent issues in medicine today.

The metabolic syndrome, a cluster of obesity-related disorders in one individual, is also known as syndrome X, the deadly quartet or the visceral fat syndrome [2–5]. The

Key words: adiponectin, adipocytokine, metabolic syndrome, prevention, treatment, visceral obesity.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute MI; AMPK, AMP-activated protein kinase; ApoE, apolipoprotein-E; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CRP, C-reactive protein; EC, endothelial cell; eNOS, endothelial NO synthase; ERK, extracellular-signal-regulated kinase; FATP-1, fatty acid transport protein-1; HDL, high-density lipoprotein; ICAM-1, intercellular cell-adhesion molecule-1; LDL, low-density lipoprotein; MI, myocardial infarction; NEFA, non-esterified fatty acid; PPAR, peroxisome-proliferator-activated receptor; RAS, renin-angiotensin system; SAP, stable angina pectoris; SNP, single nucleotide polymorphism; SR-A, class A scavenger receptor; TNF-α, tumour necrosis factor-α; TZD, thiazolidinedione; VCAM-1, vascular cell-adhesion molecule-1; VSMC, vascular smooth muscle cell.

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clustering of risk factors augments atherosclerotic cardiovascular disease, even beyond the contribution of the isolated components. In metabolic disorders, the distribution of body fat may outweigh total fat accumulation. Clinical analysis using CT (computer tomography) scanning shows that obesity with visceral fat accumulation (visceral fat obesity) associates closely with diabetes mellitus, hyperlipidaemia, hypertension and atherosclerosis [6–8].

Although traditionally regarded as a silent organ that passively stores excess energy, we now consider adipose tissue an endocrine organ. Following the discovery and characterization of leptin in 1994 [9], several studies have demonstrated that adipose tissue actively produces a variety of locally and systemically functioning bioactive molecules, including TNF-α (tumour necrosis factor-α), PAI-1 (plasminogen-activator inhibitor type-1) and resistin [10–12], that also interact in various obesity-related diseases. Thus increasing evidence suggests that adipose tissue, especially visceral fat tissue, participates directly in the pathophysiology of the metabolic syndrome and obesity-related cardiovascular diseases.

**DISCOVERY OF ADIPONECTIN AND ITS STRUCTURE**

Adiponectin was discovered during gene-expression profiling of human adipose tissue conducted by the human cDNA project, which analysed visceral and subcutaneous adipose tissues to elucidate the molecular mechanism of obesity-related diseases [13,14]. Unexpectedly, genes expressed in subcutaneous and visceral adipose tissue, 20% and 30% respectively, were bioactive secretory proteins, i.e. adipocytokines such as leptin and TNF-α. More surprisingly, 40% of the genes expressed in adipose tissue were novel and the most abundant among them, termed adiponectin, was novel as well [13,15]. Located on chromosome 3q27, a locus for diabetes susceptibility [16,17], adiponectin encodes a secretory protein apparently expressed exclusively in adipose tissue. Adiponectin contains 244 amino acids, a signal peptide, a collagen-like domain at its N-terminus and a globular domain at its C-terminus, which shares sequence similarities with collagens X and VIII as well as complement factor C1q. Despite the absence of primary sequence similarity, the crystal structure of the C-terminal globular domain resembles that of TNF-α [18]. During the same period, two other groups identified ACRP30 and AdipoQ as mouse homologues of adiponectin [19,20]. Adiponectin was independently isolated from human plasma as gelatin-binding protein-28 [21].

An ELISA has determined that the plasma range of adiponectin in human subjects is 3–30 µg/ml, accounting for 0.01% of total plasma protein [22]. Adiponectin exists in a wide range of multimer complexes in plasma and combines via its collagen domain to create three major oligomeric forms: trimers, hexamers and a high-molecular-mass form [23] (Figure 1). A smaller form of adiponectin that includes the globular domain cleaves proteolytically from full-length adiponectin and exists in plasma, although in very small amounts [24].
CLINICAL FEATURES OF ADIPONECTIN

Adiponectin and obesity

The initial clinical study of adiponectin measured its plasma levels in obese subjects. Surprisingly, obese subjects had significantly lower plasma adiponectin concentrations than did non-obese subjects, although adiponectin derives exclusively from adipose tissue (3.7 ± 3.2 compared with 8.9 ± 5.4 µg/ml respectively; \( P < 0.0001 \)) [15]. Additionally, Arita et al. [15] found a negative correlation between plasma concentrations of adiponectin and BMI (body mass index) in men and women \((r = -0.71, P < 0.0001)\) and \((r = -0.51, P < 0.0001)\) respectively [15]. Others have observed similar results in different rodent models of obesity and in rhesus monkeys [20, 25]. Moreover, plasma adiponectin concentrations in humans correlated negatively with visceral fat area in both genders [26]. This negative correlation was stronger with visceral adiposity than with subcutaneous adiposity [27, 28].

