Adiponectin: an adipokine with protective features against metabolic syndrome

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A R T I C L E I N F O	A B S T R A C T
	Metabolic syndrome (MetS) as a collection of obesity-associated disorders is associated with inflammation, oxidative stress, pro-thrombotic state, elevated risk of developing cardiovascular disease and type 2 diabetes. Adiponectin is one of the most abundant peptide hormones derived from adipose tissue. This protein plays a major role in glucose and lipid metabolism and prevents development of vascular changes. Anti-oxidative and anti-inflammatory effects are the other features of adiponectin. Hypoadiponectinemia is associated with hypertension and pro-thrombotic state. In this review, we discuss the crucial role of adiponectin in prevention of metabolic syndrome considering its effects on the components of this syndrome. Pharmacological interventions and lifestyle modification may increase plasma adiponectin level or tissue sensitivity which seems to be a promising target for prevention and therapeutic approaches of MetS and related diseases.

Introduction

Metabolic syndrome (MetS), also known as syndrome X or insulin resistance syndrome, is a collection of obesity-associated disorders that comprises dyslipidemia (triglyceride (TG) >150 mg/dl, high-density lipoprotein (HDL) cholesterol <40 mg/dl in males and <50 in females), impaired fasting glucose (fasting glucose ≥100) and visceral adiposity (waist circumference >102 cm in men and >88 cm in woman) (1-3). Also, this syndrome is associated with prothrombotic state (4), inflammation, oxidative stress (5), elevated risk of developing cardiovascular disease (CVD) like atherosclerosis (6) and type 2 diabetes (T2D) (4). MetS and atherosclerosis are the main causes of morbidity and mortality worldwide (7).

In past, adipose tissue was considered only as a storage depot of extra energy, but is now regarded to be a highly active endocrine gland secreting several bioactive molecules known as adipokines or adipocytokines. One of the most abundant peptide hormones derived from adipose tissue is known as a new adipokine with anti-atherogenic and anti-inflammatory features (8). In this review article, focusing on adiponectin effects on each component of MetS, its crucial roles in the prevention of this syndrome are reviewed.

Adiponectin, structure and its receptors

In human, adiponectin gene is located on chromosome 3q27 (9) and encodes a 244 amino acids protein (10, 11). This locus has been associated with diabetes and cardiovascular diseases (12). Primarily three isoforms are detected in plasma: a low molecular weight trimer (LMW), a medium molecular weight hexamer (MMW) and a high molecular weight (HMW) 12- to 18-mers (9, 13). HMW form may be the most active form of adiponectin (14). Also, HMW to total adiponectin ratio is more useful than total adiponectin in metabolic syndrome diagnosis (15). Adiponectin is

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mainly produced in white adipose tissue (WAT) and particularly in mature adipocytes. Also, epicardial fat expresses adiponectin (7, 16). Adiponectin plasma levels are more nearly associated with the amount of visceral than total body fat (17). This specifically indicated a close relationship between visceral obesity and metabolic or cardiovascular diseases (15). Liver, cardiomyocytes, skeletal muscle, colon, salivary glands, placenta and pituitary express adiponectin at lower levels (7). Adiponectin performs its physiological effects mainly via AdipoR1 and AdipoR2 receptors. Both receptors are ubiquitously expressed (7) especially in monocytes and macrophages (18). AdipoR1 is principally expressed in skeletal muscle (19), but it is also expressed in endothelial cells (20), cardiomyocytes (21) and pancreatic-β cells (22). AdipoR2 is primarily expressed in the liver (19) and partly in endothelial cells (23) and cardiomyocytes (24). In muscle and adipose tissue in hyperinsulinemic and hyperglycemic states, the expression of both receptors is meaningfully reduced (25). AdipoR1 and AdipoR2 effects are mediated through APPL1, an adaptor protein which has a prominent role in metabolic effects of adiponectin (26). In addition, APPL1 interactions with insulin-signaling molecules indicated a molecular link between adiponectin and downstream insulin occurrence (27). The studies revealed that AdipoR1 and AdipoR2 may be firmly associated with activation of AMPK and PPAR-α signaling pathway in the liver, respectively (28). Activation of AMP-activated protein kinase (AMPK), PPAR-α and p38 mitogen-activated protein kinase (MAPK)-signaling pathways are involved in molecular signaling of adiponectin (29).

