IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN: 2278-3008, p-ISSN:2319-7676. Volume 8, Issue 5 (Nov. – Dec. 2013), PP 32-35
www.iosrjournals.org

Adiponectin and Atherosclerosis

Majid Khandouzi
(Biological Science Department/Gauhati University, India)

Abstract: *Adiponectin is secreted by white adipose tissue and as known as for its function it is anti-diabetes, anti-atherosclerosis, anti-inflammation and antitumor activities, which have been directly linked to the high molecular weight and are abundantly present in circulating blood. adiponectin had effects on monocyte adhesion to endothelium, myeloid differentiation and macrophage cytokine production and phagocytosis. It can suppress atherogenesis by inhibiting the adherence of monocytes, reducing their phagocytic activity and suppressing the accumulation of modified lipoproteins in the vascular wall. C1q and TNF family play important roles in inflammation, the immune system and atherosclerosis. Adiponectin has protective actions in the initiation and progression of atherosclerosis through anti-inflammatory and anti-atherogenic effects. Adiponectin levels are decreased in obesity, type 2 diabetes and negatively correlated with the CRP levels in patients with CAD. With the prospect of future, adiponectin could become a promising target for future investigations in reducing the morbidity and mortality of atherosclerotic disease.*

Key word: *Adiponectin, diponectin properties, Atherosclerosis disease, inflammatory effect, Anti-inflammatory effect.*

I. Introduction:

Adipose tissue is not only an energy pool, it also secretes metabolic hormones, anti-fibrinolytic proteins, enzymes, and inflammatory cytokines[1,2]. These secretory proteins, which is named adipokines , include leptin , resistin, adipsin, plasminogen activator inhibitor type-1, tumor necrosis factor-a and adiponectin [3,4,5,6,7,8].

Obesity is the accumulation of excess body fat and it is associated with increasing risk for many common diseases such as type 2 diabetes, hypertension, dyslipidemia and atherosclerotic cardiovascular disease[9,10]. In 1998, the World Health Organization recognized the term of metabolic syndrome for the clustering of metabolic risk factors[11]. In 2001, The National Cholesterol Education Program Adult Treatment Program Guidelines defined metabolic syndrome which includes abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance and pro-inflammatory states as a secondary target for cardiovascular risk reduction, after treatment of the primary target, low density lipoprotein cholesterol[12]. Clinical studies on the morbidities of obesity suggest that the extent of fat accumulation is not necessarily a determinant of development of obesity-related diseases but body fat distribution is a more important factor for morbidity. Visceral adipose tissue accumulation may have a major role in the occurrence of diabetes mellitus, hypertension, hyperlipidemia and also atherosclerotic diseases[13,14,15,16]. It clear that obesity is a major risk factor for morbidity and mortality from cardiovascular causes[17].

Atherosclerotic are the leading cause of death in developed countries, and measures against atherosclerosis are the biggest medical subject in the 21st century[18]. Many epidemiological investigations did perform to clarify the pathogenesis of atherosclerosis and reveal the importance of hyperlipidemia as the strongest risk factor for atherosclerosis. The contribution of LDL to the development of atherosclerosis and HDL to its prevention has demonstrated with cell biological studies. The crucial roles of oxidized LDL in atherosclerotic cellular changes have been recognized. However, when we consider the subjects who suffer from atherosclerotic diseases, lipid abnormalities can only partly explain the prevalence of the development of atherosclerosis [19,20,21].

II. Structure, Synthesis, Functions and Mechanism of Adiponectin:

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism and secreted from adipose tissue into the bloodstream and is very abundant in plasma relative to many hormones[22]. Adiponectin or AdipoQ, apM1 or GBP28 is a cytokine produced exclusively and is abundant in human plasma with concentrations of 5–30 (μg/mL), thus accounting for approximately 0.01% of total plasma proteins[23]. A description of the cDNA encoding adiponectin was first reported in 1995 by Scherer and colleagues[24]. Adiponectin is a protein of 245 amino acids consisting of four domains, an amino-terminal signal sequence, a variable region, a collagenous domain (cAd) and a carboxy-terminal globular domain (gAd)[25]. Adiponectin is most similar to C1q which is a member of the complement-related family of proteins[26]. The basic building block of adiponectin is a tightly associated trimer, which is

formed by association between three monomers at the globular domains. Monomeric adiponectin has not been observed in the circulation and appears to be confined to the adipocyte. Four to six trimers associate through their collagenous domains to form higher order structures or oligomers which circulate in plasma[27,28].
The human adiponectin gene that is encoded by apM1 mRNA is located on chromosome 3q27, consisting of three exons and two introns [29,30]. The cloning of DNAs encoding adiponectin receptors 1(Adipo R1) and 2 (Adipo R2) was reported in June 2003. These receptors are predicted to contain seven transmembrane domains[30].

X-ray crystallography of the globular fragment of adiponectin reveals a striking structural homology to TNF-a, suggesting an evolutionary link between the TNF-a family members and adiponectin [31]. Both C1q and TNF family play important roles in inflammation, the immune system and atherosclerosis [32].

The synthesis and secretion of adiponectin is regulated by several mechanisms. Insulin stimulates adiponectin gene expression and its secretion from cultured 3T3-L1 adipocytes . Both insulin and insulin-like growth factor-1 (IGF-1) also increase adiponectin synthesis in adipocytes isolated from human visceral adipose tissue [33]. Peroxisome Proliferator Activated Receptors (PPAR) which belong to the nuclear hormone super family are involved in the regulation of adiponectin synthesis [34].

