ADIPONECTIN: THE FIRST TWO DECADES

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ARTICLE INFO

Article history
Received 30/06/2014
Available online 12/07/2014

Keywords
Adiponectin, AdipoRs, Obesity, Diabetes Mellitus, Cardiovascular Disease.

ABSTRACT

Adiponectin, an adipocyte derived hormone, is a 244-amino acid polypeptide bearing structural homology to collagen super family and complement C1q. Adiponectin acts as an anti-inflammatory, anti-atherogenic and insulin sensitizing hormone that exerts its actions through its receptors-AdipoR1, AdipoR2 and T-cadherin. AdipoR1 is expressed abundantly in muscle whereas AdipoR2 is predominantly expressed in liver. Circulating in the blood stream in the form of trimers, hexamers and high molecular weight molecules, adiponectin is inversely proportional to obesity, diabetes mellitus and other insulin resistant states. Adiponectin lowers plasma free fatty acid levels by stimulating fatty acid oxidation; thus preventing insulin resistance. It protects vasculature by inhibiting activation of macrophages and foam cell accumulation, increasing endothelial nitric oxide production and reducing platelet aggregation and vasodilatation. Hypoadiponectinemia, besides causing metabolic derangement, may also pose risk for the development of coronary artery disease, non-alcoholic fatty liver disease, and a wide array of cancers. Perusal of the available literature shows distinct potential of adiponectin as a suitable therapeutic agent to increase adiponectin concentration by upregulation of plasma concentration and AdipoRs or by development of AdipoRs agonists as well as administration of human recombinant adiponectin, required for the effective treatment of obesity-related diseases, ranging from metabolic syndrome to malignancies.

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Please cite this article in press as Priyanka Sharma et al. Adiponectin: The First Two Decades. Indo American Journal of Pharmaceutical Research.2014;4(06).

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INTRODUCTION

Adiponectin, secreted predominantly by white adipose tissue (WAT), is also known as gelatin-binding protein-28 (gbp28), AdipoQ, adipocyte complement-related protein (Acrp30), or apM1.

Historical perspectives

Lodish et al, in 1995, identified a secretory protein from murine 3T3-L1 adipocytes and named it adipocyte complement-related protein of 30 kDa (Acrp30) [1]. It forms large homo-oligomers that undergo a series of posttranslational modifications. It was cloned using the mRNA differential display technique, and called AdipoQ. The human adiponectin gene was cloned through systematic sequencing of an adipose-tissue library [2]. It was named as adiponectin by a group of researchers at Osaka University in 1999, who isolated the human adipose-specific transcript, the apM1 gene product which came out to be a soluble matrix protein. It became a distinctive protein among the adipokines with the plasma concentration of adiponectin decreasing upon accumulation of visceral fat [3]. Expression cloning technique enabled isolation of complementary DNAs encoding the adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) in 2003 [4]. Lodish and colleagues (2004) identified adiponectin-binding proteins through retroviral expression of a C2C12 myoblast cDNA library in Ba/F3 cells. Subsequent DNA analysis revealed T-cadherin as an adiponectin-binding protein [5]. Ever since its initial discovery, adiponectin has inspired widespread interest. Research into this hormone has revealed it to have insulin-sensitizing, anti-inflammatory and cardioprotective roles.

Adipose tissue as an endocrine organ

Traditionally, adipose tissue- the largest endocrine organ of the body was considered as a storage depot of fatty acids having passive functions. Over the last few years, studies have revealed that adipose tissue has a central role in lipid and glucose metabolism and secretes a large number of hormones and cytokines, e.g. angiotensinogen, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), adiponectin, leptin, and plasminogen activator inhibitor-1 (PAI-1) [6]. The fact that there exists a close relationship between an increased quantity of visceral fat, metabolic disturbances and cardiovascular diseases, and the unique anatomical relation to the hepatic portal circulation pointed towards the endocrine functions of this visceral fat depot whose primary functions are insulation and cushioning of the body, storage of free fatty acids (FFAs) after food intake and subsequent release of FFAs during the fasting state to maintain sufficient energy status. During the postprandial phase, FFAs are taken up from the blood in adipose tissue after hydrolysis of triglycerides (TG) from triglyceride-rich lipoproteins (very low-density lipoprotein-cholesterol (VLDL-C), chylomicrons and their remnants) by lipoprotein lipase (LPL). Mobilization of this reserve occurs by hydrolysis of adipocyte TG by hormone sensitive lipase (HSL). Insulin is the main regulator of adipocyte fat content, since it is both a potent activator of LPL, thereby enhancing FFA uptake and triglyceride synthesis in adipocytes [7].

