Review on Adiponectin: A Benevolent Adipokine

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Authors’ contributions
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ABSTRACT

Adiponectin is a most abundant secretory protein produced by adipocytes of white adipose tissue. Adiponectin circulates in blood as three different (high-molecular, middle-molecular, and low-molecular weight) isoforms, gives its effects through AdipoR1 and AdipoR2 receptor. Primary data suggesting that adiponectin has insulin-sensitizing, anti-atherogenic, and anti-inflammatory effects. High serum level of adiponectin is positively associated with inflammation severity and pathological progression in chronic kidney disease, liver disease and inflammatory bowel disease. It has emerged as a valuable biomarker for insulin sensitivity, cardiovascular risk and inflammation. Adiponectin is gaining attention for its therapeutic role in Alzheimer’s disease. Adiponectin appears to play a crucial role not only in glucose and lipid metabolism but also the development and progression of different cancers. Adiponectin also produced locally in the retinas participate in defense of various eye diseases. This review summarizes the role of adiponectin as benevolent adipokine in different disorders.

Keywords: Adiponectin; type 2 diabetes mellitus; obesity; anti-inflammatory; anti-atherogenic; cancer; neuroprotective; cardioprotective.
1. INTRODUCTION

Adiponectin is protein consisting of 244-amino acid which is part of complement 1q family [1]. Adipocytes are the main source of Adiponectin production and its transcription is controlled by peroxisome proliferator-activated receptors (PPARs) [2]. It has N terminal collagenous region and a C terminal globular domain [3]. It circulates in trimmeric, hexameric, and higher order complexes [4]. Adiponectin is classified according to molecular mass, it is classified in to low (trimmer), middle (hexameric), and high complexes [5]. Adiponectin exist mainly either as full length form or smaller globular form in circulation. Full-length adiponectin (fAd) is fragmented by leukocyte esterase in to globular adiponectin (gAd). Both adiponectin (gAd and fAd) regulate distinct signalling pathways within the same tissue. Adiponectin is seen in human cerebral cerebrospinal fluid (CSF), in trimer form. Its concentrations within the CSF are as approximately 100 fold less than that in serum [6-8].

2. OVERVIEW OF ADIPOSE TISSUE AND ADIPONECTIN BIOLOGY

White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT) are the main source of adiponectin production which is reflected in the blood in concentration of 5–30µl/ml Adiponectin (also mentioned as Acrp30, GBP-28, apM1, and Adipo Q) may be a protein mainly secreted by WAT adipocytes. Human adiponectin is encoded by the Adipo Q gene [9]. Small concentration of adiponectin is present in human murine osteoblasts, parenchyma cells, liver, myocytes, epithelial cells and placental tissue [10].

Adiponectin enhanced the fatty acid biosynthesis and inhibition of gluconeogenesis in liver [11]. Adiponectin also increases glucose uptake through the signalling pathway in skeletal muscle. Insulin resistance is improved by adiponectin through increased fatty acid oxidation via PPARα activation and increased signalling of IRS (insulin receptor substrate) in skeletal muscle and liver [12,13]. Reports suggest that adiponectin possess anti-diabetic, anti-inflammatory, cardioprotective, anti-atherosclerotic, anti-cancer and neuro-protective effects [14-17].

3. IDENTIFICATION AND MOLECULAR STRUCTURE

Adiponectin exists as three different ways, as trimmer (67 kDa), hexamer (140 kDa), and a multimer (300 kDa) (Fig. 1).

Adiponectin in its monomeric form can't be detected in native conditions [18]. Oligomeric adiponectin is made up of a low molecular weight Homotrimer. The Hexameric adiponectin form is formed by two trimmers linked through a disulphide bond and this hexameric form is the structural unit for HMW adiponectin form.
Fig. 1. Structure of adiponectin: Adiponectin exists in trimer, hexamer, multimer and globular form. Full-length adiponectin is composed of 244 amino acids, including a collagen- domain at the N terminus and globular domain at the C-terminus [18].

