The effect of Adiponectin, in diabetes, obesity, and atherosclerosis and the AMPK pathway, the PPAR pathway, as potential therapeutics on Cancer, and Metabolic disorders (Part one)

By Dr. Zelalem Kiros Bitsue, MD, PhD
United States of Africa Health Organization "US-AHO",

Abstract

Adiponectin is a white and brown adipose tissue hormone, also known as gelatin-binding protein-28 (GBP28), AdipoQ, adipocyte complement-related protein (ACRP30), or apM1. Adiponectin is an insulin sensitizing hormone that exerts its action through its receptors AdipoR1, AdipoR2, and T-cadherin.

AdipoR1 is expressed abundantly in muscle, whereas AdipoR2 is predominantly expressed in the liver.

Recent studies show that a small-molecule activator of the adiponectin receptor, AdipoRon, improves glucose tolerance and ameliorates insulin resistance in mice fed a high-fat diet; furthermore, AdipoRon improves metabolic parameters and prolongs 106 | Ruan and Dong life span in db/db mice, a genetic mouse model for diabetes

Studies in animal models of diabetes, obesity, and atherosclerosis clearly demonstrated that adiponectin can indeed have beneficial effects on those disease states.

Recent studies on the genetic mutation of adiponectin gene in human subjects and the KO mice clearly demonstrate that adiponectin may play a key role in the prevention of metabolic syndrome.

In this article, I discuss Structure and secretion of adiponectin, Adiponectin receptor signaling, APPL2 protein, The AMPK pathway, The PPAR pathway, and Physiological and Pathophysiological Regulation of Plasma Adiponectin

Key Word: Adiponectin, Adiponectin receptor signaling, The AMPK pathway, The PPAR pathway, Metabolic disorder, and Cancer

The Table of Contents

1. Introduction

The prevalence of obesity has increased substantially over the previous decades not only in industrialized countries but all over the world; recent data from several Western countries indicate that only one third of the population is normal weight, and approximately one third is obese (1),(2),(3). There is also accumulating evidence that excess body weight constitutes an established risk factor for colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer, and esophageal adenocarcinoma (EA) (3). It is believed that the metabolic changes associated with excess weight, and in particular central obesity, could lead to a dysfunctional adipose tissue causing insulin resistance, chronic inflammation, and abnormal secretion of adipocytokines (4),(5),(6),(7),(8). The main underlying mechanisms that link obesity to cancer development and progression include: 1) abnormalities of insulin resistance and the IGF-I system; 2) the impact of adiposity on the biosynthesis and bioavailability of endogenous sex hormones; 3) obesity-induced low-grade chronic systemic inflammation; and 4) alterations in the levels of adipocyte-derived factors (9),(4),(8). Adiponectin, a hormone, exerts multiple biological effects throughout the body mediated by the specific receptors AdipoR1, AdipoR2, and T-cadherin (10). In 1995, Lodish et al. identified a secretory protein from murine 3T3-L1 adipocytes and named it adipocyte complement-related protein of 30 kDa (Acrp30). It is a structural homolog to complement factor C1q and to a hibernation-specific protein isolated from the plasma of Siberian chipmunks (11). It forms large homo-oligomers that undergo a series of posttranslational modifications. Using the mRNA differential display technique, it was cloned and called adipoQ. The adipoQ cDNA encodes a polypeptide of 247 amino acids, with a secretory signal sequence at the amino terminus, a collagenous region (Gly-X-Y repeats), and a globular domain (12). The human adiponectin gene was cloned through systematic sequencing of an adipose-tissue library. The apM1 gene encodes a 244 amino acid open reading frame

containing a putative signal sequence repeat (66 amino acids) followed by a cluster of aromatic residues near the C terminus having high local resemblance to collagens X and VIII and complement factor C1q (13). In 2003, a group from Japan isolated complementary DNAs encoding the adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) by expression cloning. These two adiponectin receptors have seven-transmembrane domains, but they are distinct from the topology of G-protein-coupled receptors. 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. Suppression or expression of AdipoR1 and AdipoR2 revealed that AdipoR1 is a high-affinity receptor for globular adiponectin and a low-affinity receptor for full-length adiponectin, whereas AdipoR2 has an intermediate affinity for both (14). 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. The expression of T-cadherin was observed to confer binding of hexameric and HMW multimers but not trimeric adiponectin (10). The physiological role of adiponectin has not yet been fully elucidated, but it is believed that it has the ability to reduce glucose, triglycerides, and free fatty acids and that it plays a major role in the pathogenesis of metabolic syndrome. Metabolic syndrome comprises a cluster of metabolic disorders that give rise to such metabolic risk factors as visceral obesity, insulin resistance, hyperglycaemia, dyslipidaemia, and hypertension. In addition, numerous experimental and clinical observations have shown decreased adiponectin bioactivity in obesity and obesity-related complications, including insulin resistance, diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD).