Adipose tissue produces a wide range of hormones and cytokines, known as adipokines (Figure 1), involved in glucose metabolism (e.g. adiponectin, resistin), lipid metabolism (e.g. cholesteryl ester transfer protein, CETP), inflammation (e.g. TNF-α, IL-6), coagulation (e.g. PAI-1), blood pressure (e.g. angiotensinogen, angiotensin II), and feeding behaviour (e.g. leptin) thus affecting metabolism and functions of many organs and tissues including muscle, liver, vasculature, and brain.

![Figure 1: Adipocytokine.](image)

The source of these adipokines is either the adipocytes themselves or the stromal vascular fraction within adipose tissue, comprising preadipocytes, endothelial cells, fibroblasts, leukocytes and macrophages [8]. Plasma adipokine levels elevate with an increase in adipose tissue and adipocyte volume, except for plasma adiponectin which decreases in obesity. It was observed that the total absence of adipose tissue in homozygous peroxisome proliferator-activated receptor gamma (PPAR-γ) knock-out mice resulted in failure to thrive, thus suggesting the essential role of adipose tissue. Thus, adipose tissue has presumably acquired an intermediary role between nutritional status and essential body functions such as feeding behaviour, growth, metabolism, and even fertility [9, 10].

Adiponectin

Adiponectin, a 30-kDa complement C1q-related protein, is the most abundant gene product secreted by fat cells [2] and is a key regulator of insulin sensitivity and inflammation [11]. The gene for adiponectin is located on human chromosome 3q27, a region identified as a susceptibility locus for the metabolic syndrome and type 2 diabetes in whites [12]. Adiponectin is a 244-amino acid protein that circulates in human plasma as a homopolymer or as full-length adiponectin (fAd or Acrp30) that comprises up to 18
monomeric units. It has an N-terminal region with high structural homology to collagen VIII, X, and complement C1q and a C-terminal globular domain region that resembles the trimeric topology of tumor necrosis factor [13] (Figure 2).

Acrp30 is highly abundant in the circulation, with plasma concentrations in healthy humans of 10g/mL, and accounts for 0.01% of total plasma protein. At least 3 distinct and stable isoforms of Acrp30 have been isolated from Escherichia coli or cultured mammalian cells in both mouse and human serum [14]. Although most active adiponectin appears to exist in the form of full-length or high molecular weight (HMW) adiponectin in plasma, low molecular weight (LMW) or trimeric complexes are also present in low abundance [14]. Proteolytic cleavage of the full-length molecule at amino acid 110 produces globular adiponectin (gAd orgAcrp30), which is thought to have enhanced potency. Oligomerization and posttranslational modifications (i.e., glycosylation) of adiponectin are apparently critical for binding to its receptors and determining biological activity. Thus, the different forms of adiponectin (i.e., trimeric versus hexameric and HMW, or globular versus full-length) show distinct biological effects through differential activation of downstream signaling pathways. Recent evidence suggests that the HMW adiponectin complex may be the active form of the hormone, but this remains to be confirmed. HMW adiponectin correlates more strongly with post load glucose concentrations than does total adiponectin, and changes in the ratio of HMW to total adiponectin are closely associated with improvements in insulin sensitivity during thiazolidinedione treatment in humans, whereas changes in total adiponectin concentrations are not [15].

