PHYSIOLOGICAL ROLES AND ASSOCIATED DISORDERS OF ADIPONECTIN

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ABSTRACT

Among the adipokines, adiponectin is the first one to be described just over a decade ago. It is produced exclusively by adipose tissue and circulates in high concentration in human plasma accounting for 0.01% of proteins in plasma, almost thousand times higher than that of leptin. The normal circulating level of adiponectin ranges from 2 to 30 µg/ml. It is now observed that besides adipose tissue, adiponectin can also be produced by several other tissues such as hepatocytes, cardiomyocytes, and placenta. Adiponectin executes its action via autocrine as well as paracrine effects. Researchers working in this area have revealed that adiponectin has insulin-sensitizing, anti-inflammatory and cardioprotective effects. Our review focuses on adiponectin, its mode of action on different peripheral tissues such as skeletal muscles, heart, liver, brain and its the correlative account in various diseases.

Keywords: Adiponectin, Obesity, Type 2 diabetes, Inflammation, Malignancies, Cardiovascular disease.

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INTRODUCTION

Adiponectin, chief adipokine of adipocytes [1] is a 30 kDa secretory protein made up of 244 amino acids [2] coded by APM1 gene located on chromosome 3q27 [3]. Not only adipocytes but other some cells such as cardiomyocytes, hepatocytes, and placenta also have the ability to produce adiponectin in small quantity [2]. It is denoted by various terms such as AdipoQ [4], the other ones being gelatin-binding protein-28 [5] and adipocyte complement-related protein of 30 kDa [6]. Domains present are namely: a C-terminal globular domain, a collagen-like domain, and an N-terminal domain [3]. Three homooligomeric forms of adiponectin namely trimeric form, hexameric form, and high molecular weight multimeric form (HMW) have been identified in humans [7]. HMW being most active form [8] and the collagennous domain being important for the oligomerization [9]. G-protein coupled receptors commonly known as adiponectin receptors, viz., adipon R1, adipon R2, and T-cadherin modulate the action of adiponectin in various tissues. [10]. Major receptor in skeletal musclle is adipon R1, whereas that in the liver and vascular endothelial cells is adipon R2 and T-cadherin, respectively [11].

ACTION OF ADIPONECTIN ON VARIOUS TISSUES AND ORGANS

As a hormone, adiponectin exhibits autocrine and paracrine action in adipose tissue, whereas endocrine activity in distal ones [12].

Adipose tissue

In adipocytes, it regulates cellular differentiation, suppresses inflammatory markers such as interleukins (IL-6 and 8), inflammatory, and chemotactic proteins production, thus inhibiting lipid storage and enhancing insulin sensitivity [13].

Skeletal muscles

Earlier, adiponectin was thought to produce its metabolic effects on skeletal muscle via endocrine activity [14]. However, according to recent studies, myocytes are also capable of secreting adiponectin that can exert local effects and hence, it may be regarded as a myokine [15].

Adiponectin has an insulin sensitizing effect on skeletal muscle [9] that is achieved by lowering muscular lipid levels [16]. It causes glucose utilization [17], uptake of fatty acids and oxidation [18], lowers ceramide levels [19] and stimulates mitochondrial biosynthesis [18]. These actions are brought about by stimulation of adenosine monophosphate kinase (AMPK), peroxisome proliferator activator receptor α (PPARα), and p38 mitogen-activated protein kinase [17]. AMPK translocates glucose transporter Type 4 transporters to cell membrane [20] and regulates glucose utilization and β oxidation, whereas PPARα regulates lipid metabolism by controlling the expression of genes involved [21], AMPK renders acetyl-CoA carboxylase (ACC) inactive via phosphorylation and decreases levels of malonyl-CoA [22], a molecule that allosterically inhibits carnitine palmitoyl transferase 1, which is the enzyme required for fatty acid transport to mitochondria for oxidation [23]. Fatty acids in muscles are derived from triglyceride hydrolysis caused by lipoprotein lipase [24] that is activated by adiponectin [25].

Stefan et al. showed a positive association of adiponectin with insulin-mediated glucose utilization and decreased insulin sensitivity with lower adiponectin levels [26]. In a cohort follow-up study, Teres et al. stated that older age individuals with hyperinsulinaemia possess a high risk of skeletal muscle wasting [27]. Ceramide has been recently identified as a new factor impairing muscle insulin sensitivity [28]. Adiponectin via activation of ceramidase lowers myocellular ceramide level and enhances insulin sensitivity as well as mitochondrial biosynthesis [19].