2. Structure and secretion of adiponectin

Adiponectin is a 30 kDa protein with a C-terminal globular domain and a collagen-like N-terminal domain. The collagen domain allows for trimeric or hexameric formation and other multimeric isoforms before being secreted. A cysteine residue at collagenous rod is an essential mediator of multimeric complexes, which may represent the most biologically active form of the protein. Adiponectin is structurally related to proteins of the complement system (C1q) and tumor necrosis factor alpha (TNF-α), which are prototype members of a growing family of proteins known as CTRPs (C1q/TNF bonds) (15). Adiponectin, a product of the APM1 gene, is a protein composed of 244 amino acids, also known as GBP- 28 (galatin binding protein-28), ADOPOQ and ACRP30. This protein is largely secreted by adipocytes, although it can also be secreted by cardiomyocytes, hepatocytes and placenta at lower concentrations. Its structure is divided into three domains: the N-terminal domain, which has large variation in amino acids between species, the collagen-like domain, and the globular domain of the C-terminal region (16). The secretion of adiponectin is strictly controlled by the retention of protein thiols, so that two molecular endoplasmic reticulum chaperones play a critical role: 44 kDa ER proteins (endoplasmic reticulum protein 44, ERp44) and Ero1-La (endoplasmic reticulum oxidoreductin 1-like alpha), both induced during adipogenesis. ERp44 forms a disulfide bond with adiponectin, which is important for the maturation of trimeric and hexameric proteins of high-, medium- and low-molecular weight in oligomers. It is also involved in the specific intracellular retention of adiponectin, so that the overexpression of ERp44 reduces the secretion of the adipokine. The Ero1-La protein, in turn, is a close partner of ERp44 and is involved in the weakening of the disulfide covalent bond between adiponectin and ERp44 and consequently the release of adiponectin (15).

3. Biosynthesis of adiponectin and receptors

Adiponectin is mainly produced from white adipose tissue and specifically in mature adipocytes. Three major adipose tissue deposits are recognized as producers of this protein: subcutaneous, visceral and perivascular. The concentration of circulating adiponectin in plasma is very high (2 to 30 µg/mL). The plasma levels of this protein in the Japanese population is around 5 to 10 µg/mL, while in *serum* it is lower in Indo-Asians compared to Caucasians (median 3.3 *vs*. 4.9 µg/mL). Women have circulating adiponectin levels approximately 40% higher than men.

Interestingly, visceral fat compartments are largely responsible for the secretion of adiponectin, when compared to subcutaneous deposits. This is of particular interest because of the close association between visceral obesity and metabolic/cardiovascular disease; however, *in vitro* and *in vivo* studies performed in humans have shown that adipocytes with exhausted lipid storage, filled with fatty acids, and located in the intra-abdominal region can inhibit transcription of the adiponectin gene by secreting inflammatory and angiogenic factors, reducing its plasma levels.12 The epicardial fat is also a source of adiponectin. Lower levels are also expressed in the liver, cardiomyocytes, skeletal muscle, colon, salivary gland, placenta and hypophysis, but the contributions of these tissues to the circulating adiponectin is considerably small. Adiponectin can also be detected in breast milk and cerebrospinal fluid, although in low concentrations (17).

The role of adiponectin is mediated by receptors known as adiponectin receptors 1 and 2 (Adipor1 and Aipor2). These receptors have seven transmembrane portions, but are functionally different from the G protein– coupled receptors, particularly because they have opposite polarity (i.e., the N-terminal faces the intracellular compartment). Although in relative proportions, Adipor1 and Adipor2 may vary from tissue to tissue and, in general, are expressed simultaneously (18). An additional cell surface molecule called T-cadherin shows significant affinity for adiponectin. T-cadherin binds to adiponectin, which is not a signaling receptor due to lack of intracellular signaling domains, to confer full cardioprotective potential to the latter.14

Adiponectin works in an autocrine and paracrine manner in the adipose tissue, and in an endocrine manner in distal tissues. The autocrine effects are illustrated by their role in adipocyte differentiation. Induction is greater than 100 times that of adiponectin mRNA during the course of differentiation of adipose cells (19). Similarly, in experiments involving adipocytes overexpressing adiponectin, cell differentiation was accelerated, leading to increased lipid accumulation and insulin-stimulated glucose transport activity in fully differentiated cells. Thus, adiponectin promotes adipocyte differentiation and increased insulin sensitivity (20),(21). Also, recent *in vivo* and *in vitro* studies provided evidence of a regulatory feedback loop by which adiponectin controls its own production and the expression of its receptor. In addition to the regulatory capacity, adiponectin acts as an autocrine and paracrine factor to inhibit the secretion by adipocytes of interleukins 6 and 8, macrophage inflammatory protein 1α/β and monocyte chemotactic protein-1, which, in turn, can inhibit the storage of lipids and insulin sensitivity in adipocytes (21),(22). Adiponectin can also act as an endocrine factor. It has been shown that adiponectin administration leads to a rise in insulin-stimulated tyrosine phosphorylation of insulin receptors in muscle, both for rodents and humans (23). This effect may contribute to the

improvement of insulin sensitivity. According to Bacha et al. (24), adiponectin levels are responsible for 73% of the variation in insulin sensitivity (24).