The third adiponectin receptor is T-cadherin, a glycosylphosphatidylinositol (GPI) which is anchored to the surface membrane and lacks cytoplasmic domain. This receptor is not effectively expressed in muscles and liver, but is expressed in vascular endothelial and smooth muscle cells (27, 30).

The Effect of adiponectin on glucose metabolism

AMPK, a stress-responsive kinase, has an important role in the regulation of cellular and whole body energy balance. AMPK has several functions such as inhibition of hepatic gluconeogenesis, increasing muscle glucose transport (31), phosphorylation of phosphor-fructokinase-2 (PFK-2) and increasing glycolytic glucose disposal (32). Adiponectin signaling causes an increase in the phosphorylation of P-38MAPK and AMPK in skeletal muscle (33, 34), liver (27) and adipocytes (35). Adiponectin knockout (KO) mice showed decreased expression of glucokinase, phosphofruktokinase and pyruvate dehydrogenase (important enzymes that control glycolysis), also isocitrate dehydrogenase which is a major enzyme of tricarboxilic acid (TCA) cycle (36).

Adiponectin directly sensitizes body tissues to insulin. There is a significant inverse relationship of adiponectin and its receptors with insulin resistance. Hemoglobin A1c (HbA$_1$C), an indicator of glycemic control, showed a negative correlation with serum adiponectin (8). Serum adiponectin level is a precise index that can predict insulin resistance in patients with T2D and may have an important role in the pathogenesis of diabetes (37, 38). Therefore, hypoadiponectinemia may place individuals at risk for developing diabetes (9)and MetS patients are at high risk for developing T2D (39).

Adiponectin and lipid metabolism

Proteins such as CD-36 (fatty acid transporter/-scavenger receptor), acyl-coenzyme A (acyl-CoA) oxidase and uncoupling protein-2 are involved in fatty acid transport and oxidation. Adiponectin can stimulate these proteins in muscle and increase fat combustion and energy waste (19, 40). Liver lipid metabolism is regulated by AMPK activation, which is involved in the regulation of lipogenesis and cholesterol synthesis (41) and can be directly activated by adiponectin (42).

Expression of several genes which are involved in proximal and mitochondrial β-oxidation are regulated by PPAR-α (43, 44). Adiponectin induces PPAR-α transcriptional activity through AMPK and P38-MAPK activation (45). Adiponectin induces phosphorylation and inactivation of acetyl Co-A carboxylase (via AMPK activation) and enhances fatty acid oxidation rates (46). This suggested that adiponectin can initiate long and short-term stimulation of fatty acid oxidation (45).

Hepatocyte nuclear factors (Hnf1, Hnf3, Hnf4a, Hnf6) are principally involved in the regulation of liver complex function (47, 48) in which especially Hnf1a, Hnf6 and Hnf4a have central roles (49). Hnf4a regulates the expression of transcription factors such as Hnf1, a chief regulator in hepatocytes, SREBP1 and ChREBP1, these two factors participate in hepatic lipogenesis. The expression of Hnf4a is reduced in adiponectin KO mice (36). Adiponectin regulates the expression of several important hepatic metabolic genes through Hnf4a (36). Whilst AMPK activation suppresses the expression of SREBP1c; this transcription factor is involved in the expression of genes which encode proteins that are involved in liver fatty acid synthesis (42).

The ATP binding cassette A1 (ABCA1) is a key participant in the reverse cholesterol process whereby it mediates cholesterol efflux directly to HDL particles (50). Adiponectin enhances Apo-A1 and ABCA-1 expression in hepatocytes that are involved in HDL formation (51). Adiponectin meaningfully enhances mRNA transcription of ABCA-1 in the liver (52). Hypoadiponectinemia may be associated with smaller low-density lipoprotein

(LDL) size, reduction of lipoprotein lipase (LPL) activity, decrease in HDL and increase in TG levels (53). Plasma adiponectin level has negative relevance with apolipoprotein B-100 and triglyceride in T2D patients (53).