HMW oligomer adiponectin is the chief bioactive isoform having anti-diabetic and cardioprotective effect. Post-translational alterations such as hydroxylation and successive glycosylation of numerous lysine residues are vital for HMW oligomer adiponectin formation. Globular adiponectin is also biologically active which is produced from full length protein by the process of proteolysis. Numerous molecular chaperones such as Ero1-La (ER oxidoreductase 1-La), ERp44 (Endoplasmic Reticulum resident protein 44) and DsbA-L (disulphide-bond A oxidoreductase-like protein) in the endoplasmic reticulum are responsible for controlling the production and secretion of adiponectin [19-23].

4. ADIPONECTIN RECEPTOR

AdipoR1 and AdipoR2 are main two receptor through which adiponectin gives its effect. Chemically it has seven trans membrane domain which slightly differ from GPCR (G-protein coupled receptors). More amounts of AdipoR1 and AdipoR2 are present in muscle and liver respectively. Confusion is still alive for T cadherin, it may be a binding protein or a adiponectin receptor. Though its pharmacological activity in cardioprotective, endothelial and Vascular Smooth Muscle cells (VSMCs) proliferation, migration and survival is notified.

Oestrogen and Testosterone have an important role in maintaining plasma levels of adiponectin. So, in female adiponectin levels are slightly higher as compared to male. This co-relation clarify the reason why men have more chances for insulin resistance and atherosclerosis than women [24-31].

5. SIGNALLING PATHWAY

APPL1 (adaptor protein) facilitates adiponectin signalling by interacting with adiponectin receptor to stimulate AMPK muscle cells. AMPK can be activated by adiponectin through the APPL1/LKB1-independent and PLC/Ca\(^{2+}\)/CaMKK-dependent pathway by secreting calcium from the endoplasmic reticulum via stimulation of IP\(_3\) receptor.

APPL2 utilizes two separate mechanisms to down regulate signalling in C2C12 cells which is dependent on AdipoR1 receptor. Firstly, APPL1 and APPL2 compete with each other for binding with AdipoR1 receptor. Secondly APPL2 forms a heterodimer with APPL1 there by anticipates the binding of the latter with AdipoR1 receptor [32-33].
6. THERAPEUTIC ROLE OF ADIPONECTIN

6.1 Type 2 Diabetes Mellitus

Person with lower level of adiponectin is more prone for type 2 diabetes mellitus [34] Insulin resistances, triglycerides, C-reactive protein, tissue plasminogen activator, and alanine aminotransferase are inversely associated with adiponectin levels. High-density lipoprotein, cholesterol and factor VIII are directly associated with adiponectin. Hypoadiponectinemia is commonly linked with insulin resistance suggesting a process during the primary stages of hyperinsulinemia where high insulin levels results in a decrease of adiponectin levels which subsequently lowers the insulin sensitivity. Further this process prompts to have an increased level of circulating insulin for the maintenance of glucose homeostasis [35].

In adiponectin Knock-out (KO) mice it was found that administration of PPAR gamma agonists improved glucose tolerance and increased the sensitivity of insulin [36]. The correlation between HMW adiponectin levels and glucose tolerance is better than the correlation between total circulating levels of adiponectin and glucose tolerance.

It was demonstrated that down regulation of AdipoR1 and AdipoR2 receptors caused decreased insulin sensitivity thereby causing obesity. Different isoform of adiponectin plays separately for glucose tolerance effect. Levels of HMW isoform of adiponectin gives better effect for insulin sensitivity as compared to LMW isoform. In diabetic patient, level of expression of AdipoR1 and AdipoR2 receptors also is decreased along with adiponectin level [37].

6.2 Inflammation

Anti-inflammatory property of adiponectin is mainly due to that improvement of metabolic functions which is reflected by reduced levels of pro-inflammatory indicators like TNF-α and C-reactive protein [38,39]. In vivo and vitro data suggested that adiponectin decreases the pro-inflammatory cytokines, decreased the expression of macrophage attracting adhesion molecule, interference of the inflammatory signalling pathway and finally reducing the mitochondrial ROS (reactive oxygen species) production that would eventually leads to oxidative damage [40-42].