Atherosclerotic cardiovascular diseases

Patients with CAD (coronary artery disease) have significantly lower plasma adiponectin levels than age- and BMI-adjusted control subjects in men \((3.4 ± 1.8 \text{ compared with } 7.4 ± 3.5 \text{ µg/ml respectively; } P < 0.01)\) and women \((4.3 ± 1.5 \text{ compared with } 9.3 ± 6.8 \text{ µg/ml respectively; } P < 0.05)\) [29]. Another study [30] found adiponectin levels were significantly lower in male patients with both CAD and Type II diabetes than in those with diabetes alone \((4.0 ± 0.4 \text{ compared with } 6.6 ± 0.4 \text{ µg/ml respectively, } P < 0.001)\), even when adjusted for BMI and other cardiovascular risk factors. Multiple logistic regression analysis revealed that the prevalence of CAD increases 2-fold in male patients with hypoadiponectinaemia \(< 4.0 \text{ µg/ml; } 95\% \text{ CI (confidence interval), 1.29–4.95, independent of traditional CAD risk factors.} \)

Prospective studies also analysed the relationship between plasma adiponectin concentration and cardiovascular events (Table 1). A prospective study of patients with renal failure demonstrated that patients who experienced new cardiovascular events had lower plasma adiponectin levels than did event-free patients [32]. Risk decreased 3% for each 1 µg/ml increase in plasma adiponectin levels, and the relative risk of adverse cardiovascular events was 1.56 times \((95\% \text{ CI, 1.12–1.99 times})\) higher among patients in the first adiponectin tertile compared with those in the third tertile [32]. In another prospective study with 6 years follow-up, high plasma adiponectin concentrations associated with lower risk of MI (myocardial infarction) in healthy men \((relative \text{ risk, 0.39; } 95\% \text{ CI, 0.23–0.64})\) [33]. Moreover, a recent prospective study also suggests that increased adiponectin levels associate with a moderately decreased CAD risk in diabetic men \((relative \text{ risk, 0.71; } 95\% \text{ CI, 0.53–0.95})\) [34].

Table 1 Association of low plasma adiponectin (hypoadiponectinaemia) with CAD and Type II diabetes in prospective studies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study population</th>
<th>Association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>Renal failure patients</td>
<td>Yes</td>
<td>[32]</td>
</tr>
<tr>
<td>American men</td>
<td>Yes*</td>
<td>[33]</td>
<td></td>
</tr>
<tr>
<td>Diabetic men</td>
<td>Yes*</td>
<td>[34]</td>
<td></td>
</tr>
<tr>
<td>American Indians</td>
<td>No</td>
<td>[41]</td>
<td></td>
</tr>
<tr>
<td>British women</td>
<td>No</td>
<td>[42]</td>
<td></td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Pima Indians</td>
<td>Yes</td>
<td>[43]</td>
</tr>
<tr>
<td>Japanese subjects</td>
<td>Yes</td>
<td>[44]</td>
<td></td>
</tr>
<tr>
<td>Asian Indians</td>
<td>Yes</td>
<td>[45]</td>
<td></td>
</tr>
<tr>
<td>Japanese subjects</td>
<td>Yes</td>
<td>[46]</td>
<td></td>
</tr>
<tr>
<td>Elderly Korean subjects</td>
<td>Yes</td>
<td>[47]</td>
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</tbody>
</table>