4. Adiponectin receptor signaling

Adiponectin elicits a number of downstream signaling events. However, no intrinsic protein kinase activity or phosphorylation in response to adiponectin has ever been detected in either Adipo R1 or Adipo R2. Furthermore, replacement of the tyrosine residues within the intracellular N-terminus by site-directed mutagenesis has no impact on adiponectin signaling (25). Thus, the adiponectin receptors are likely transmembrane receptors that undergo conformational change and couple the intracellular domain with other signaling molecules upon extracellular adiponectin binding. Using yeast two-hybrid technology, our laboratory identified APPL1 as the intracellular binding partner of AdipoR1 and AdipoR2 (25). The human Appl1 gene is located in the 3p14.3-21.1 region and encodes a 709-amino acid protein of 78 kDa. Human genetic studies suggest that SNPs and point mutations in the Appl1 coding region correlate with body fat distribution and a high prevalence of diabetes (26),(27). APPL1 is highly hydrophilic with no potential transmembrane region and consisted of multiple structural and functional domains including BAR, PH, PTB, and coiled coil (CC) (28),(29). APPL1 directly binds to the intracellular domains of AdipoR1 and AdipoR2 via its C-terminal PTB and CC domains, thereby mediating the actions of adiponectin in the regulation of energy metabolism and insulin sensitivity. In cultured skeletal muscle cells, suppression of APPL1 expression diminished adiponectin-induced glucose uptake and GLUT4 translocation (25). On the other hand, overexpression of APPL1 enhanced the stimulatory actions of adiponectin in glucose metabolism in muscle (25). Rab5, a GTPase downstream of APPL1, plays an important role in APPL1-mediated adiponectin signaling (25). The major action of adiponectin on lipid metabolism is to promote fatty acid oxidation, a process in which AMPK and acetyl CoA carboxylase (ACC) play a critical role. Research in our laboratory revealed the significance and detailed mechanisms by which APPL1-mediated signaling activates AMPK (30),(31). Upon adiponectin stimulation, APPL1 binds to protein phosphatase 2A (PP2A) and protein kinase Cz (PKCz), thereby activating PP2A and inactivating PKCz via dephosphorylation. The inactivation of PKCz results in the dephosphorylation of Ser307 on liver kinase B1 (LKB1), allowing LKB1 to translocate from nucleus to cytoplasm and activate AMPK (Deepa et al., 2011). In addition to the AMPK pathway, we further demonstrated that APPL1 also mediates adiponectin-induced activation of the p38 MAPK pathway (25). and investigated its impact on the anti-inflammatory actions of adiponectin (32). We show that upon induction of adiponectin, APPL1 tethers p38 MAPK together with its upstream activating kinases including transforming growth factor-b activated kinase 1 (TAK1) and mitogen-activated protein kinase kinase 3 (MKK3), thereby expediting the phosphorylation of keyenzymes of this pathway (32). Interestingly, the action of APPL1 on p38 MAPK pathway is specific to adiponectin, whereas its impact on TNF-a-induced p38 MAPK activation is limited (32). We further demonstrated the in vivo involvement of APPL1 in mediating the actions of adiponectin. Whole-body knockout of APPL1 impairs adiponectin signaling and results in insulin resistance in major insulin target tissues (33). Subsequent studies by several laboratories further corroborated that APPL1 functions downstream of adiponectin in various tissues and cell types. (34), reported that in cultured HUVEC cells, APPL1 binds to the cytoplasmic tails of AdipoR1 and AdipoR2 in response to adiponectin, thereby activating AMPK and eNOS and resulting in the production of

NO. APPL1 overexpression potentiates insulin-stimulated AKT signaling and suppresses hepatic gluconeogenesis, whereas knocking downAPPL1 attenuates insulin-stimulated AKT phosphorylation (35),(36), showed that adiponectin treatment blocks IL-18-induced endothelial cell death by activating AMPK, which inhibits IKK/NF-kB/PTENtriggered apoptosis. (37), reported that binding of APPL1 to AdipoR1 mediates adiponectin-induced AMPK activation in cardiac myocytes. (38), demonstrated that injection of adiponectin into the third ventricle triggers interactions of APPL1 with AdipoR1 and AdipoR2, and that the insulin- and leptin-sensitizing actionsofadiponectin aremediated throughAdipoR1butnotAdipoR2.