Adiponectin and TNF-α antagonists neutralize rheumatoid arthritis which is due to that inhibitory effect of this adipokine on TNF-α [38,43]. Many of anti-inflammatory drugs seem to produce their effect by increasing the level of adiponectin. This anti-inflammatory mechanism of action is due to inhibition of TNF-α. Crohn’s disease, Systemic lupus erythematos and inflammatory bowel disease (IBD) reported to have higher level of adiponectin. Recent study of adiponectin
transgenic models indicated the both beneficial and harmful sides of adiponectin in inflammatory bowel disease pathophysiology [44-46].

The adipose tissue from the lean subject and obese subject produce anti-inflammatory cytokines and pro-inflammatory cytokines respectively. Anti-inflammatory cytokines includes adiponectin, IL (Interleukin)-4, IL-10, IL-1 Receptor antagonist (IL-1Ra), IL-13, Transforming Growth Factor Beta (TGFβ) and apelin. While pro-inflammatory cytokines include TNF-α, resistin, leptin, IL-6, visfatin, angiotensin II, and plasminogen activator inhibitor. Pro-inflammatory cytokines like TNF-α, IL-1b, IL-6, iNOS and reactive oxygen species (ROS) are secreted by M1 macrophage which can inhibit adipogenesis in adipocytes and insulin signalling [47-49]. IL-10, IL1 receptor antagonists and arginase-1 like anti-inflammatory cytokines are secreted by macrophage M2 which can help in tissue remodelling and in the protection against obesity induced insulin resistance [50,51].

6.3 Obesity

Scientific data from various studies propose that low adiponectin levels are a major contributing factor for the obesity-linked illness [52-55]. Obese patient has more prone to become diabetic and hypertensive. Obesity is also linked to circulatory system diseases like IHD (ischemic heart disease) and peripheral artery disease [54]. Adipokines modulate inflammatory and metabolic processes, so adipokine play a crucial role in pathophysiology of obesity-linked diseases. Adiponectin plasma levels are inversely related with adult's body fat percentage. Adiponectin regulate the fatty acid oxidation, glucose and lipid metabolism. Regulatory role of adiponectin in atherogenesis, endothelial function and vascular remodelling is also documented. Adiponectin levels are fundamentally decreased in obese subjects contrasted with non-obese subjects or non-diabetics [52-61].

6.4 Cancer

6.4.1 Oesophageal adenocarcinoma (OAC)

Recently, Obesity is major important health problem in the developed countries. Weight is related with an expanded danger of building up certain disease like oesophageal adenocarcinoma (OAC) [62]. Obesity is an important risk factor for an oesophageal adenocarcinoma [63-65]. As an obese person has more chances of oesophageal cancer by approximately 1.5-fold in both sexes [66].

In studies, we found that leptin increase multification and restrains apoptosis in OAC cells [67]. Adiponectin is managed conversely to leptin and seem to have contraindicated metabolic activities, we have concluded that adiponectin may restrict the development impact in OAC cells. There is some primer information recommending that adiponectin may have anticancer effect.

Adiponectin act as a physiological inhibitor of developing impact of leptin. Adiponectin insufficiency with hyperleptinemia impact may expanded the danger of progression of oesophageal adenocarcinoma and other obesity associated cancers [61-68].

6.4.2 Breast cancer

In postmenopausal woman for the development of breast cancer, obesity is the one of the major risk factor [69-70]. Over abundance of fat tissue (adipose tissue) favours metastasis progression and recurrence of breast cancer, which is associated with higher mortality [71]. Consequently overweight and obese female with breast carcinoma are 2.5 occasion as prone to die off within 5 years of disease diagnose history as compared to non-obese female [72]. Number of factors have been suggested to narrate the clear connection between obesity and breast cancer.

Various investigations have surveyed the movement of adiponectin on cell development and reported the anti-proliferative capability of adiponectin in different breast cancer cell lines, including T47D.21-25, MDA-MB-231 and MCF-7. Recently, demonstrated that the treatment of adiponectin for 24 hours, diminished MCF-7 cell expansion, and this restraint effect was seen up to 96 hour [73].