Anti-Inflammatory effects

MetS patients often have a pro-inflammatory state, as displayed by increased levels of cytokines such as tumor necrosis factor alpha (TNF-α), IL-6 and C-reactive protein (CRP) (4), an important marker for systemic inflammation (53). MetS is closely associated with systemic inflammation and it is suggested that CRP could be considered as an appropriate marker for MetS diagnosis (54). However, liver is an important source of CRP, human adipose tissue can express CRP mRNA (55). Human studies reported an inverse association between adiponectin level and CRP (56), TNF-α and IL-6 (54). Also, there is a reverse association between adiponectin mRNA and CRP mRNA in human adipose tissue (55). It is suggested that adiponectin can control the expression of CRP in adipose tissue (57).

Monocyte chemo-attractant protein-1 (MCP-1) has a great role in the recruitment of monocytes and regulation of migration and infiltration of monocyte/-macrophages (58), hence it induces inflammation and insulin resistance (14). It is reported that concurrent adipoR1 and adipoR2 disturbances caused an increase in MCP-1 expression in WAT. It seems that reduced adiponectin signaling increases inflammation in WAT (28).

In macrophages, the production of pro-inflammatoy cytokines such as TNF-α and IL-6 is inhibited by chronic treatment with adiponectin which can be associated with nuclear factor kappa B (NF-kβ) and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) activation by adiponectin (59-61). Also, this protein suppresses TNF-α mRNA expression in adipocytes (62). Following stimulation with adiponectin, human monocytes are primed into M2 macrophages with anti-inflammatory properties (63).

In vitro studies showed that adiponectin induces the production of anti-inflammatory cytokines such as interleukin 10 (IL-10), interleukin-1 receptor antagonist (IL-1RA) in primary human monocytes and monocyte-derived dendritic cells (Mo-DCs) and macrophages. Low circulating level of IL-10 is associated with metabolic syndrome in women (64).

Perivascular adipose tissue has a significant role in vascular inflammation (65). The experiments suggested that MetS is associated with perivascular adipose inflammation and endothelial dysfunction due to reduced NO (66). Insulin resistance and hyperglycemia, as major factors involved in MetS, have negative effects on the synthesis and release of NO (67). NO has vasodilatory effect and it can decrease vascular permeability, reduce LDL oxidation rate and suppress vascular smooth muscle cell proliferation (68, 69). Adiponectin activates endothelial nitric oxide synthase (eNOS) in endothelial cells and stimulates NO production (61) via activation of AMPK signaling and phosphoinositide-3-kinase (PI3K)-Akt pathway (7, 64) and increases eNOS expression in endothelial cells. Adiponectin reverts the inhibition of eNOS activity by oxidized LDL (ox-LDL) (70) and hyperglycemia (71). Also, CRP has direct pro-inflammatory effect on vessel wall (72, 73). An experiment using human recombinant CRP showed that this protein causes down-regulation of eNOS, up-regulation of adhesion molecules and simplification of endothelial cell apoptosis and increases angiotensin type I receptor and neointima formation (73). As noted above, adiponectin has negative effect on CRP production.

In summary, Adiponectin suppresses endothelial cell activation and monocyte attachment and inhibits interplay between leukocyte and endothelial cells (67).