5. APPL2 protein

APPL2 is an isoform of APPL1 and shares 54%homology in amino acid sequence with APPL1 protein (39),(40). Similar to APPL1, APPL2 has an N-terminal BAR domain, central PH domain, and C-terminal PTB domain. APPL2 mediates FSH signal transduction by binding to APPL1 via their respective BAR domains, which results in the formation of the FSH receptor– APPL1–AKT2 complex (41). Notably, APPL2 does not directly interact with AKT2 (41),(42). Research in our laboratory revealed that APPL2 negatively modulates adiponectin signaling in skeletal muscle cells (40). APPL2 directly binds to AdipoR1 or AdipoR2 via its BAR domain, thereby preventing the interaction of APPL1 with AdipoRs. Thus, APPL2 blocks adiponectin signaling through AdipoR1 and AdipoR2 by competitive inhibition of APPL1. In addition, APPL2 heterodimerizes with APPL1, thereby reducing the binding ofAPPL1to AdipoRs andimpairing the actions of adiponectin. Interestingly, adiponectin modulates the dissociation of the APPL1/APPL2 heterodimers, which can also be triggered by insulin and metformin (40). Because APPL1 and APPL2 exert opposite actions in mediating adiponectin signaling, we originally proposed the 'Yin and Yang' modulatory concept (40). Adiponectin circulates at a high concentration without major Fluctuations (43). In moving forward, it is important to address the following questions: (i) Does adiponectin bind to its receptors continuously? (ii) If the binding is relatively continuous, the intracellular regulatory mechanisms become the key checkpoints in modulating adiponectin signaling transduction and action. Then what are the regulatory mechanisms? The Yin and Yang modulatory concept involving APPL1/APPL2 offers a detailed molecular mechanism by which adiponectin regulates lipid and carbohydrate metabolism. Consistent with the Yin-Yang theory, mice with muscle-specific APPL2 ablation or overexpression show respective enhanced or impaired insulin sensitivity, insulin-stimulated GLUT4 translocation, and glucose uptake in skeletal muscle (44). The opposing roles of APPL1 and APPL2 were also observed in the regulation of the PI3K/AKT/NF-kB pathway in macrophages (45).

6. The AMPK pathway

AMPK, a protein kinase regulated by AMP, is a widely recognized cellular sensor for metabolic state. In skeletal muscle, both fulllength adiponectin and the globular domain have been shown to trigger AMPK phosphorylation, leading to AMPK activation (46),(47). We found that APPL1 plays a key role in adiponectin-mediated AMPK phosphorylation (15),(30),(31). In primary culture of skeletal muscle isolated from obese individuals or patients with type 2 diabetes, AMPK phosphorylation in response to adiponectin is greatly reduced, demonstrating that impaired signaling downstream of the adiponectin receptor may impair the actions of adiponectin or cause adiponectin resistance (48). Adiponectin has also been shown to induce

AMPK phosphorylation in the liver (49). Notably, recent reports suggest a limited role of the AMPK pathway in the regulation of gluconeogenesis (50). At present, however, no other mechanisms, i.e. non-AMPK pathways, have been shown to mediate the effects of adiponectin on gluconeogenesis in the liver.

7. The PPAR pathway

Another key transcription factor in metabolic regulation is PPAR-a. In skeletal muscle, adiponectin drastically increases the expression and activity of PPAR-a, which in turn up regulates acetyl CoA oxidase (ACO) and uncoupling proteins (UCPs), thereby promoting fatty acid oxidation and energy expenditure (51). In the liver, adiponectin upregulates several PPAR-a target genes including CD36, which modulates hepatic fatty acid uptake and metabolism (Yamauchi et al., 2001), and ACO, which regulates fatty acid oxidation (52). In addition, adiponectin has been shown to increase hepatic glucose uptake via PPAR-a, thereby improving hepatic insulin sensitivity (53). Thiazolidinedione (TZD) class of PPAR-g ligands upregulates adiponectin expression in adipocytes (54),(55). The effect of TZDs on improving glucose tolerance is impaired in adiponectin-deficient mice, indicating that adiponectin mediates, at least in part, the insulin-sensitizing actions of TZDs (56). The expression of PPAR-g is markedly increased in 3T3-L1 cells overexpressing adiponectin, which is associated with enhanced adipocyte differentiation (Fu et al., 2005), indicating that adiponectin promotes the PPAR-g pathway, thereby activating a positive feed-back loop that increases adiponectin expression and adipocyte differentiation.

8. Other adiponectin signaling pathways

In addition to the pathways discussed above, adiponectin has been shown to induce calcium release from sarcoplasmic reticulum in myocytes or promote calcium influx, thereby activating Ca2+ /calmodulin-dependent protein kinase kinase (CaMKK-b) and AMPK,which results in activation of SIRT1 and PPAR-aand increase of mitochondria biogenesis (30),(57). In addition, ceramide-mediated pathways also have been implicated in mediating the actions of adiponectin. (58), reported that both AdipoR1 and AdipoR2 are associated with ceramidase activities, which, upon adiponectin binding, potently enhances ceramides conversion to S1P, a process that is independent of AMPK. Administration of recombinant adiponectin in leptin-deficient Lepob/ob mice markedly reduced hepatic ceramide content, which is associated with increased insulin sensitivity (58). The p38 MAPK pathway also plays a role in adiponectin signaling (15),(32). Thus, multiple cellular pathways likely mediate the pleiotropic effects of adiponectin in various insulin target tissues, depending on contexts

9. Cross talks with the insulin signaling pathway

Several groups independently reported the insulin-sensitizing actions of adiponectin in 2001 (59),(60),(61). Overexpression or administering recombinant adiponectin reduces blood glucose levels and ameliorates insulin resistance in obese mice, which are independent of plasma insulin levels (59),(60),(61),(62). Conversely, ablation of the adiponectin gene exacerbates insulin resistance and hyperglycemia in mice fed on a high-fat diet (63),(64),(56). Research in our laboratory focused on the mechanisms underlying the insulin-sensitizing actions of adiponectin.