In these studies, the association is due, in part, to the effect of adiponectin on lipid profiles, including HDL (high-density lipoprotein)-cholesterol levels [33, 34]. Other case-control studies assessed plasma adiponectin in patients with AMI (acute MI) and ACS (acute coronary syndrome) [35, 36]. On admission, patients with AMI had lower plasma adiponectin concentrations than did control subjects \((8.1 ± 4.8 \text{ compared with } 10.9 ± 5.5 \text{ µg/ml respectively; } P < 0.05)\) [35]. Moreover, patients with ACS had lower plasma adiponectin levels than patients with SAP (stable angina pectoris) or the control group \((ACS, 6.5 ± 3.0 \text{ µg/ml; SAP, 11.3 ± 5.9 \text{ µg/ml; control 12.8 ± 4.3 \text{ µg/ml; } P < 0.01})\) [36]. Multiple logistic regression analysis showed that low adiponectin concentration, smoking and fasting glucose concentration correlated independently with the incidence of ACS [36].

Inflammation characterizes atherosclerosis and obese subjects, and individuals at high risk of atherosclerosis have high levels of acute-phase reactants such as CRP (C-reactive protein), a powerful marker for systemic inflammation and an independent risk factor for CAD [37]. Plasma adiponectin and CRP levels in human male subjects have significant negative correlation [38]. Another study reported an association between low plasma adiponectin concentrations and CRP elevation in women [39]. CRP levels correlate with body weight and percentage of body fat [40]. Interestingly, human adipose tissue can express CRP mRNA, and CRP levels inversely correlate with adiponectin mRNA levels in human adipose tissue \((r = -0.29, P < 0.01)\) [38]. Thus adiponectin may regulate the expression of CRP in adipose tissue and influence plasma CRP levels. A recent clinical report noted that reduced plasma adiponectin levels correlated significantly with plasma CRP concentrations during the early stage of AMI \((r = -0.594, P < 0.01)\) [35].

Such clinical studies suggest that adiponectin plays a key regulatory and anti-inflammatory role in the
development of atherosclerotic diseases. On the other hand, two recent prospective studies found no association between plasma adiponectin levels and the future risk of coronary heart disease in American Indians [41], a group at particular risk for obesity and Type II diabetes, and in British women [42]. These inconsistent observations might be due to the study population, i.e., men compared with women, diabetic compared with non-diabetic. Further prospective studies of various populations are needed to examine whether hypoadiponectinaemia can independently predict atherosclerosis.

**Insulin resistance and Type II diabetes**

Several studies have investigated the relationship between plasma adiponectin levels and diabetes. The initial study with diabetic patients showed lower plasma adiponectin concentrations compared with age- and BMI-matched control men (6.6 ± 0.4 compared with 7.9 ± 0.5 µg/ml) and women (7.6 ± 0.7 compared with 11.7 ± 1.0 µg/ml) \( (P < 0.001) \) [30]. Plasma adiponectin levels decrease in rhesus monkeys, which develop obesity spontaneously and frequently progress to overt Type II diabetes mellitus [25]. In addition, plasma adiponectin decreased before the onset of diabetes, paralleling diminished insulin sensitivity [25]. A retrospective study of Pima Indians, a unique population with high propensity of obesity and Type II diabetes, confirmed these results [43]. Low concentrations of plasma adiponectin correlated strongly with reduced insulin sensitivity, and individuals with high concentrations of adiponectin were less likely to develop Type II diabetes than those with low concentrations (incidence rate ratio 0.63; 95% CI, 0.43–0.92; \( P = 0.02 \)) [43]. Moreover, high levels of adiponectin offered stronger protection against Type II diabetes than age, fasting glucose, 2 h glucose, fasting insulin and waist circumference [43]. In a 5-year follow-up study, Japanese subjects with serum levels of adiponectin in the lowest tertile developed diabetes 9.3 times more often than those in the highest tertile (95% CI, 1.046–83.1; \( P = 0.046 \)) [44]. Other human clinical studies in different populations also support these outcomes, suggesting that concentration of plasma adiponectin independently predicts the progression of diabetes [45–47]. These clinical studies provide an indication that adiponectin contributes to the development of insulin resistance and diabetes.