Both animal [21] and human studies [29] have confirmed the stimulatory role of adiponectin on mitochondrial biosynthesis and its oxidative capacity. These effects are mediated via activated AMPK [30]. In addition, a strong correlation exists between adiponectin levels and mitochondrial DNA content in human skeletal muscle [29].

Cardiovascular system

Adiponectin is considered as cardioprotective adipokine [3] because it not only prevents vascular remodeling by suppressing tumor necrosis factor α (TNF-α) [32] and platelet-derived growth factor [32] but also possesses protective antithrombotic [33], anti-inflammatory [34], and antithrombotic effects [35]. These protective actions are provided via the activation of AMPK [36] and cyclooxygenase 2 [37].
Adiponectin prevents monocyte attachment to endothelium [38] and nuclear factor-kappa beta (NF-kB) signaling, suppressing the expression of cell adhesion molecule and IL-8, a proinflammatory cytokine [38]. All these effects contribute to the anti-inflammatory role. Further, as an antiatherogenic agent, it is able to prevent the formation of foam cells. On one hand, it reduces the expression of receptors for Class A scavenger [39], whereas, on another hand, it depresses acyl-CoA cholesterol acyltransferase enzyme responsible for the synthesis of cholesteryl esters [39]. As per Kumada et al., adiponectin upregulates IL-10, stabilizes atheromatous plaque [40], and also inhibits thrombus formation [41].

Adiponectin as an antioxidant protects the vasculature from oxidative stress via augmentation of endothelial nitric oxide synthase (eNOS) synthase [42]. This enzyme is activated by phosphorylation, thereby increasing the production of NO [43]. Furthermore, adiponectin also suppresses superoxide formation and stimulates eNOS interaction with heat shock protein 90 that allows eNOS to render its function at maximum level [44].

Adiponectin also regulates fatty acid oxidation and glucose transport via mechanism similar to skeletal muscle and thus maintains hydraulic work of cardiomyocytes, therefore, increasing cardiac efficiency [45].

Liver
Adiponectin exerts its effect in the liver via activation of AMPK, PPARα [12] pathways, and sterol regulatory element-binding protein 1c (SREBP) [46]. First, AMPK inactivates ACC by phosphorylation; second, it reduces levels of malonyl-CoA, and third, it increases oxidation of fatty acids by favoring its transport to mitochondria [47]. In addition, PPARα stimulates fatty acid oxidizing enzymes [46] and SREBP 1c, also known as a transcription factor, downregulates the lipogenic genes [48].

Adiponectin also exerts antifibrotic through suppression of profibrotic factor [49] induced hepatic stellate cells transformation to myofibroblast [50]. Adiponectin as an anti-inflammatory agent in liver mediates its role by inhibiting TNF-α [51] and activating toll-like receptor-4 [52]. However, mechanism involved is still unclear and requires further researches.

Lungs
Receptors for adiponectin, especially adip R1 [53], are expressed in pulmonary epithelium suggesting lung to be one of the target organs of adiponectin [54]. Thyagarajan et al. demonstrated a positive relation among lung function and adiponectin [55]. In vitro studies on mice model elucidated the protective role of adiponectin against inflammation [56] and post-ischemic lung injury [57]. As per Summer et al., adiponectin inhibits the action of alveolar macrophages and maintains vascular homeostasis [58].

Kidney
Kidney possesses plenty of perirenal fat [59] and expresses adip R1 [60] that on activation by AMPK regulates renal synthetic activities and protects glomeruli from oxidative stress. According to Fang et al., angiotensin causes activation of nicotinamide adenine dinucleotide phosphate (NADH) oxidase and results in oxidative stress, but these effects are attenuated by adiponectin [61]. Adiponectin activates caspase-8 and preserves podocytes of glomerulus from apoptosis [62]. It also upregulates nephrine, a podocyte-derived protein, and decreases of which contributes to proteinuria [63]. Adiponectin is mainly cleared from the body via liver but kidneys also contribute to some extent [64]. Thus, urinary adiponectin, only monomeric and dimeric isoforms, can be traced in small quantity [65] as they can cross glomerular barrier [66].