**Regulation of adiponectin production**

Different multimeric forms (3, 6, and 18–36 subunits) of adiponectin exist stably in plasma, with little or no inter-conversion between the forms. Various assembling factors, such as the protein folding enzymes and redox environment in the endoplasmic reticulum (ER), are critical for the complex structure with the associated multimerization of adiponectin e.g., trimeric form is predominantly seen in human cerebrospinal fluid [16]. An interesting sexual dimorphism is observed in adiponectin multimer composition in mice and humans. HMW (18–36 multimers) adiponectin is generally more abundant in females, both in proportion as well as absolute amounts, while males show predominance of trimers or hexamers [14]. The circulating levels and secretion rate of adiponectin in humans are markedly reduced in obesity and insulin resistance [17]. Though the relationship between plasma insulin and adiponectin levels in humans is well established, the exact role of insulin in adiponectin biosynthesis and secretion remains debatable. It has been suggested that insulin suppresses the activity of FoxO1 (member of forkhead box O transcription factor family), a transrepressor (suppressor) of PPARγ, which is an inducer of adiponectin biosynthesis. However, the well acknowledged negative correlation between insulin and adiponectin levels seen in vivo needs to be explained. Multiple transcription factors have been reported to direct adiponectin expression in obesity and type 2 diabetes mellitus. The adiponectin promoter contains binding elements for C/EBP α, PPAR γ, SREBPs (sterol response element binding protein) and LRH-1 (liver receptor homolog-1). Adiponectin gene transcription is activated by the formation of complex of FoxO1 with C/EBP α which, in turn is facilitated by SirT1 (Sirtuin, silent mating type information regulation 2 homolog). The complex formation is impaired in dietary or genetic type 2 diabetes mouse models, due to suppression of SirT1.

In comparison, FoxO1 binds to PPAR γ, blocking its occupancy on the promoter of target genes, and it is this interaction which is prevented by insulin signaling. Similar mechanism of transcriptional repression of adiponectin is observed in case of iron overload. Other signaling pathways leading to transcriptional inactivation of adiponectin include the 5-hydroxytryptamine 2A receptor and CREB – ATF3 [18]. While these transcriptional regulatory steps are unquestionably important, it is not clear whether they present rate-limiting control over adiponectin protein release from adipocytes or whether primary control on adiponectin levels are exerted at the level of post-translational handling of the protein in the secretory pathway. TNFα suppresses the expression levels of activators involved in promoting adiponectin gene expression, such as PPARγ and Super Conserved Receptors Expressed mainly in Brain (SREBs); this action may be mediated by c-Jun N-terminal kinase (JNK), which phosphorylates PPARγ and decreases its DNA-
binding activity. TNFα also suppresses the transcription of the adiponectin gene by inhibiting transcripational Sp1-binding activity while IL-6 suppresses levels of adiponectin transcript as well as its secretion by 3T3-L1 adipocytes, in vitro [19].

This post-translational regulation of adiponectin involves its folding and processing in the ER, as well as its trafficking through the Golgi. ER chaperones ERP44 and Ero1 α are crucial for assembly of high-order adiponectin complexes. Residue cysteine-39 is required for the covalent interaction with ERP44, and Ero1 α mediates their dissociation. DsbA-L (disulphide-bond A oxidoreductase-like protein also known as glutathione transferase which is an adiponectin-interactive protein) acts as an another key regulator of adiponectin multimerization. The increasing amount of evidence suggests the existence of specialized subcategories of secretory vesicles for different cargo molecules produced by the adipocyte. Adiponectin vesicles are distinct from leptin containing vesicles, and concentrated in “Golgi-localizing γ-adaptin ear homology ARF-binding protein” (GGA)-1 coated vesicles [20].

Oxidative stress has been reported to enhance insulin resistance by simultaneous inhibition of the expression of adiponectin. This may explain decrease in plasma adiponectin in obesity, which is associated with increased oxidative stress in adipose tissue, even though the exact mechanism underlying this regulation is imprecise. Obesity results in ER stress, which has been in concurrence with the inhibition of adiponectin production in adipose tissue. In cultured adipocytes, stimulation of increased mitochondrial biogenesis (via adenosinoviral overexpression of nuclear respiratory factor-1) increased adiponectin synthesis, whereas impaired mitochondrial function decreased it via activation of JNK and following induction of ATF3. During oxidative stress, the expression of adiponectin mRNA is inhibited by glucose oxidase. H2O2 also reduced the expression of adiponectin via the Akt and JAK/STAT pathway. Increased fat mass has been associated with the decreased levels of adiponectin owing to the resultant hypoxic microenvironment. The inhibition of adiponectin transcription, observed in obesity, is mediated by insulin-like growth factor binding protein-3 (IGFBP-3) via hypoxia inducible factor-1 (HIF-1α) dependent pathway [21].