We show that in skeletal muscle, adiponectin promotes tyrosine phosphorylation of IRS1 and AKT phosphorylation via inhibiting p70 S6K phosphorylation and serine phosphorylation of IRS1, thereby increasing insulin sensitivity (65). In parallel, adiponectin activates the LKB1/AMPK/TSC1/2 pathway, which blocks the inhibitory actions of the mTOR/p70 S6K pathway on insulin signaling (65). Interestingly, APPL1 promotes IRS1/2 binding to the insulin receptor (IR) (33). Under basal conditions, APPL1 forms a complex with IRS1/2; the presence of insulin or adiponectin triggers phosphorylation of Ser401 on APPL1, which brings APPL1 to the IR, forming the IR–APPL1–IRS1/2 complex (Figure 2). This process plays a key role in improving insulin sensitivity (33). UsingAPPL1knockout mice, we find that APPL1 sensitizes insulin actions via modulating IRS1/2 but not tyrosine phosphorylation of the IR, further corroborating the mechanisms of APPL1 action. Notably, recent studies on the in vivo effects of APPL2 on insulin signaling also demonstrated the 'Yin-Yang' modulatory actions of APPL1 and APPL2 (44). Yet, APPL2 does not seem to directly regulate the interactions between IRS1/2 and the IR (33). Thus, APPL1 plays a key role in the crosstalk between adiponectin and insulin signaling pathways. Elucidating the mechanisms underlying the insulin-sensitizing actions of adiponectin will provide a guide to our understanding and treatment of insulin resistance

10. Physiological and Pathophysiological Regulation of Plasma Adiponectin

Caloric restriction/starvation/fasting have been reported to result in upregulation of plasma adiponectin levels. Accili and his colleagues indeed showed that SirT1 gain of function increases adiponectin messenger RNA (mRNA) levels, protein levels, and both HMW and MMW adiponectin in mice fed either a standard diet or HFD, which resulted in increased insulin sensitivity in the liver (66). SirT1 has recently been reported to deacetylate Lys268 and Lys293 of PPARg and to cause selective PPARg modulation, leading to upregulation of adiponectin and repression of proinflammatory cytokines (67). for insulin in the regulation of adiponectin levels, it is reported that adipocyte-specific insulin receptor knockout mice exhibited increased adiponectin expression levels in adipose tissue (68). In this context, it is noteworthy that subjects with mutations in the insulin receptor, despite having the most severe degree of insulin resistance, had elevated plasma adiponectin (69). Moreover, Scherer and his colleagues proposed that an increase in serum insulin levels may trigger the induction or activation of a serum reductase that triggers the dissociation of the HMW adiponectin, leading to the transient appearance of the lower-molecular-weight adiponectin (59). In contrast to caloric restriction/starvation/fasting, obesity results in decreased adiponectin levels via multiple mechanisms, including decreased levels of SirT1, hyperinsulinemia, oxidative stress, and inflammation (70). Conversely, TZDs reverse hyperinsulinemia, oxidative stress, and inflammation, thereby increasing adiponectin levels especially those of HMW adiponectin. Moreover, TZDs directly increase the expression of adiponectin gene itself via peroxisome proliferator response element (PPRE) (54). Scherer et al. reported that one mechanism for increasing circulating levels of HMW adiponectin by TZDs may be selective upregulation of rate-limiting chaperones such as ERp44 and Ero1-La (71). There is a sexual dimorphism in the circulating levels of adiponectin. Indeed, females have higher plasma adiponectin levels than males in humans and rodents, suggesting that sexual hormones regulate the production of adiponectin, although it is controversial how these hormones, such as estrogen and testosterone, are involved in the regulation of plasma adiponectin level. Regulatory Mechanisms of Adiponectin Multimer Formation The Adiponectin gene expressed exclusively in adipocytes has been reported to be regulated by transcriptional factors, including C/EBPs,

sterol regulatory element binding protein 1c (SREBP1c), and peroxisome proliferator-activated receptor g (PPARg). SirT1 has recently been reported to deacetylate Lys268 and Lys293 of PPARg and to cause selective PPARg modulation, leading to up regulation of adiponectin. There is an abundant pool of properly folded adiponectin in the secretory pathway through thiol-mediated retention, and that adiponectin is covalently bound to the ER chaperone ERp44. Another ER chaperone, Ero1-La, plays a critical role in the release of adiponectin from ERp44, and that these chaperones play a major role in the assembly of HMW adiponectin. Hyperinsulinemia, oxidative stress and inflammation observed in obesity have been reported to reduce HMW adiponectin, whereas TZDs and caloric restriction have been reported to increase HMW adiponectin. Cell Metabolism 17, February 5, 2013 [a]2013 Elsevier Inc. 187 (72),(73),(74). Nevertheless, this may partly account for the fact that females are more sensitive to insulin than are males. Concentrations of serum adiponectin were higher in a hyperthyroid state than in a hypothyroid state. A strong positive correlation of adiponectin with thyroid hormones has been noted. Thus, the plasma adiponectin level is affected by multiple factors, such as insulin (insulin signaling in adipocytes and insulin-dependent reductase), intracellular stress in adipocytes (inflammation and oxidative stress), other hormones (estrogen, testosterone and thyroid hormone), sex, aging, and lifestyle.