Anti-oxidative effect of Adiponectin

MetS patients have increased oxidation damage in the form of elevated malondialdehyde (a product of lipid peroxidation), protein carbonyls and xanthine oxidase activity. On the other hand, in these patients antioxidant defense, vitamin C and E concentrations, superoxide dismutase activity (74, 75), and adiponectin level have decreased (76). Animal models indicated that oxidative stress promoted insulin resistance (77). It should be noted that ROS have important role in oxidative stress (78). Human studies showed that plasma adiponectin level had inverse association with oxidative stress markers e.g. plasma thiobarbituric acid reactive substance (TBARS) and urinary 8-epi-prostaglandin-F2α (8-epi-PGF2α) (79). Also, another study indicated that in MetS patients, adiponectin has positive association with reduced glutathione (GSH) (80). The production of ROS generated by high glucose (81), ox-LDL (82) (by cAMP/PKA activation) (83) and palmitate (84), is inhibited by adiponectin in endothelial cells. Decreased adiponectin levels are indicators of increased oxidative state in the arterial wall and are associated with high ox-LDL levels in patients with type 2 diabetes mellitus and coronary artery disease (85). The studies suggested that adiponectin suppresses vascular endothelial growth factor (VEGF)-induced ROS production which -when considered with anti-inflammatory effect of adiponectin- denoted an important antioxidant role of adiponectin in the vasculature (83). As mentioned above, adiponectin has negative effect on the production of CRP, a protein that stimulates ROS production (73). Homocysteine has pro-oxidant activity (86) and there is an inverse association between adiponectin and homocysteine levels in MetS patients (87). Therefore, hypoadiponectinemia has been closely associated with oxidative stress in these patients.
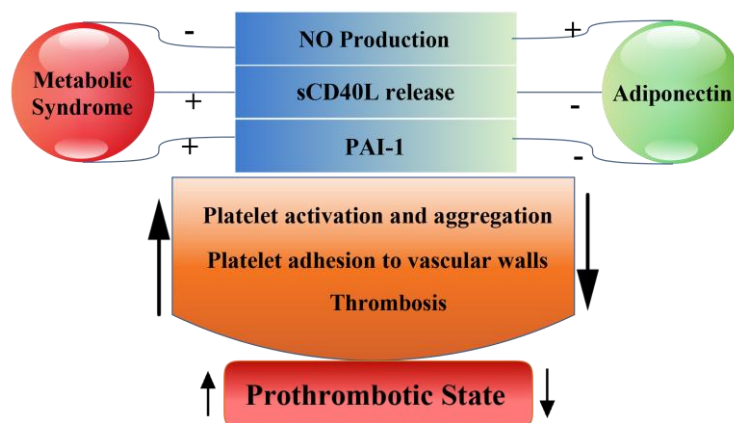
Figure 1. The suppression of prothrombotic state by adiponectin
NO: nitric oxide; sCD40L: soluble form of CD40 Ligand; PAI-1: Plasminogen activator inhibitor type-1

Adiponectin and hypertension

Hypertension is a significant health problem worldwide and affects more than 20% of the adult population (88). This disorder is regarded as an important feature of MetS (89). Arterial stiffness is associated with hypertension development (90) and MetS (89). Hyperglycemia, a significant constituent of MetS, enhances arterial stiffness (91). Increased collagen deposition is correlated with intensified arterial stiffness. Collagen deposition in hypertension is related to serum level of procollagen type I carboxyterminal propeptide (PICP) (92). Serum adiponectin level has an important negative association with PICP (93). Hypoadiponectinemia is a determinant of elevated peripheral stiffness (94). Low levels of adiponectin can predispose to hypertension through several mechanisms like insulin sensitizing, involvement in fatty acid metabolisms and vasoprotective effects (95).

Renin-angiotensin system (RAS) has an important role in the regulation of blood pressure and cardiovascular function. This system is activated in MetS and leads to elevation of angiotensin II levels, arterial wall inflammation, oxidative stress and development of atherosclerosis (96, 97). New finding indicated that elevating adiponectin level may be an efficient strategy to suppresses RAS activation related disorders in MetS (52).

The relationship of oxidative stress and inflammation (both are involved in MetS) with hypertension is well recognized (98). As noted above, adiponectin has antioxidative and anti-inflammatory effects. Cross-sectional studies revealed that hypoadiponectinemia may be an independent risk factor for hypertension (99, 100).