Adiponectin Receptors

Adiponectin receptors (AdipoRs)-1 and -2 were first cloned in 2003. These two adiponectin receptors, discrete from the topology of G-protein-coupled receptors, possess seven-transmembrane domains. The AdipoR1 gene encodes for a 375-amino-acid protein with an estimated molecular mass of 42.4 kDa, whereas AdipoR2 encodes for a 311-amino-acid protein of 35.4 kDa (Table 1). Suppression or expression of AdipoR1 and AdipoR2 revealed that AdipoR1 has high affinity for globular adiponectin and low affinity receptor for full-length adiponectin, whereas AdipoR2 shows an intermediate affinity for both. Overexpression and siRNA knockdown of adipoR1 and R2 revealed their important roles in cellular binding of adiponectin, as well as the downstream AMPK and PPAR α signaling. Hence, the regulation of AdipoR1 and AdipoR2 is important for facilitating essential physiological functions. AdipoR1 mRNA is demonstrable in skeletal muscle, spleen, lung, heart, kidney, and liver. AdipoR2 is expressed in liver, but also evident in heart, lung, skeletal muscle, and kidney [4]. AdipoR1 suppresses the gluconeogenic and lipogenic gene expression by modulating the activation of AMPK, although the involvement of AMPK in this process in the liver is debatable. AdipoR2 stimulates glucose uptake and fatty acid oxidation and reduces inflammation and oxidative stress by induction of PPARα activity [22]. In addition, APPL1, Ca2+ and SIRT1 are emerging downstream effectors of the AdipoRs.

The mainstream physiological effects of adiponectin including insulin sensitizing, anti-inflammatory and anti-apoptotic effects can be explained by the very potent ceramide lowering effects of adiponectin and its receptors on sphingolipids. Ceramide impairs insulin sensitivity in peripheral tissues by blocking the plasma membrane translocation and promoting dephosphorylation of Akt/PKB, an indispensable effector of insulin signaling. The binding of adiponectin with AdipoRs either activate an intrinsic, or associate with a cellular protein with ceramidase activity that converts ceramides into sphingosines [23]. Furthermore, T-cadherin seems to play an important role as an adiponectin binding protein, especially for high-order multimers. T-cadherin is a unique cadherin molecule that lacks the transmembrane and cytoplasmic domains and is bound to the surface membrane through a glycosylphosphatidylinositol (GPI) anchor. T-cadherin was observed to preferentially bind hexameric and HMW multimeric forms of adiponectin, which is quite significant for the cardioprotective action of adiponectin [20].

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<tr>
<th>Table 1: Adiponectin receptors.</th>
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<tr>
<td><strong>Primary structure</strong></td>
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<tr>
<td>Molecular Mass</td>
</tr>
<tr>
<td>42.4 kDa</td>
</tr>
<tr>
<td>Ligand affinity</td>
</tr>
<tr>
<td>↓affinity for full length adiponectin</td>
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<tr>
<td>Signaling molecule</td>
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<td>Metabolic significance</td>
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Metabolic Significance of Adiponectin

**Adipose tissue:**

Adiponectin plays important roles in selective adipogenesis and fat storage in adipose tissue besides increasing glucose uptake. Healthy fat expansion is an essential metabolic cornerstone that fends off the hallmarks of the metabolic
syndrome, and adiponectin is an integral mediator of this process. In addition, adiponectin reduces systemic inflammation. The manipulation of local adipose tissue ceramides is also a likely mechanism by which adiponectin achieves systemically beneficial effects through local action at the level of the adipocyte [20].