**Hypertension**

Obese individuals have a high incidence of hypertension. Essential hypertensive subjects had significantly lower concentrations of plasma adiponectin compared with normotensive healthy subjects (9.1 ± 4.5 compared with 13.7 ± 5.2 µg/ml; \( n = 33 \) each; \( P < 0.001 \)) [48]. Plasma adiponectin concentrations correlated negatively with mean, systolic and diastolic blood pressures in all subjects [48]. After adjustment for confounding factors in men, another case-control study using multiple regression analysis revealed significantly lower adiponectin concentration in patients with hypertension (5.2 ± 0.2 compared with 6.1 ± 0.2 µg/ml; \( P < 0.001 \)) [49]. Moreover, blood pressure associated inversely with adiponectin concentration in normotensive patients regardless of insulin resistance [49]. Such results suggest that hypoadiponectinaemia can relate to hypertension independent of classical factors.

**Dyslipidaemia**

Several clinical reports have pointed to an association between plasma adiponectin and dyslipidaemia. Adiponectin correlates negatively with serum triacylglycerol (triglyceride) and positively with serum HDL-cholesterol in non-diabetic women or young healthy men [50,51]. Subjects with low plasma adiponectin levels have low lipoprotein lipase activity [52]. Hypoadiponectinaemia also associates with smaller LDL (low-density lipoprotein) particle size [53]. In patients with Type II diabetes, plasma adiponectin levels correlate positively with HDL-cholesterol and negatively with triacylglycerols and apolipoprotein B-100. Such associations persist when adjusted for potential confounders such as lifestyle exposures, co-morbid conditions or obesity-associated variables [54].

**Genetic factors related to adiponectin levels**

The adiponectin gene maps on chromosome 3q27, which may contain a susceptibility locus for Type II diabetes and metabolic syndrome [16,55]. Several analyses of SNPs (single nucleotide polymorphisms) and missense mutations in the adiponectin gene have suggested a genetic link between adiponectin and metabolic diseases. The frequency of a missense mutation at position 164 in the globular domain with isoleucine substituted for threonine [Ile164 → Thr (II164T)] was significantly higher in Japanese Type II diabetic or CAD patients compared with control subjects [56,57]. Subjects with this mutation had significantly lower plasma adiponectin concentrations than those without it, independent of BMI [56,57]. The I164T adiponectin gene polymorphism has an oligomerization profile and insulin-sensitizing activity similar to the wild-type; however, this variant has impaired secretion from adipose tissue [58]. Additionally, another SNP at position 94 (SNP94) associates closely with Type II diabetes, as do SNP45 and SNP276 [59,60]. Moreover, some mutations associate with reduced formation of adiponectin trimers or high-molecular-mass multimers, which may exert important adiponectin actions [61]. Such findings demonstrate that some variations of the adiponectin gene may determine plasma concentration or multimer distribution of adiponectin and contribute to various disease states.
Adiponectin and metabolic syndrome

**Figure 2** Role of adiponectin as an anti-atherogenic and anti-inflammatory molecule

In adipose tissue, adiponectin suppresses the production of TNF-α and CRP; in contrast, TNF-α inhibits production of adiponectin. In the vasculature, adiponectin inhibits monocyte adhesion to ECs, foam cell formation of MΦs and VSMC migration and proliferation. In ECs, adiponectin stimulates NO production and modulates vasodilation or angiogenesis.

**PATHOPHYSIOLOGY OF ADIPONECTIN**

**Atherosclerosis**

The structural resemblance of adiponectin to the fibrillar collagen family, e.g., collagens VIII and X, suggested that adiponectin might interact with other matrix components in arteries. In solid-phase binding assays, adiponectin bound specifically to collagens I, III and V [62]. Indeed, immunohistochemical analysis in rats revealed that plasma adiponectin accumulated rapidly in the subendothelial space of balloon-injured arterial walls [62]. In humans, adiponectin accumulates in injured aortae, but not in the subendothelial space of atherosclerotic lesions covered with an intact layer of ECs (endothelial cells) [63]. These findings indicate that disruption of the EC barrier may induce adiponectin accumulation in the arterial wall.

EC activation by various inflammatory stimuli increases monocyte adherence, an initial step in atherosclerosis. In cultured cells, physiological concentrations of adiponectin attenuate the attachment of monocytes to ECs by reducing TNF-α-induced expression of adhesion molecules such as VCAM-1 (vascular cell-adhesion molecule-1), E-selectin (endothelial-leucocyte adhesion molecule-1) and ICAM-1 (intercellular cell-adhesion molecule-1) [29]. In this step, these effects may result from suppression by adiponectin of TNF-α-induced IκB-α (inhibitory κB-α) phosphorylation and subsequent NF-κB (nuclear factor κB) activation through a cAMP/PKA (protein kinase A) pathway [64].