6.4.3 Prostate cancer

In experimental studies, safe and protective role of adiponectin to prevent progression of prostate cancer is identified. AdipoRs, JNK, NOX, NF-κB, AMPK are key molecule for signalling pathway of its tumorigenesis effect. Drug molecule can be developed based on the beneficial effects induced by adiponectin. Developed molecule should be in a position to increase the level of adiponectin which can take as tumorigenesis on prostate [74].
6.4.4 Colon cancer

Relationship between adiponectin level and risk factor for colon cancer is inverse. Person with lower level of adiponectin has higher (60%) chances of occurrence of colon cancer as compared to person with higher adiponectin levels [75].

6.4.5 Gastric cancer

Person with upper gastric cancer seems to have lower adiponectin level as compared to normal subjects. This narrates the inverse relationship between adiponectin level and occurrence of gastric cancer. Amount of adiponectin gives clear picture about size and spread and stage of tumor in different body parts [76].

6.4.6 Leukaemia

It has been demonstrated that the adiponectin reduces the growth of myelomonocyte cells lines, and also produces cell death of this monocytic progenitor cells (leukemic cells). It has been found clinically that adiponectin inversely related to the development of acute leukemia [77-78].

6.4.7 Myocardial ischemia

In vitro study suggests that adiponectin directly protect cardiomyocytes through inhibition of cell death, which further promote the cell survival. Adiponectin knock-out mice have worse MIR (myocardial ischemia reperfusion) injury such as myocardial cell apoptosis and increase infarct size that causes decreased efficacy of heart as compared to control mice. In compared to knock-out mice heterozygous (Adipoq+/-) mice, shows less circulating adiponectin levels and also severity of MIR injury [79,80]. Activity of enzymes (eNOS and iNOS) is controlled by adiponectin so it regulated the production of NO. Adiponectin differentially regulates NO production by both eNOS and iNOS. Under physiologic conditions, adiponectin stimulates NO production by phosphorylating eNOS and give its vasodilatory, antiinflammatory, vascular-protective actions. While under pathologic conditions when iNOS is induced, adiponectin prevent excess NO generation by inhibiting iNOS expression. NO is not toxic; however, NO reacts with superoxide and resultant product, peroxynitrite, is extremely cytotoxic and causes oxidative as well as nitrative stress and tissue injury. Adiponectin inhibits iNOS expression, NADPH oxidase expression and subsequent superoxide production in ischemic-reperfused cardiomyocytes. Inhibition of the both gp91phox (the cytochrome b-245 heavy chain subunit of NADPH oxidase) expression and superoxide production, found in globular adiponectin treated mice. Due to the double inhibitory effect of adiponectin on excess superoxide and NO production induced by ischemia-reperfusion, peroxynitrite formation is intensified in Adipoq-/- mice after ischemia-reperfusion and is inhibited by exogenous adiponectin. Adiponectin inhibit the synthesis of excess peroxynitrite mainly through metabolic and TNF-suppressing actions which is mediated by AMP kinase and COX-2 enzyme respectively. Anti-ischemic and cardioprotective effects of adiponectin is due to inhibition of nitrative stress and oxidative stress induced by peroxynitrite [81-84].

6.4.8 Atherosclerosis/stroke

Hypertension, Type-II diabetes and a modified lipid profile having a positive co-relations with adiponectin levels. Therefore a link between stroke and adiponectin is expected [85]. There is a possibility of risk of 5 year mortality with lower adiponectin level after first episode of stroke [86]. Few investigations suggests the protective role of adiponectin in stroke and atherosclerosis pathogenesis. The mechanism by which adiponectin gives its effect in pathogenesis of atherosclerosis is depicted in Fig. 3.

As per few investigations, adiponectin-facilitated mechanistic effects have shown protection against stroke pathogenesis and atherosclerosis. Circulating adiponectin causes inhibition of monocyte adhesion to endothelial cells and subsequent inhibition of transformation of macrophage to foam cells through reducing binding and uptake of oxidized LDL [87,88]. VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intracellular cell adhesion molecule-1) bind to leucocyte and stimulate the process of atheroma after endothelial cell injury [89,90]. Adiponectin inhibit the effect of VCAM-1 and ICAM-1, this inhibitory effect occur due to activation of AdipoR2. Activated AdipoR2 increases PPAR γ activity [91]. Rosiglitazone, PPAR γ agonists increase the adiponectin levels and decrease the circulating VCAM-1, therefore it is considered to be useful in atherosclerosis treatment [92-94]. Higher levels of adiponectin also protect the endothelial cell from vascular injury which is due to hypercholesterolemia and
suppress the uptake of modified LDL into foam cells. Administration of exogenous adiponectin decrease the infarct size in both adiponectin knockout mice and wild type mice. Protective role of adiponectin is proved due to its anti-atherogenic properties and regulation of vascular remodelling [94-96].