11. Conclusion

Adiponectin is the most abundant peptide secreted by adipocytes, being a key component in the interrelationship between adiposity, insulin resistance and inflammation. Central obesity accompanied by insulin resistance is a key factor in the development of metabolic syndrome (MS) and future macrovascular complications. Adiponectin exerts an insulin-sensitizing action via an enhancement of AMPK and PPARα, this having profound effects on fatty acid oxidation and inflammation. Drugs affecting the levels of adiponectin may have a role in the treatment of NAFLD, cardiovascular disease, type II diabetes, and possibly in preventing metabolic syndrome-related cancers. Clinical studies aimed at reducing the deleterious effects of a number of ailments have been undertaken and this, in conjunction with a better understanding of the adiponectin genetic bases for these processes and the cellular events that underlie them should enhance our ability to devise new and better approaches aimed at minimizing the adverse effects of these diseases. Adiponectin is an unique and essential adipocytokine that is produced very abundantly in adipocytes and stably present in the plasma at very high concentration. Moreover, orally active AdipoR1 and AdipoR2 agonists were already satisfactorily used in rodent models. T-cadherin, a membraneassociated adiponectin-binding protein lacking intracellular domain seems to be a main mediator of the antiatherogenic adiponectin actions, and maybe a component of insulin granules. Both adiponectin and T-cadherin were found to be inversely associated with human aortic and coronary atherosclerosis, and it appears that a majority of the whole body adiponectin is conveyed to cardiovascular tissues by T-cadherin. T-cadherin seems to be a clue novel signaling pathway at the crossroads of vascular and metabolic disorders.

12. Reference

1. Oh K, Jang MJ, Lee NY, Moon JS, Lee CG, Yoo MH, et al. Prevalence and trends in obesity among Korean children and adolescents in 1997 and 2005. Korean Journal of Pediatrics. 2008;51(9):950-5.
2. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet. 2008;371(9612):569-78.
3. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocrine reviews. 2012;33(4):547-94.
4. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiology and Prevention Biomarkers. 2009;18(10):2569-78.
5. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. The American journal of clinical nutrition. 2007;86(3):858S-66S.
6. Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. The American journal of clinical nutrition. 2010;91(1):258S-61S.
7. Kelesidis I, Kelesidis T, Mantzoros C. Adiponectin and cancer: a systematic review. British journal of cancer. 2006;94(9):1221-5.
8. Gallagher EJ, LeRoith D. Minireview: IGF, insulin, and cancer. Endocrinology. 2011;152(7):2546-51.
9. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocrine reviews. 2011;32(4):550-70.
10. Hug C, Wang J, Ahmad NS, Bogan JS, Tsao T-S, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(28):10308-13.
11. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. Journal of Biological chemistry. 1995;270(45):26746-9.
12. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. Journal of Biological Chemistry. 1996;271(18):10697-703.
13. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPoseMost abundant Gene transcript 1). Biochemical and biophysical research communications. 1996;221(2):286-9.
14. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003;423(6941):762-9.
15. Turer A, Scherer P. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012;55(9):2319-26.
16. Peterlin BL, Alexander G, Tabby D, Reichenberger E. Oligomerization state-dependent elevations of adiponectin in chronic daily headache. Neurology. 2008;70(20):1905-11.