The accumulation of lipid-laden foam cells and ongoing MΦ (macrophage)-related inflammation characterizes plaque formation and influences atherosclerotic lesion stability. The family of scavenger receptor proteins contribute to lipid accumulation and MΦ foam cell formation by taking up modified LDL. In cultured human monocyte-derived MΦs, adiponectin reduces intracellular cholesteryl ester content by suppressing expression of MΦ SR-As (class A scavenger receptors) [63]. In addition, treatment of human MΦs with adiponectin inhibits phagocytic activity and LPS (lipopolysaccharide)-induced production of TNF-α [65]. Furthermore, adiponectin may favour plaque ‘stabilization’ by increasing IL-10 (interleukin-10) secretion and subsequent production of TIMP-1 (tissue inhibitor of metalloproteinases-1) [66].

VSMC (vascular smooth muscle cell) proliferation induced by growth factors can also contribute to atherogenesis. In cultured VSMCs, adiponectin suppresses VSMC proliferation and migration via direct binding to PDGF-BB (platelet-derived growth factor-BB) and generally inhibits growth-factor-stimulated ERK (extracellular-signal-regulated kinase) signalling in VSMCs [22]. These in vitro data indicate that adiponectin can modulate the progression of atherosclerosis as an anti-inflammatory and anti-proliferative mediator (Figure 2).
Several *in vivo* studies in mice have confirmed the anti-inflammatory and anti-atherogenic properties of adiponectin. Mechanically injured arteries in adiponectin-deficient (APN−/−) mice showed exuberant neo-intimal thickening and increased accumulation of VSMCs [67]. Supplementing adiponectin with recombinant adenovirus reversed abnormal neointimal thickening in APN−/− mice [67]. Moreover, ApoE (apolipoprotein-E)-deficient (ApoE−/−) mice, a rodent model of atherosclerosis, had plasma adiponectin levels 48-fold greater than control mice when treated with adenovirus-mediated adiponectin [68]. Adenovirus-mediated adiponectin colocalized with foam cells in fatty streak lesions and inhibited plaque formation in the aortic sinus by 30% compared with control mice [68]. This anti-atherogenic effect of adenovirus-mediated adiponectin accompanied suppression of VCAM-1, SR-A and TNF-α, but did not affect CD36 expression [68]. Importantly in these *in vivo* studies, glucose and lipid profiles did not differ between adiponectin-treated mice and controls [67,68]. Such results indicate that the adiponectin can modulate vascular remodelling by direct interactions with injured arteries, rather than through systemic effects, i.e. improvement of glucose and lipid metabolism. In another study [69], globular domain adiponectin transgenic mice crossed with ApoE−/− mice had fewer atherosclerotic lesions compared with ApoE−/− mice. Together, the studies discussed above have documented various protective roles of adiponectin in the development of atherosclerosis and also established elevated plasma adiponectin levels as probable contributors to the prevention of atherosclerosis.

**Adiponectin regulates vascular vasomotor function**

Endothelial dysfunction, a crucial feature of atherosclerosis, associates closely with obesity-related pathological conditions, such as hypertension, insulin resistance and dyslipidemia [70,71]. In hypertensive patients, plasma adiponectin levels correlate highly with vasodilator response to reactive hyperaemia assessed by FBF (forearm blood flow; \( r = 0.257, P < 0.001 \)) [72] (Table 2). In addition, APN−/− mice had significant reduction in endothelium-dependent vasodilation compared with control mice [72]. Another study in Japanese subjects with no history of cardiovascular or cerebrovascular disease, diabetes mellitus, or hepatic or renal disease suggested that hypoadiponectinaemia correlates closely with the severity of endothelial dysfunction [73]. Moreover, plasma levels of adiponectin associate with impaired endothelium-dependent or -independent vasodilation, apart from diabetes mellitus or insulin resistance [74,75]. On the other hand, two studies did not find an association of plasma adiponectin with vasodilation in diabetic patients and subjects at risk for diabetes or in young healthy adolescents [76,77]. Furthermore, increased levels of adiponectin following troglitazone treatment do not accompany improved endothelium-dependent vasodilation [78].