**Energy homeostasis:**

Adiponectin also has a central action in regulating energy homeostasis by enhancing AMP-activated protein kinase activity in the arcuate hypothalamus (ARH) via its receptor AdipoR1 by stimulating food intake. Adiponectin also decreases energy expenditure. Fasting results in an increase in serum and cerebrospinal fluid levels of adiponectin and expression of AdipoR1 in the ARH, which is countered by re-feeding. Therefore, adiponectin stimulates food intake and decreases energy expenditure during fasting through its effects in the central nervous system [24].

**Liver:**

Adiponectin displays its insulin sensitizing, anti-fibrogenic, and anti-inflammatory properties by acting on hepatocytes, hepatic stellate cells, and hepatic macrophages (Kupffer cells), respectively. In the liver, adiponectin decreases gluconeogenesis and FFA influx, and increases FFA oxidation through the activation of the AMPK and PPAR-α pathways and inhibition of toll-like receptor-4 mediated signaling. In addition, adiponectin exerts its antifibrogenicity mainly through down-regulation of the expression of aldehyde oxidase, TGF and CTGF, while anti-inflammatory action is mediated through suppression of TNF-α and other proinflammatory cytokines and induction of anti-inflammatory cytokines, such as IL-10 [25].

**Skeletal muscle:**

Adiponectin increases fatty acid oxidation in skeletal muscle, one of the major site for nutrient and energy disposal, through its key downstream mediator –AMPK which inhibits acetyl-CoA carboxylase, increases the expression of acetyl-CoA oxidase, UCP-2and-3, and activates p38MAPK and PPARα [20].

**Cardiovascular system:**

Adiponectin has been documented as a powerful biomarker for cardiovascular diseases with adiponectin levels being inversely correlated with the risk of coronary heart disease (CHD). Epidemiological data also suggests that adiponectin might improve lipoprotein/cholesterol metabolism and protects against coronary lesions. Interestingly, T-cadherin has a critical role in the binding of adiponectin to cardiomyocytes. The inherent ceramidase activity of AdipoR1 and AdipoR2 also mediate the potent pro-survival and anti-lipotoxic actions of adiponectin which has been reported to ameliorate caspase-8 induced-apoptosis in cardiomyocytes on treatment with sphingosine-1-phosphate (S1P) [26].

**Endothelium:**

Adiponectin improves the endothelial function, both under normal and metabolically challenging conditions. Oxidative stress and reduced nitric oxide bioavailability are found as culprits for impairment of endothelial function under conditions of cellular stress. Adiponectin alleviates oxidative stress by activating signalling cascades, such as AMPK–eNOS and the cAMP–PKA module [20].

**Kidneys:**

Adiponectin reduces oxidative stress and albumin permeability in podocyte. After caspase 8-mediated podocyte ablation, over-expression of adiponectin ameliorates renal interstitial fibrosis and promotes recovery of podocytes and kidney function. Epidemiologically, adiponectin positively correlates with the severity of proteinuria in patients with chronic kidney disease [27].

**Pancreas:**

The insulin-producing pancreatic β cells shows marked expression of adiponectin receptors. Studies have proposed that adiponectin promotes glucose-stimulated insulin secretion (GSIS) via PPARγ, the MEK–Erk, and PI3K–Akt signalling axis. It also prevents apoptosis, and enhances the viability of β cells by activation of Erk and Akt pathway. In addition, the adipoR1/2 mediated ceramides lowering effects also play a central role in all these processes, as seen in cardiomyocytes [23,28].

**Macrophages:**

Adiponectin may also exert its anti-inflammatory effects by acting directly on the macrophage. Experimental evidence suggested a shift in the macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 category under the influence of adiponectin leading to reduction in the M1 macrophage population which partially overlaps with those decreased by the autocrine action of adiponectin on adipocyte secretion. Adiponectin also stimulates the production of IL-6 from macrophages which, in turn increases hepatic IRS-2 expression and the potency of insulin signaling [20].