Brain
The role of adiponectin in brain and actual mechanism involved is poorly elucidated. Although some researches are published in this regard, conflicting results are obtained. According to some authors, cerebrospinal fluid lacks adiponectin as the brain cells are incapable of secreting adiponectin, but they do express its receptors [67]. In contrast, recent studies have shown local expression of adiponectin in the cells of pituitary gland suggesting that adiponectin may locally regulate systemic metabolism through the central nervous system [68]. Adiponectin may be also regarded as a starvation gene as there is an increase in adiponectin levels in the arcuate hypothalamus during fasting state, and this effect may lead to increased hypothalamic AMPK activity promoting food intake [69].

ASSOCIATION OF ADIPONECTIN IN VARIOUS PATHOLOGICAL CONDITIONS

The serum concentration of circulating adiponectin ranges from 2 to 30 µg/ml which accounts for 0.01% of proteins present in plasma [70]. The level of adiponectin is approximately 40% higher in females as compared to males [71]. First, plausible reason for this may be inhibition of adiponectin secretion by androgens [9] and second may be gender-based differential in body fat distribution [72]. Because adiponectin affects number of tissues and organs, it has been implicated in various pathological states.

Obesity and adiponectin
Obesity, a condition of increased total body fat mass [73], determined by anthropometric indices such as body mass index (BMI) [74], waist-hip ratio [75] correlate negatively with adiponectin [76] which may be due to transcriptional suppression of adiponectin by inflammatory cytokines [77], but obese person when reduce their weight [78] leads to increase in adiponectin level suggesting reversibility of obesity-associated hypo-adiponectinemia [79]. Hoffstedt et al. reported lower adiponectin mRNA in obese person [80]. Adiponectin gene polymorphism at 276 G→T is linked with obesity and related complication [81].

Diabetes and adiponectin
Adiponectin is considered to be the potent biomarker of Type 2 diabetes mellitus [82]. Jee et al. [83] and Tan et al. [84] demonstrated the negative relation of adiponectin with diabetes prevalence and the risk of prediabetic to develop diabetes. In addition, marker of glycemic control, also called glycated hemoglobin, correlated inversely with adiponectin [85]. Complications of the diabetes are also shown to be associated with adiponectin. It is involved in pathogenesis of diabetic retinopathy, one of the major causes of blindness [86]. Lower level has been detected in the diabetic patients with retinopathy than those without it [86]. Further similar level of adiponectin was observed in normoalbuminuric and microalbuminuric patients, whereas the concentration was high in diabetic patients having macroalbuminuria [87]. Lin et al. in their study including 733 diabetic patients observed that serum adiponectin is inversely correlated with the presence of renal dysfunction [88]. In diabetic patients, there is increased the risk of cardiovascular complication as the level of adiponectin decreases [89]. According to Glikor et al., adiponectin protects myocardium by increasing the level of cardioprotective agent high-density lipoprotein (HDL) cholesterol [90].

Researches have shown that one of the mechanisms, by which drugs used for the treatment of diabetes acts, is by increasing adiponectin levels [91] suggesting that adiponectin might be used as a novel therapeutic regimen for insulin resistance and Type 2 diabetes.

Adiponectin and cardiovascular diseases
Several studies have supported the roles of low adiponectin in the development of vascular disease [92]. Inverse relation of adiponectin with carotid intimal thickening [33], myocardial infarction [93], and essential hypertension [94] has been observed. Factors that determine the cardiovascular disorder risk such as serum cholesterol and triglycerides were negatively correlated, whereas HDL was positively correlated with adiponectin [29].

As stated in previous studies, adiponectin protects ischemic myocardium by suppressing the activity of NADH oxidase and inducible
Adiponectin also correlates positively with progenitor cells involved in vascular repair [96]. It modulates angiotensin II action in hypertension and renders protective effect [97]. Kumada et al. linked hypoadiponectinemia independently with coronary artery disease in men [98]. Although cardioprotective in action, increased adiponectin is a risk factor of heart failure and cardiovascular mortality [99], especially in cachexic patients [100]. The causative factor may be adiponectin resistance or increased production of brain natriuretic peptide, a vascular disease marker [101]. Some studies, such as those of Lindsay et al. [102], Lawlor et al. [103], and Sattar et al. [104], could not obtain any association between adiponectin levels and cardiovascular disease status. Therefore, the role of adiponectin in coronary artery disease development remains controversial, and the possible reason for the anomaly may be that the heart disease causes decreased adiponectin clearance by affecting kidney function thereby conflicting the analysis.