Vascular ECs also play pivotal roles in angiogenesis, and dysregulated angiogenesis characterizes obesity-related disorders, including atherosclerosis, hypertension and diabetes [79]. Adiponectin stimulates blood vessel growth *in vivo* in mouse matrigel plug implants and in rabbit corneal models of angiogenesis [80]. APN−/− mice have impaired angiogenic repair of ischaemic hindlimbs compared with control mice; in contrast, adiponectin supplementation accelerated the repair process [81].

NO (nitric oxide) acts as an important mediator of endothelial function, including vasodilation and angiogenesis. Several *in vitro* experiments suggest that adiponectin induces NO production in human aortic ECs, a site of adiponectin receptor expression [74,82,83]. Increased NO production in human ECs treated with adiponectin accompanied phosphorylation of AMPK (AMP-activated protein kinase), Akt/PKB (protein kinase B) and eNOS (endothelial NO synthase) [80,82]. Adiponectin also ameliorates oxidized LDL-induced suppression of eNOS activity [83]. Such results suggest that adiponectin prevents vascular diseases via modulation of endothelium-dependent vasorelaxation and angiogenesis.

**Adiponectin and cardiac remodelling**

Pathological cardiac remodelling with myocardial hypertrophy and diastolic dysfunction can accompany diabetes and obesity-related conditions [84,85]. A recent study reported that pressure overload caused concentric cardiac hypertrophy and increased mortality in APN−/− mice compared with wild-type mice [86]. Additionally, ERK increased in the hypertrophic myocardium, whereas AMPK signalling diminished [86]. Another study suggested that decreased plasma adiponectin concentration associates with progression of left ventricular hypertrophy accompanied by diastolic dysfunction in human subjects [87]. These results suggest the need for...
future study of adiponectin as a treatment for cardiac hypertrophy related to diabetes or obesity.

**Insulin resistance and diabetes**

Many experimental studies have demonstrated that adiponectin associates with the mechanism of disordered glucose metabolism. Administration of full-length recombinant adiponectin in mice enhanced insulin action in the liver, but did not affect insulin levels [88]. Injecting the globular form of adiponectin in mice that consumed a high-fat/high-sucrose diet resulted in fatty acid oxidation by muscle and caused weight reduction without affecting food intake [24]. Other studies have demonstrated that adiponectin modulates insulin sensitivity by stimulating glucose utilization and fatty acid oxidation via phosphorylation and activation of AMPK in muscle and liver [89,90]. One report indicated that both full-length and globular adiponectin induce AMPK activation in skeletal muscle; however, only the full-length form induces activation of this enzyme in the liver [89]. On the other hand, another report concluded that only globular adiponectin enhances fatty acid oxidation via the activation of AMPK in skeletal muscle [90].

While consuming normal chow, APN−/− mice show no significant phenotype [91]; however, during consumption of a high-fat/high-sucrose diet, APN−/− mice exhibit severe insulin resistance and reduced IRS-1 (insulin-receptor substrate-1)-associated PI3K (phosphoinositide 3-kinase) activity in muscle [91]. These mice also had delayed clearance of NEFAs (non-esterified fatty acids) in plasma, low levels of FATP-1 (fatty acid transport protein-1) mRNA in muscle, high levels of TNF-α mRNA in adipose tissue and high plasma TNF-α concentrations. Adenovirus-mediated supplementation of adiponectin in APN−/− mice ameliorated insulin resistance, reversing the reduction of FATP-1 mRNA and increasing adipose TNF-α mRNA [91]. One possible explanation for the seemingly paradoxical reduction in plasma adiponectin in visceral obesity invokes increased production of TNF-α, leading to inhibition of adiponectin promoter activation and thus reduced plasma adiponectin. This putative mechanism, however, requires further investigation [91]. Another study also noted that heterozygous and homozygous adiponectin-deficient mice had mild and moderate insulin resistance with glucose intolerance [92]. These data suggest that adiponectin deficiency participates in the development of insulin resistance under certain dietary conditions, e.g., high-fat/high-sucrose diet similar to a Western-type diet.

**STRATEGIES FOR THE PREVENTION OF METABOLIC SYNDROME WITH ADIPONECTIN**

As discussed above, low plasma adiponectin concentration and its impaired action relate closely to the prevalence of obesity-related disorders. Therefore increased plasma adiponectin and enhancement of its action may mitigate the metabolic syndrome.