17. Vaiopoulos AG, Marinou K, Christodoulides C, Koutsilieris M. The role of adiponectin in human vascular physiology. International journal of cardiology. 2012;155(2):188-93.
18. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nature medicine. 2007;13(3):332-9.
19. Awazawa M, Ueki K, Inabe K, Yamauchi T, Kubota N, Kaneko K, et al. Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. Cell metabolism. 2011;13(4):401-12.
20. Fu Y, Luo N, Klein RL, Garvey WT. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. Journal of lipid research. 2005;46(7):1369-79.
21. Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Current opinion in lipidology. 2007;18(3):263-70.
22. Sell H, Dietze-Schroeder D, Eckardt K, Eckel J. Cytokine secretion by human adipocytes is differentially regulated by adiponectin, AICAR, and troglitazone. Biochemical and biophysical research communications. 2006;343(3):700-6.
23. Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes. 2002;51(6):1884-8.
24. Bacha F, Saad R, Gungor N, Arslanian SA. Adiponectin in youth. Diabetes care. 2004;27(2):547-52.
25. Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, et al. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. Nature cell biology. 2006;8(5):516-23.
26. Fang Q, Jia W, Gao F, Zhang R, Hu C, Wang C, et al. Association of variants in APPL1 gene with body fat and its distribution in Chinese patients with type 2 diabetic mellitus. Zhonghua Yi Xue Za Zhi. 2008;88(6):369-73.
27. Prudente S, Jungtrakoon P, Marucci A, Ludovico O, Buranasupkajorn P, Mazza T, et al. Loss-of-function mutations in APPL1 in familial diabetes mellitus. The American Journal of Human Genetics. 2015;97(1):177-85.
28. Mitsuuchi Y, Johnson SW, Sonoda G, Tanno S, Golemis EA, Testa JR. Identification of a chromosome 3p14. 3-21.1 gene, APPL, encoding an adaptor molecule that interacts with the oncoprotein-serine/threonine kinase AKT2. Oncogene. 1999;18(35).
29. Liu J, Yao F, Wu R, Morgan M, Thorburn A, Finley RL, et al. Mediation of the DCC apoptotic signal by DIP13α. Journal of Biological Chemistry. 2002;277(29):26281-5.
30. Zhou L, Deepa SS, Etzler JC, Ryu J, Mao X, Fang Q, et al. Adiponectin activates AMP-activated protein kinase in muscle cells via APPL1/LKB1-dependent and phospholipase C/Ca2+/Ca2+/calmodulin-dependent protein kinase kinase-dependent pathways. Journal of Biological Chemistry. 2009;284(33):22426-35.
31. Deepa SS, Zhou L, Ryu J, Wang C, Mao X, Li C, et al. APPL1 mediates adiponectin-induced LKB1 cytosolic localization through the PP2A-PKCζ signaling pathway. Molecular endocrinology. 2011;25(10):1773-85.
32. Xin X, Zhou L, Reyes CM, Liu F, Dong LQ. APPL1 mediates adiponectin-stimulated p38 MAPK activation by scaffolding the TAK1-MKK3-p38 MAPK pathway. American Journal of Physiology-Endocrinology and Metabolism. 2011;300(1):E103-E10.

33. Ryu J, Galan AK, Xin X, Dong F, Abdul-Ghani MA, Zhou L, et al. APPL1 potentiates insulin sensitivity by facilitating the binding of IRS1/2 to the insulin receptor. Cell reports. 2014;7(4):1227-38.
34. Cheng KK, Lam KS, Wang Y, Huang Y, Carling D, Wu D, et al. Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. Diabetes. 2007;56(5):1387-94.
35. Cheng KK, Iglesias MA, Lam KS, Wang Y, Sweeney G, Zhu W, et al. APPL1 potentiates insulin-mediated inhibition of hepatic glucose production and alleviates diabetes via Akt activation in mice. Cell metabolism. 2009;9(5):417-27.
36. Chandrasekar B, Boylston WH, Venkatachalam K, Webster NJ, Prabhu SD, Valente AJ. Adiponectin blocks interleukin-18-mediated endothelial cell death via APPL1-dependent AMP-activated protein kinase (AMPK) activation and IKK/NF-κB/PTEN suppression. Journal of Biological Chemistry. 2008;283(36):24889-98.
37. Fang X, Palanivel R, Cresser J, Schram K, Ganguly R, Thong FS, et al. An APPL1-AMPK signaling axis mediates beneficial metabolic effects of adiponectin in the heart. American Journal of Physiology-Endocrinology and Metabolism. 2010;299(5):E721-E9.
38. Coope A, Milanski M, Araújo EP, Tambascia M, Saad MJ, Geloneze B, et al. AdipoR1 mediates the anorexigenic and insulin/leptin-like actions of adiponectin in the hypothalamus. FEBS letters. 2008;582(10):1471-6.
39. Miaczynska M, Christoforidis S, Giner A, Shevchenko A, Uttenweiler-Joseph S, Habermann B, et al. APPL proteins link Rab5 to nuclear signal transduction via an endosomal compartment. Cell. 2004;116(3):445-56.
40. Wang C, Xin X, Xiang R, Ramos FJ, Liu M, Lee HJ, et al. Yin-Yang regulation of adiponectin signaling by APPL isoforms in muscle cells. Journal of Biological Chemistry. 2009;284(46):31608-15.
41. Nechamen CA, Thomas RM, Dias JA. APPL1, APPL2, Akt2 and FOXO1a interact with FSHR in a potential signaling complex. Molecular and cellular endocrinology. 2007;260:93-9.
42. Chial HJ, Wu R, Ustach CV, McPhail LC, Mobley WC, Chen YQ. Membrane targeting by APPL1 and APPL2: dynamic scaffolds that oligomerize and bind phosphoinositides. Traffic. 2008;9(2):215-29.
43. Schwartz MW, Seeley RJ. Neuroendocrine responses to starvation and weight loss. New England Journal of Medicine. 1997;336(25):1802-11.
44. Cheng KK, Zhu W, Chen B, Wang Y, Wu D, Sweeney G, et al. The adaptor protein APPL2 inhibits insulin-stimulated glucose uptake by interacting with TBC1D1 in skeletal muscle. Diabetes. 2014;63(11):3748-58.
45. Mao L, Lin W, Nie T, Hui X, Gao X, Li K, et al. Absence of Appl2 sensitizes endotoxin shock through activation of PI3K/Akt pathway. Cell & bioscience. 2014;4(1):60.
46. Tomas E, Tsao T-S, Saha AK, Murrey HE, cheng Zhang C, Itani SI, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: Acetyl–CoA carboxylase inhibition and AMP-activated protein kinase activation. Proceedings of the National Academy of Sciences. 2002;99(25):16309-13.
47. Wu X, Motoshima H, Mahadev K, Stalker TJ, Scalia R, Goldstein BJ. Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. Diabetes. 2003;52(6):1355-63.
48. Chen MB, McAinch AJ, Macaulay SL, Castelli LA, O'brien PE, Dixon JB, et al. Impaired activation of AMP-kinase and fatty acid oxidation by globular adiponectin in cultured human