Adiponectin and prothrombotic state in metabolic syndrome

Several studies indicated the association between MetS and higher risk of pro-thrombotic state which includes elevated plasmatic coagulation, decreased fibrinolysis, reduced endothelial thrombo resistance and platelet hyperactivity (101, 102). Pro-thrombotic markers have positive correlations with various component of MetS (103). P-selectin, an integral membrane glycoprotein, and sCD40L, a soluble form of CD40 Ligand, are markers of platelets activation. MetS patients have higher levels of these markers than control subjects (104, 105). It should be noted that continual platelet activation is important for progression of acute vascular events (106). AdipoR1/R2 is expressed on platelets and adiponectin reduces platelet aggregation and sCD40L release from platelet. (107). It is indicated a proagregatory platelet phenotype in adiponectin-null mice (108). Also, adiponectin acts as anti-thrombotic agent via NO which inhibits platelet aggregation and adhesion to vascular walls (68, 71).

Plasminogen activator inhibitor type-1 (PAI-1) antigen, a single chain glycoprotein with pro-inflammatory effect, has an important function in the fibrinolysis (109). PAI-1 is closely associated with MetS (110, 111) and atherosclerosis development (112). It has been suggested that in overweight hypertensive patients, adiponectin is independently and negatively associated with PAI-1 antigen, (113) (Figure 1).

Adiponectin and atherosclerosis

MetS is an important predictor of CVD (114). Particularly, MetS has independent association with atherosclerosis (115). Hypoadiponectinemia is correlated with elevated risk factors of atherosclerotic cardiovascular disease. Plasma adiponectin level is associated with atherosclerosis markers such as inflammation, oxidative stress, and endothelial dysfunction (116). Adiponectin functions as a molecular regulator of atherosclerosis. Lipid laden macrophages or foam cells illustrating early atherosclerotic lesions. Adiponectin inhibits foam cell formation by weakening the attachment of monocytes to endothelial cells via inhibiting synthesis of adhesion
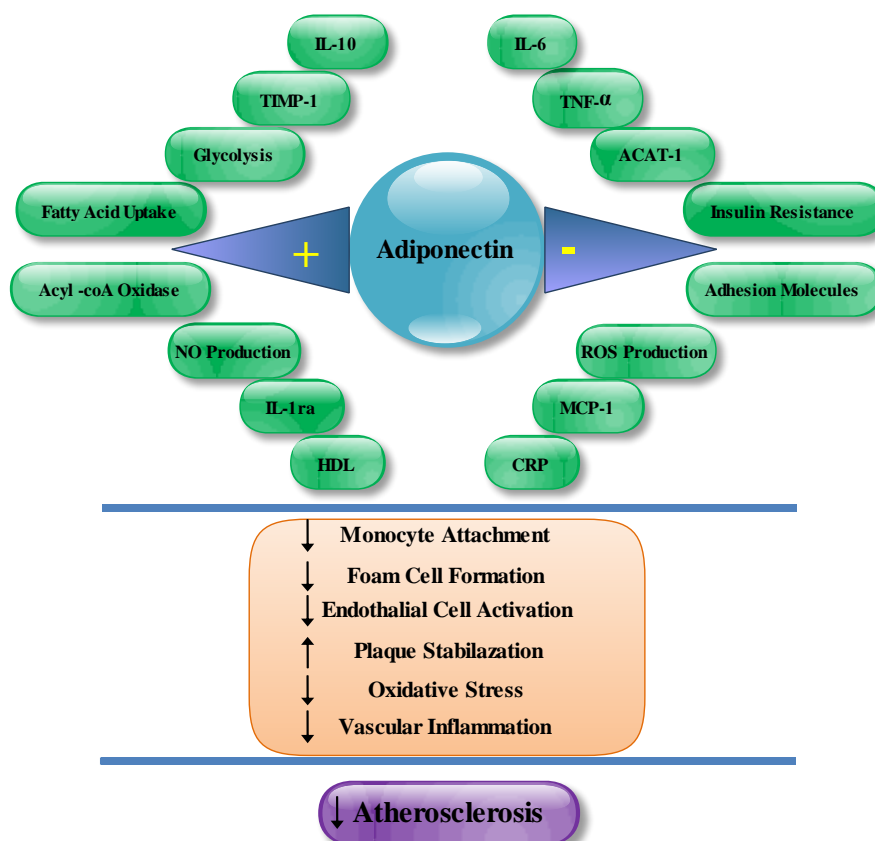
Figure 2. MetS has independent association with Atherosclerosis. Adiponectin reduces the progression of atherosclerosis through several mechanisms.