**Cancer cells:**

Epidemiological studies have established the strong association between low circulating adiponectin level and a variety of cancers including endometrial, breast, colon, and renal cancers. Adiponectin was also suggested as a potential
biomarker for haematological malignancies, such as leukemia, lymphoma, myeloma, and B-cell chronic lymphocytic leukemia. Although the underlying mechanism is intricate and needs further studies, it has been proposed that the adipoR-mediated cellular signaling, as well as the pleiotropic effects on insulin sensitivity, inflammation, and angiogenesis may influence the action of adiponectin on cancer. At the cellular level, elevated adiponectin with its potent pro-angiogenic and pro-mitogenic effects owing to increase in local sphingosine concentration by inherent ceramidase activity of AdipoRs has been linked to increased tumor growth [29].

Clinical Correlations of Adiponectin

Non-alcoholic fatty liver disease (NAFLD):

NAFLD, characterized by insulin resistance, is commonly associated with obesity and type 2 diabetes. Hypoadiponectinaemia might be a risk factor for NAFLD. Serum adiponectin level has been found to be significantly lower in the early stage NAFLD, which attenuates liver inflammation and fibrosis, possibly by reduction in hepatic and insulin resistance. Increased serum level of adiponectin has been observed in liver cirrhosis which correlates with the clinical stage of the disease. Expression of AdipoR1/R2 is significantly decreased in NAFLD leading to decreased AMPKα1/α2 and PPARα activities. This, in turn, results in increased FA synthesis and decreased FA oxidation, and thus contributing towards the progression of NAFLD [30].

Cardiovascular diseases:

Cardiovascular diseases are associated with obesity and other metabolic disorders. The potential role of adiponectin in cardiovascular diseases has been observed in patients with coronary artery diseases (CAD), which present with lower levels of adiponectin irrespective of ethnic group and the severity of hypoadiponectinemia correlates to coronary lesions. Intriguingly, HWM adiponectin has been linked to CAD, perhaps due to the functional priorities and tissue specificity shown by the adiponectin isoforms. Hence, plasma adiponectin levels can be helpful in identifying patients susceptible to CAD [26]. In addition, adiponectin favours reshaping of myocardial infarction during acute injury. Adiponectin inhibits adhesion of monocytes to human aortic endothelial cells (HAECs) facilitated by TNF-α by reducing the expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1) on the surface of HAECs. The transformation of human monocyte-derived macrophages into foam cells is also prevented by adiponectin by inhibiting the class A macrophage scavenger receptor. Adiponectin also binds to collagen (I, III and V) present in vascular walls but only in injured vessels. Some findings suggest a role of adiponectin in atherosclerosis by inhibiting binding of LDL to biglycan, which is a vascular proteoglycan. This ultimately decreases lipid accumulation in the subendothelial space, the cause of atherosclerotic plaque formation [30]. Furthermore, single nucleotide polymorphisms (SNPs) at position +276 in the adiponectin gene have also been linked with CAD. Adiponectin has been shown to activate both the AMPK and PPAR-α pathway and to increase the expression of AdipoR1 in CAD. Despite elevated adiponectin levels, the PPAR-α/AMPK pathway is suppressed in patients with coronary heart failure, leading to decreased expression of AdipoR1 and enzymes involved in fatty acid and glucose metabolism. All these observations point towards the existence of a state of adiponectin resistance in this disease [31]. Cardiac myocytes and heart tissue express adiponectin receptors which are decreased in hyperinsulinemia related to obesity, via the PI3K/Akt and FoxO1 pathway. A decrease in AdipoR1 also decreases AMPK-dependent angiogenic response, and the down regulation of the adiponectin receptor pathway may be causally related to decrease in cardiovascular function [32].

Obesity and type 2 diabetes:

Adiponectin serves as a negative marker of metabolic syndrome as obesity is associated with decreased levels of adiponectin. Furthermore, the expression of the receptors AdipoR1 and AdipoR2 decline by 30% in the subcutaneous fat of obese individuals, which revert back to normal after weight loss. It is by now well established that adiponectin plays an important role in type 2 diabetes, hypertension, multiple sclerosis (MS), and the dyslipidemias. The most significant role played by adiponectin is that of its insulin sensitizing effect with high levels of adiponectin in plasma minimizing the risk of developing type 2 diabetes. Additionally, adiponectin has a negative correlation with blood glucose and insulin levels. Total adiponectin, HMW adiponectin, and the HMW ratio all are inversely related to homeostasis model assessment (HOMA) insulin resistance index. The HMW ratio is considered to be a better indicator of insulin resistance than total plasma adiponectin levels, due to the fact that mutations, which affect the multimerization of adiponectin, render a person more susceptible to diabetes. All studies on the putative role of adiponectin in insulin resistance and type 2 diabetes suggest that decreased levels of adiponectin cause increased susceptibility to these disorders [30].