**Body weight loss**

Weight reduction significantly elevated plasma adiponectin levels in diabetic and non-diabetic subjects [30]. Obese patients who underwent gastric reduction surgery had increased levels of mean plasma adiponectin (46%) and reduced mean BMI (21%) [93]. The change in plasma adiponectin levels correlated significantly with the changes in BMI, waist and hip circumferences and steady-state plasma glucose levels [93]. A Mediterranean-type diet and increased physical activity also induced weight loss and a significant increase of adiponectin in premenopausal obese women [94]. In addition, a recent study of obese subjects demonstrated that weight loss altered the distribution of adiponectin isoforms during weight reduction, i.e. the high-molecular-mass form, which confers the vasculoprotective activities, increased and the trimer and hexamer forms decreased [95]. Body weight loss may prevent obesity-linked diseases via modulation of adiponectin not only by plasma levels, but also by the distribution of isoforms.

**Dietary effect**

Consumption of vegetable protein, such as soy, may reduce the risk of atherosclerotic vascular diseases. Obese KK-Ay mice consuming a calorie-restricted diet with soy protein had elevated levels of both adiponectin mRNA in adipose tissue and plasma adiponectin, but decreased levels of plasma lipid and glucose [96]. Notably, this study showed no significant difference in plasma adiponectin levels between a soy protein and an isocaloric casein diet [96]. However, Wistar rats that consumed dietary soy protein isolate for 10 days had higher levels of plasma adiponectin than those consuming casein, although body weight did not differ significantly in either group [97]. Dietary linoleic acid increased plasma adiponectin levels by enhancing mRNA expression in adipose tissue of Zucker diabetic fatty rats; body weight did not differ from controls [98]. Moreover, plasma adiponectin increased in human subjects who consumed Oolong tea for 1 month [99]. The molecular basis of the effects of these diets on plasma adiponectin levels remains unclear. These results, however, raise the intriguing concept that regulation of adiponectin may, in part, account for the cardiovascular benefits of dietary intervention.

**Pharmacological interventions**

TZDs (thiazolidinediones)

PPAR (peroxisome-proliferator-activated receptor)-γ is a master regulator of adipocyte differentiation, and PPAR-γ agonists, TZDs, improve insulin sensitivity. TZDs normalized or increased adiponectin mRNA...
expression and secretion in adipose tissue of obese mice and also in cultured 3T3-L1 adipocytes in a dose- and time-dependent manner [100]. TZDs activated the adiponectin promoter, leading to increased production of adiponectin [100]. In mildly overweight subjects with glucose intolerance, administration of troglitazone for 12 weeks dose-dependently increased plasma adiponectin levels [102]. Additionally, another study in lean, obese and diabetic subjects showed significantly increased concentrations of plasma adiponectin after 3 months of treatment with troglitazone [101]. In a randomized double-blind placebo-controlled trial in patients with Type II diabetes, rosiglitazone therapy for 6 months increased plasma adiponectin levels more than 2-fold [102]. Similarly, pioglitazone increased plasma adiponectin concentration in Type II diabetes patients and healthy male subjects [103,104].

ACEIs (angiotensin-converting-enzyme inhibitors) and ARBs (angiotensin II receptor blockers)

The RAS (renin–angiotensin system) participates not only in vascular physiology, but in insulin signalling as well [105,106]. RAS blockade with temocapril, an ACEI, or candesartan, an ARB, increased adiponectin concentrations in insulin-resistant essential hypertensives, but did not affect BMI [107]. Other reports have shown that losartan, another ARB, elevated plasma adiponectin levels in patients with Type I diabetes or hypertension [108,109]. However, the precise mechanism involved in increase adiponectin by RAS blockade remains incompletely understood.