6.4.9 Renal disease
Numerous studies related to renal disorder revealed positive correlation between the systemic adiponectin with renal dysfunction. Transcriptional downregulation of adiponectin mRNA in adipose tissue has been found in subjects with renal disease. Higher adiponectin levels confers a protective response to a heightened cardiovascular risk owing to endothelial damage as a consequence of dyslipidemia in renal dysfunction. In vivo data suggest that patients suffering from renal dysfunction with higher amount of adiponectin are found to be less prone to cardiac events. These findings support the protecting role of adiponectin against the cardiac events [97-100].

6.4.10 Liver disease
Quiescent hepatic stellate cell produce adiponectin, which induces apoptosis in activated cell but not affecting normal hepatic stellate cell apoptosis [101]. The increase in hepatic lipid oxidation by adiponectin might also play a role...

Fig. 3. Adiponectin signalling mechanism in atheroma: Adiponectin AdipoR1 activates the phosphorylation of protein kinase B (Akt) and activation of vascular endothelial growth factor (VEGF). Activation of (Akt) through calcium calmodulin kinase kinase (CAMKK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and AMPK contributes to activation of endothelial nitric oxide synthase (eNOS) which leads to No Production. AdipoR2 activated PPARα which reduce vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1). PPAR γ increases production of adiponectin [17]
for the beneficial effect of adiponectin on hepatic glucose metabolism. Insulin resistance causes abnormalities on lipid storage and lipolysis in insulin-sensitive tissues, which may induce an increased flux of free fatty acids from adipose tissue to the liver and cause steatosis. Experimental data also suggest the role of adiponectin as an indicator for cholestasis [102]. Insulin sensitivity effect of adiponectin is due to its activation of fatty acid oxidation and decreased gluconeogenesis in liver. Adiponectin is an important treatment target for non-alcoholic fatty liver disease due to its insulin sensitizing and anti-fibrotic action. Clinical data also suggest the beneficial role of adiponectin in other liver diseases also [103].

### 6.4.11 Eye diseases

Adipose tissue is main source for adiponectin production, but it also produced locally in brain and in some of retinal regions. These tissues also contain adiponectin receptor. Adiponectin plays an important role in neurodegenerative diseases due to its neuroprotective effect. Clinical studies also suggest the beneficial role of adiponectin in some diseases of eye. Adiponectin produces beneficial effects in eye diseases such as Retinis Pigmentosa (RP), Glaucoma, Age Related Muscular degeneration (AMD), diabetic retinopathy and light-induced retinal degeneration. Exercise seems to increase the adiponectin production both locally and systemically. Protective role of adiponectin is due to boosting the expression in plasma and also in retinal region [104].

#### 6.4.12 Alzheimer’s disease

Some in vivo studies shown that adiponectin levels in the mouse CSF is 100-fold lower than plasma levels. AdipoR1 and AdipoR2 are also highly expressed in different brain regions, like hypothalamus, cortex, hippocampus, pituitary glands, and area postrema. Adiponectin acts on the hypothalamus and activates AdipoR1-AMPK