Cancer:

A good deal of compelling evidence has shown that circulating adiponectin levels are inversely associated with the risk of malignancies linked to obesity and insulin resistance, including endometrial cancer, postmenopausal breast cancer, leukemia, and colon, gastric, and prostate cancer. Adiponectin modulates several intracellular signaling pathways and stimulates AMPK, PPARγ, and MAPK in classical insulin target organs such as the liver and skeletal muscles. Adiponectin inhibits cancer progression and invasion through its receptors (AdipoR1, AdipoR2). Several studies have revealed that individuals with hypoadiponectinemia could be at a higher risk of developing tumors, including those suffering from polycystic ovary syndrome (PCOS). The mechanism by which adiponectin and its receptors reduces cancer risk is probably indirectly through reduction in hyperinsulinemia as well as directly on tumor cells [29]. These results have led to the hypothesis that impaired adiponectin action is a hallmark of obesity linked diseases, with hypoadiponectinemia and down regulation of adiponectin receptors (Table 2). Impaired adiponectin actions via AdipoR1 in muscle,
liver and macrophages may cause type 2 diabetes and atherosclerosis. Impaired adiponectin actions via AdipoR1 and AdipoR2 in liver and cancer cell may cause fatty liver and cancer. Impaired adiponectin actions via AdipoR2 in endothelial cell may cause atherosclerosis.

Table 2: Implications of hypoadiponectinemia.

<table>
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<th>• Insulin resistance</th>
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<tr>
<td>• Obesity</td>
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<tr>
<td>• Type 2 diabetes mellitus</td>
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<tr>
<td>• Metabolic syndrome</td>
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<tr>
<td>• NASH/NAFLD</td>
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<tr>
<td>• CAD</td>
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<td>• Cancer</td>
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CONCLUSIONS

Obesity and the associated comorbidities warrant urgent development of specific therapeutics agents [33]. Hypoadiponectinemia seems to precede the development of obesity-related diseases such as diabetes and cardiovascular diseases. To offset this situation, the drugs altering the levels of adiponectin as well as administration of recombinant adiponectin may prove useful in the treatment of NAFLD, cardiovascular disease, type 2 diabetes, and in prevention of various cancers. In this respect, regulation of adiponectin levels and its actions through expression of adiponectin receptors seems to be a promising therapeutic target. For example, increase in expression of both AdipoR1 and AdipoR2 resulting from PPARα activation by its agonist, Wy-14,643 clearly reveals the potential of AdipoR agonist as a novel and promising therapeutic candidate [32]. Future research focusing on elucidation of mechanism of action of AdipoRs may prove helpful in better understanding of molecular mechanisms of adiponectin actions in various metabolic disorders. Even detailed studies on the interaction of two AdipoRs with different adiponectin complexes in circulation will further improve our current understanding.

However, many questions need to be addressed before adiponectin can be used as a potent therapeutic target. For example, the presence of different oligomeric isoforms and production sites of adiponectin, the sexual dimorphism in adiponectin concentration and oligomeric isoform distribution, and the identification of multiple receptors with differing affinity for adiponectin oligomers, add to the complexity of adiponectin actions across an array of physiological processes and diseases. Nevertheless, studies in animal models of diabetes, obesity, and atherosclerosis clearly demonstrated the therapeutic potential of adiponectin in treatment of these disease states. The bottom line is that adiponectin or adiponectin receptor agonists are promising candidates in the context of potentially enhancing our pharmacologic armamentarium for treating obesity-related diseases in near future.

Author’s Statements

Competing interest

The authors declare no conflict of interest.

REFERENCES


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