TIMP-1: tissue inhibitor of metalloproteinase-1; ACAT-1: acyl-CoA:cholesterol acyltransferase-1; MCP-1: Monocyte chemo attractant protein-1; IL-: interleukin-; NO: nitric oxide; CRP: C-reactive protein; TNF-α: tumor necrosis factor alpha; HDL: high-density lipoprotein

molecules such as intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and E-selectin (12). Also, adiponectin represses the class A macrophage scavenger receptor (SR-A) expressing (117), down-regulates acyl-CoA:cholesterol acyltransferase-1 (ACAT-1) (118) and induces IL-10 secretion from macrophages (119). Matrix metalloproteinase (MMP) enzymes which are involved in degradation of supportive collagen and fibrous cap thinning can increase the risk of plaque rupture and eventual thrombosis (120). Adiponectin enhances the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) in human monocytes-derived macrophages, which results in plaque stabilization (121) (Figure 2). Adiponectin null mice showed increased thrombus formation and platelet aggregation at locations of vascular damage (108). Besides, apolipoprotein E-null (apoE-null) mice overexpressing adiponectin had fewer atherosclerotic lesion than control apoE-null mice (122).

Adiponectin and lifestyle modification

It has been indicated that lifestyle modification has important effects on MetS as it reduces the intensity of related abnormalities (123). Obesity is closely associated with an increase in adipocytes size and number (124). Furthermore animal studies indicated that enlarged adipocyte cells in obese mice caused similar condition with T2D and insulin resistance (125). A negative correlation has been reported between adipocyte size and adiponectin level (126). Adiponectin plasma level decreases with weight gain and increases with weight loss (127, 128) and has inverse correlation with body mass index (BMI), intra-abdominal fat and insulin resistance (129). In coronary artery disease, considerable weight reduction is correlated with elevation of HMW adiponectin (130). It was shown that acute weight loss (4-6 weeks) did not change adiponectin level (131).

Diet-induced weight loss increased different forms of adiponectin (HMW,MMW and LMW) in plasma (132). Also, dietary changes affects adiponectin level as it was seen in animal studies that fish oil (rich in n-3 fatty acids) incrementally raised adiponectin level in a dose dependent manner. Fish oil induces adiponectin gene expression in epididymal fat in a PPAR-γ dependent fashion (133). Also, low glycemic load and fiber rich diets may increase plasma adiponectin level in diabetic

patients (134). However, it has been reported that there is no association between total energy intake, protein, fat or carbohydrate intake and adiponectin levels (135).

Exercise training or increased physical activity, especially with reduction in fat mass, increased adiponectin in adipose tissue and decreased production of inflammatory cytokines (136, 137).

Visceral adipose tissue (VAT) secretes high levels of PAI-1 and accumulation of VAT is associated with hypo-secretion of adiponectin (138). Regular exercise training can reduce VAT with minimum change in weight (139, 140). It has been shown that 12 weeks of aerobic exercise training in older obese adults, independent of dietary glycemic index, significantly increased HMW adiponectin secretion that is inversely correlated with reduction in VAT. It was concluded that VAT is a key factor in the regulation of HMW adiponectin (141).

Acute sessions of low or moderate exercise do not affect adiponectin levels in healthy lean subjects (142-144), even a decrease in adiponectin levels was seen in young athletes after acute strenuous rowing. However, adiponectin levels do not change in response to low and moderate running or cycling (145). But in case of obese individuals, a recent study demonstrated that in inactive, abdominally obese men, acute and short-term (one week) aerobic exercise training significantly increased plasma adiponectin levels independent of intensity (146). Also, seven consecutive days of vigorous aerobic exercise improves insulin sensitivity, fat oxidation and HMW adiponectin, independent of changes in body weight and composition (147). The effect of various intensities of acute exercise on changes in total adiponectin level and its oligomers in middle-aged abdominally obese men has been studied. Moderate-intensity exercise has no effect on total adiponectin level but high-intensity exercise decreases it without changing HMW form and mainly by reduction of MMW and LMW form (148). The researchers indicated that epinephrine may partially regulate the decrease in total and MLMW adiponectin levels during high-intensity exercise (148).