Adiponectin receptors

The adiponectin receptors AdipoR1 and AdipoR2 have been cloned [110]. These receptors contain seven transmembrane domains, but are structurally and functionally distinct from other known GPCRs (G-protein-coupled receptors). AdipoR1 is expressed abundantly in skeletal muscle as a high-affinity receptor for globular adiponectin. Expression of AdipoR2 occurs predominantly in the liver and has an intermediate-affinity receptor for globular adiponectin. AdipoR2 expression and secretion in adipose tissue of obese mice and also in cultured 3T3-L1 adipocytes in a dose- and time-dependent manner [100]. TZDs activated the adiponectin promoter, leading to increased production of adiponectin [100]. In mildly overweight subjects with glucose intolerance, administration of troglitazone for 12 weeks dose-dependently increased plasma adiponectin levels [102]. Additionally, another study in lean, obese and diabetic subjects showed significantly increased concentrations of plasma adiponectin after 3 months of treatment with troglitazone [101]. In a randomized double-blind placebo-controlled trial in patients with Type II diabetes, rosiglitazone therapy for 6 months increased plasma adiponectin levels more than 2-fold [102]. Similarly, pioglitazone increased plasma adiponectin concentration in Type II diabetes patients and healthy male subjects [103,104].

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The adiponectin receptors AdipoR1 and AdipoR2 have been cloned [110]. These receptors contain seven transmembrane domains, but are structurally and functionally distinct from other known GPCRs (G-protein-coupled receptors). AdipoR1 is expressed abundantly in skeletal muscle as a high-affinity receptor for globular adiponectin. Expression of AdipoR2 occurs predominantly in the liver and has an intermediate-affinity receptor for globular adiponectin. AdipoR2 expression and secretion in adipose tissue of obese mice and also in cultured 3T3-L1 adipocytes in a dose- and time-dependent manner [100]. TZDs activated the adiponectin promoter, leading to increased production of adiponectin [100]. In mildly overweight subjects with glucose intolerance, administration of troglitazone for 12 weeks dose-dependently increased plasma adiponectin levels [102]. Additionally, another study in lean, obese and diabetic subjects showed significantly increased concentrations of plasma adiponectin after 3 months of treatment with troglitazone [101]. In a randomized double-blind placebo-controlled trial in patients with Type II diabetes, rosiglitazone therapy for 6 months increased plasma adiponectin levels more than 2-fold [102]. Similarly, pioglitazone increased plasma adiponectin concentration in Type II diabetes patients and healthy male subjects [103,104].

ACEIs (angiotensin-converting-enzyme inhibitors) and ARBs (angiotensin II receptor blockers)

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Collectively, several types of adiponectin receptors may participate in the intracellular signalling pathway depending on the structural forms of adiponectin. Although the mechanisms of receptor and signalling pathways remain unclear, new adiponectin receptor agonists or PPARα/γ agonists may increase adiponectin levels or tissue sensitivity.

CONCLUSIONS

A series of clinical and experimental studies has reported that adiponectin functions as an anti-atherogenic, anti-inflammatory and anti-diabetic adipocytokine, and protects against obesity-related cardiovascular and metabolic diseases (Figure 3). Several recent studies have implicated adiponectin in the pathogenesis of cancer, liver fibrosis and bone metabolism [118–120]. Hypoadiponectinemia may confer heightened risk for these diseases. In some studies, however, the association of adiponectin with several diseases remains controversial. Since adiponectin has genetic determinants, the Mendelian randomization approach may allow investigation of causality unconfounded by behavioural and environmental exposure [121].

Therapeutic approaches that increase adiponectin levels or tissue sensitivity deserve evaluation for the prevention of these diseases, particularly among obese subjects with visceral fat accumulation. Leptin, another major adipocytokine that acts to reduce appetite via the central
Adiponectin and metabolic syndrome

Environmental factors, such as overnutrition and physical inactivity, induce visceral fat accumulation and lead to low plasma adiponectin level (hypoadiponectinaemia). Genetic factors, such as I164T SNP, also associate with hypoadiponectinaemia. Hypoadiponectinaemia enhances a cluster of diabetes mellitus, hypertension and dyslipidaemia, and ultimately causes atherosclerosis. In addition, hypoadiponectinaemia augments atherosclerosis by reducing the preventive interaction between adiponectin and the arteries.

nervous system, has limited efficacy in the treatment of obese subjects despite wide initial enthusiasm for its clinical application. Obese subjects generally have high plasma levels of leptin due to leptin resistance. In light of this example, consideration of adiponectin as a novel therapy will require rigorous clinical interventional studies. Further clinical and experimental investigations should illuminate the pathophysiological mechanisms of adiponectin, a potentially promising target for the prevention and treatment of the metabolic syndrome and other diseases.

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