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**Fig. 4. Signalling of adiponectin in normal brain and Adiponectin deficient brain.** Adiponectin bind to its receptor and activate the phosphorylation of AMPK which inhibits IRS-1 phosphorylation at serine residues. This increases insulin-mediated IRS-1 phosphorylation at tyrosine residues and promotes downstream Akt-mediated GSK3 inhibition which leads to phosphorylation of Tau and APP metabolism. In AD, chronic adiponectin deficiency leads to an increase of IRS-1 phosphorylation at serine residues which reduced reduced pIRS-1Tyr and results in GSK3 activation. Activated GSK3 increase the Tau phosphorylation and Aβ production in neurons. Arrows denote promotion; T-bars denote inhibition [110]
signaling to regulate food intakes and lipid and glucose metabolism during fasting. Adiponectin regulates neurogenesis and proliferation of hippocampal neural stem cells. Deficiency of adiponectin reduces dendritic growth and spine density in the hippocampal dentate gyrus in which the neural progenitor cells proliferation and differentiation is suppressed. Protective role of adiponectin is also reported against ischemic brain injury. Decreased adiponectin level has more prone to alzheimer’s disease in type-II diabetic patient with decreased glucose metabolism, gray matter volume and hippocampal volume. Neuroprotective effect of adiponectin is due to its positive correlation with amyloid and inversely correlated with hippocampal volume with mild cognitive impairment (MCI) in woman [105,106]. Increasing alzheimer’s disease bio-markers such as CSF Aβ42, CSF p-Tau and the presence of hippocampal atrophy were found with decreased adiponectin levels in CSF [105,107-108]. Old aged people face problem regarding memory and learning impairment because transport of adiponectin to brain decreased with increasing age, while peripheral level of adiponectin has no any effect of age factor [109]. Though, therefore there is a definitive role of adiponectin in memory and learning. Some data revealed that rodents do not develop amyloid pathologies, probably because of the longevity and low aggregating propensity of rodent Aβ.

Neurodegenerative changes such as impairment in memory and learning, anxiety and unusual fear seems present in aged people with specially in chronic adiponectin deficient subjects, increased microgliosis, astrogliosis with increased cerebral TNFα and ILLβ levels that are the common hallmarks of AD. Deregulated cerebral insulin signalling activities and reduced hippocampal insulin sensitivity developed during the aging of APN-KO mice. In adiponectin knock-out aged mice, decreased pGSK3βS9 (GSK3β phosphorylated in S9 residue) and increased pGSK3βY279 (GSK3β phosphorylated in Y279 residue) levels due to activation of enzyme Glycogen synthase kinase (GSK3β),WhenS9 residue of GSK3β is phosphorylated, it remains inactive in cells. However it becomes active its tyrosine (Y) 279 residue undergoes phosphorylation. These correlation gives explanation for increased bio-markers such as phosphorylated Tau, Aβ42 production and stained Aβ deposition. In aged or type-2 diabetic patient, deregulation of cerebral insulin signalling and pathogenesis Alzheimer’s disease was found with decreased adiponectin levels. The inhibition of GSK3β activity can decrease BACE1 (β-site APP cleaving enzyme 1) expression, which results in reduced Aβ production. Aβ*56 is a specific Aβ oligomer found in patients with MCI and transgenic AD mice at a young age. Aβ*56 leads to dose-dependent cognitive decline in mice, whereas trimeric Aβ does not. Reduced adiponectin and its signalling activities can be pathogenesis cause of alzheimer’s disease. This is also correlated with deregulated insulin signalling activities and decreased insulin sensitivity in brain [111-114].

7. CONCLUSION
Adiponectin is one of the Benerouvent adipokine which has beneficial therapeutic role in Type -2 Diabetes mellitus, inflammation, different type of cancer, MI and stroke. Decreased levels of adiponectin play important role in development of type 2 diabetes, obesity and cardiovascular disease in humans. Research in persons and rodent models has reliably proven the significant role of adiponectin as an physiological regulator of insulin sensitivity, glucose, and lipid metabolism as well as cardiovascular homeostasis. Recent studies showed in human and animal models for obesity, diabetes, and atherosclerosis have described on the potential role of adiponectin and adiponectin receptors for these metabolic diseases.

8. SUMMARY
Adipocyte is the main source of Adiponectin production. Adiponectin has beneficial therapeutic role in Type -2 Diabetes mellitus, inflammation and different type of cancer such as OAC, gastric cancer, colon cancer breast cancer and leukaemia. Adiponectin has cardioprotective role in MI and stroke. Neuroprotective role of Adiponectin is also proven in Alzheimer’s disease. Adiponectin produces beneficial effects in eye diseases such as RP, Glaucoma and AMD.

COMPETING INTERESTS
Authors have declared that no competing interests exist.
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