Chronic exercise training can improve MetS by several mechanisms as it increases insulin sensitivity, reduces body weight and improves fitness levels. Also, it can increase adiponectin resting levels and expression of adiponectin mRNA and AdipoR1/R2 mRNA in skeletal muscle (145, 149, 150). The studies showed 12 weeks of regular aerobic training decreases the potential risk of coronary heart disease by increasing adiponectin levels and decreasing inflammatory markers in non-athlete obese men (151).

Different results may be attributed to the nature of exercise program i.e. type (endurance, resistance, combined), intensity (high, moderate, low), duration (short- vs. long-term), and subject status (healthy vs. patient; trained vs. untrained; overweight and obese vs. lean) while the form of measured adiponectin (total or multimers) is another issue (152). However, it seems that overweight and obese individuals may benefit more than normal-weight persons from exercise training. Hence, further and better controlled studies are required.

Smoking has an important role in health status. Hypoadiponectinemia is associated with smoking habits (153- 155). An important dose-response association was detected between the number of cigarettes and plasma adiponectin level (153). Hypoadiponectinemia in smokers may be associated with smoking not to concurrent presence of insulin resistance (156). Nicotine enhances inflammation and directly affects human adipose tissue (157). *In vitro* studies in mice 3T3-L1 showed that nicotine and H_2O_2 decreased mRNA expression and secretion of adiponectin in a dose-dependent fashion (158).

Lifestyle controls synthesis and secretion of adiponectin via several mechanisms: PPAR-γ and AMPK activation, post-translational modification, modification of adipose tissue morphology, infiltration of macrophages and inflammation (159).

Adiponectin and pharmacological intervention

PPAR γ agonists such as TZDs (thiazolidine-diones) enhance insulin sensitivity. *In vivo* and *in vitro* studies showed that TZDs can normalize or increase adiponectin mRNA expression and adiponectin secretion in a dose-time dependent fashion (160). Natural compounds may increase adiponectin level (161). Recent studies indicated that *Zataria multiflora* can increase adiponectin level, which may be due to increase in PPAR γ protein (162). A recent study showed that using aged garlic extract for 12 weeks can increase adiponectin level in MetS patients (163). Also, resveratral, a natural polyphenol, can regulate adiponectin expression and multimerization in adipocytes. This is caused by activation of FOX1, a transcription factor involved in the regulation of adiponectin gene expression and AMPK signaling pathways (164). It seems that the expression of AdipoR1 and AdipoR2 in skeletal muscle and adipose tissue are increased by PPAR-γ agonists and this may activate adiponectin intracellular signaling pathway (9). Also, another study showed that dual PPAR α/γ agonists like MK-0767 increases plasma adiponectin level in healthy subjects (165). Troglitazone therapy for 3 months up-regulates adiponectin synthesis and secretion in obese T2D patients (166). An *in vitro* study indicated that PPAR-α agonists enhance insulin sensitivity and increase serum total adiponectin (167). Fenofibrate increases HMW adiponectin in hypertriglyceridemic patients (168). RAS blockers such as ACEIs

(angiotensin converting-enzyme inhibitors) and ARBs (angiotensin II receptor blockers) increase adiponectin level in MetS patients (169). Also, temocapril (an ACEI) or candesartan (an ARB) increases adiponectin level in insulin-resistant essential hypertensives and losartan (an ARB) increases adiponectin level in type-1 diabetes or hypertensive patients (53).

Conclusion

MetS is considered as an important world health problem, which has close association with T2D and CVD. A large body of evidence suggested that adiponectin has an important role in the prevention of MetS. Adiponectin is known as an anti-inflammatory, antioxidative, anti-atherogenic adipokine and it has insulin sensitizing effect. Several clinical and experimental studies have emphasized these biological functions. It is suggested that pharmacological approaches and lifestyle modification may increase plasma adiponectin level or tissue sensitivity which could be a promising target for prevention and treatment of MetS and related diseases.

Conflict of interest

Authors have no conflict of interest to declare.

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