Adiponectin and inflammation

Increased levels of serum adiponectin have been found in the inflammatory disorders such as systemic lupus erythematosus [105], cystic fibrosis [106], inflammatory bowel disease [107], and rheumatoid arthritis [108]. Anti-inflammatory effects of adiponectin are rendered by direct action on inflammatory cells [109], suppression of NF-kB [52], inhibition of TNF-a [110], C-reactive protein (CRP) [111], and IL-8 [112] production. Further, it binds with C1q induces classical complement system and facilitates apoptotic cell clearance [113]. Venkatesh et al. have shown an inverse association between CRP and adiponectin levels [114] similar to that of Engeli et al., who also found a significant inverse correlation of adiponectin with the inflammatory mediators such as CRP and IL-6 [115].

Adiponectin and malignancies

Obesity-related malignancies can develop at different sites of the body such as endometrium, breast colon, stomach, and prostate; all of which are negatively associated with adiponectin [116]. It may be either due to the indirect effects of adiponectin through hormonal and cytokine level modifications or due to direct effects through inhibition of mitogenic growth factors related to cell proliferation [117]. A meta-analysis research of Wei et al., on the association of adiponectin with the development of cancer, indicated that the circulating adiponectin was lower in the patients with various cancers [118]. Study of Kang et al. revealed that the breast cancer patients with lower median adiponectin are more prone to lymph node metastasis [119].

The risk of endometrial cancer in women having high BMI and low adiponectin level increases nearly by 6-folds [120]. Men with the highest adiponectin concentration have almost 60% reduced the risk of colorectal cancer [121] and nearly 70% reduced the risk of developing prostate cancer [122]. Small case-control study has shown a negative association of renal carcinoma [123] and acute myeloblastic leukemia with adiponectin [116] supporting the fact that adiponectin treatment suppresses myelomonocyte cell proliferation [110].

Adiponectin and other disorders

Studies have established role of adiponectin in other peripheral tissues such as lungs, liver, and kidney disorders too. A recent study on mice with genetic deficiency of adiponectin demonstrated increased systemic and local inflammation, alveolar simplification, and enlargement due to abnormal postnatal alveolar development [55]. These defects in such mice were attenuated by adenoviral adiponectin therapy [124]. Decreased serum adiponectin correlated with poor asthmatic lung function and chronic obstructive pulmonary disease [125].

In hepatocytes, lower adiponectin level is seen hepatic steatosis [126] fatty liver and injuries [127]. Due to insulin resistance, there is increased lipolysis in adipocytes but increased lipogenesis in hepatocytes causing accumulation of lipid [128]. However, increased levels of adiponectin have been detected in liver cirrhosis. Possible reasons may be decreased hepatic clearance or compensation to excess production of proinflammatory cytokines [34]. Available researches indicated adiponectin to be renoprotective [129]. It protects the kidney from progression toward fibrosis and hypertrophy [130]. Doumey et al. observed an inverse relationship of adiponectin with estimated glomerular filtration rate (eGFR) [131], whereas Kawamoto et al. found a positive association of HMW adiponectin with GFR [132]. Several studies have reported a significant excretion of adiponectin in the urine of patients with various renal diseases, whereas the question is still unanswered whether adiponectin is synthesized within nephron itself or simply filtered by glomerulus [133].

CONCLUSION

The purpose of this review is not to requote whatever has been done in earlier investigations but is to help the researchers who are investigating the utility of adiponectin in different sectors of health. The pathophysiology of various inflammatory diseases, cancer, and disorders related to kidney, lung, liver, and their association with adiponectin remain unclear. This review may be worthful for the researchers to elucidate such unclear facts and the related mechanism behind this. In conclusion, among the various adipokines, adiponectin is the abundant protein produced by adipose tissue. It plays an important role in carbohydrate and lipid metabolism in various tissues. It has been found to be associated with various disorders such as diabetes mellitus, atherosclerotic, inflammations, cancers, renal, and pulmonary disorders. Further investigations including large sample size are required to unveil in depth the clinical roles of adiponectin so that it can be used as a potent therapeutic regimen for the management of associated disorders in future.

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