skeletal muscle of obese type 2 diabetics. The Journal of Clinical Endocrinology & Metabolism. 2005;90(6):3665-72.
49. Yamauchi T, Kamon J, Minokoshi Ya, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nature medicine. 2002;8(11):1288.
50. Miller RA, Chu Q, Le Lay J, Scherer PE, Ahima RS, Kaestner KH, et al. Adiponectin suppresses gluconeogenic gene expression in mouse hepatocytes independent of LKB1-AMPK signaling. The Journal of clinical investigation. 2011;121(6):2518-28.
51. Yamauchi T, Kamon J, Ito Y, Tsuchida A. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003;423(6941):762.
52. Yamauchi T, Kamon J, Terauchi Y, Kubota N, Waki H, Mori Y, et al. Replenishment of fat-derived hormone adiponectin reverses insulin resistance in lipoatrophic diabetes and type 2 diabetes. Diabetes. 2001;50:A70.
53. Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell metabolism. 2013;17(2):185-96.
54. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, et al. PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes. 2001;50(9):2094-9.
55. Combs TP, Wagner JA, Berger J, Doebber T, Wang W-J, Zhang BB, et al. Induction of adipocyte complement-related protein of 30 kilodaltons by PPARγ agonists: a potential mechanism of insulin sensitization. Endocrinology. 2002;143(3):998-1007.
56. Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, et al. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor γ agonists. Journal of Biological Chemistry. 2006;281(5):2654-60.
57. Iwabu M, Yamauchi T, Okada-Iwabu M, Sato K, Nakagawa T, Funata M, et al. Adiponectin and AdipoR1 regulate PGC-1 [alpha] and mitochondria by Ca^ sup2+^ and AMPK/SIRT1. Nature. 2010;464(7293):1313.
58. Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nature medicine. 2011;17(1):55-63.
59. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin implications for metabolic regulation and bioactivity. Journal of Biological Chemistry. 2003;278(11):9073-85.
60. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. The Journal of clinical investigation. 2001;108(12):1875-81.
61. Fruebis J, Tsao T-S, Javorschi S, Ebbets-Reed D, Erickson MRS, Yen FT, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proceedings of the National Academy of Sciences. 2001;98(4):2005-10.
62. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, et al. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. Journal of Biological Chemistry. 2003;278(4):2461-8.
63. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. Journal of Biological Chemistry. 2002;277(29):25863-6.

64. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nature medicine. 2002;8(7):731.
65. Wang C, Mao X, Wang L, Liu M, Wetzel MD, Guan K-L, et al. Adiponectin sensitizes insulin signaling by reducing p70 S6 kinase-mediated serine phosphorylation of IRS-1. Journal of Biological Chemistry. 2007;282(11):7991-6.
66. Banks AS, Kon N, Knight C, Matsumoto M, Gutiérrez-Juárez R, Rossetti L, et al. SirT1 gain of function increases energy efficiency and prevents diabetes in mice. Cell metabolism. 2008;8(4):333-41.
67. Qiang L, Wang L, Kon N, Zhao W, Lee S, Zhang Y, et al. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Pparγ. Cell. 2012;150(3):620-32.
68. Blüher M, Michael MD, Peroni OD, Ueki K, Carter N, Kahn BB, et al. Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Developmental cell. 2002;3(1):25-38.
69. Semple R, Soos M, Luan J, Mitchell C, Wilson J, Gurnell M, et al. Elevated plasma adiponectin in humans with genetically defective insulin receptors. The Journal of Clinical Endocrinology & Metabolism. 2006;91(8):3219-23.
70. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. The Journal of clinical investigation. 2004;114(12):1752-61.
71. Wang ZV, Schraw TD, Kim J-Y, Khan T, Rajala MW, Follenzi A, et al. Secretion of the adipocyte-specific secretory protein adiponectin critically depends on thiol-mediated protein retention. Molecular and cellular biology. 2007;27(10):3716-31.
72. Combs TP, Berg AH, Rajala MW, Klebanov S, Iyengar P, Jimenez-Chillaron JC, et al. Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. Diabetes. 2003;52(2):268-76.
73. Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes. 2002;51(9):2734-41.
74. Xu A, Chan KW, Hoo RL, Wang Y, Tan KC, Zhang J, et al. Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. Journal of Biological Chemistry. 2005;280(18):18073-80.