Adiponectin may augment and mimic metabolic actions of insulin by increasing fatty acid oxidation and insulin-mediated glucose disposal in skeletal muscle as well as decreasing hepatic glucose output[35].
The mechanisms of adiponectin are largely unknown. Adiponectin administration has been shown to increase insulin induced tyrosine phosphorylation of the insulin receptor in skeletal muscle in association with increased whole-body insulin sensitivity[36]. Stimulation of glucose utilization and fatty acid oxidation in skeletal muscle and liver by adiponectin may also occur through activation of 5′-AMP kinase. 5′-AMP-activated protein kinase play a crucial role in the regulation of energy expenditure and glucose and lipid metabolism[37]. In the liver, the decreased free fatty acid influx and increased fatty acid oxidation contribute to reduced hepatic glucose output and very low density lipoprotein triglyceride synthesis. In vascular endothelium, adiponectin decreases monocyte adhesion to endothelium, suppresses macrophage-to foam cell transformation, and inhibits vascular smooth muscle cell proliferation and migration[38].

III. Atherosclerosis:

Adiponectin appears to protect the vasculature at each stage of atherogenesis. Atherosclerosis is largely considered an inflammatory disease and developing atherosclerosis have high levels of circulating inflammatory markers such as CRP[39]. CRP emerged as not only an independent risk factor for CVD but is also considered to be a biological mediator of atherosclerosis [40]. Decreased plasma adiponectin levels in women similarly demonstrated positive correlation with CRP elevation[41].

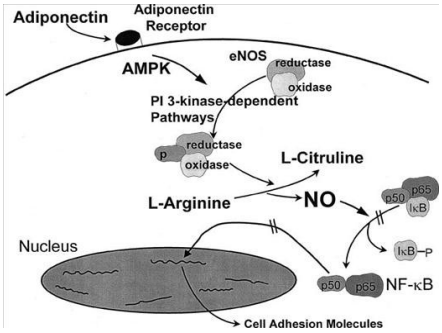
The initial atherosclerotic lesion consists of monocytes and T lymphocytes. The first change of lesions of atherosclerosis is endothelial injury which is mediated by various inflammatory stimuli such as TNF-a. When the vascular endothelium injured, adiponectin accumulates in the subintimal space of the arterial wall through its interaction with collagens in the vascular intimal[42]. Adiponectin dose dependently inhibited TNF-a induced monocyte adhesion and expression of endothelial leukocyte adhesion molecule-1, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 on the endothelium [43]. It suggest that the intracellular signal by which adiponectin suppressed adhesion molecule expression is inhibition of endothelial nuclear transcription factor kB signaling through the activation of cAMP protein kinase A[44]. TNF-a activates nuclear transcription factor kB in endothelial cells by stimulating protein kinase NIK (NF-kB inducing kinase) which phosphorylates NF-kB inhibitor, IkB, initiating its degradation of IkB. The effect of adiponectin is specific for the IkB-NF-kB pathway. The inhibition of IkB phosphorilation is most likely mediated by the cAMP-protein kinase A pathway because it is mimicked by the membrane permeable cAMP analogue, dibutyryl-cAMP and blocked by inhibitors of protein kinase A [44].

In addition, Ouchi and colleagues [43] found that adiponectin had effects on monocyte adhesion to endothelium, phagocytosis, myeloid differentiation and macrophage cytokine production. Adiponectin also suppresses lipid accumulation in monocyte derived macrophages through the suppression of macrophage scavenger receptor expression[45].

Atherogenesis involves endothelial dysfunction which culminates from diminished production or availability of Nitric Oxide and an imbalance in the relative contribution of endothelium derived relaxing factors, such as angiotensin, endothelin-1 and oxidants[46]. NO is the key endothelium derived contracting factor that plays a pivotal role in the regulation of vasomotor function and vascular tone.

Nitric Oxide protects against vascular injury and inflammation by inhibiting leukocyte adhesion to the endothelium and maintaining of vascular smooth muscle in a non-proliferative state and limiting platelet aggregation[47]. Adiponectin have anti-inflammatory properties by altering the level of NO at the level of the endothelium. In vitro, adiponectin induces Nitric Oxide production in human aortic endothelial cells via activation of the AMPK pathway and enhanced endothelial NO synthase (eNOS) mRNA and protein

expression[48,49]. By promoting NO generation, adiponectin serves as against the onset of endothelial dysfunction.



IV. Conclutions:

In conclusion we find that the adipose tissue is not only a simple energy pool but it also secretes metabolic hormones, enzymes, anti-fibrinolytic proteins and inflammatory cytokines. Among, Adiponectin which is solely in adipose tissue, appears to play a very important role in carbohydrate and lipid metabolism and vascular biology. Adiponectin is an adipocyte-specific plasma protein which acts as an endogenous regulator of endothelial cells in response to inflammatory stimuli. It can suppress atherogenesis by inhibiting the adherence of monocytes, reducing their phagocytic activity and suppressing the accumulation of modified lipoproteins in the vascular wall. Adiponectin could become a promising target for future investigations in reducing the morbidity and mortality of atherosclerotic disease.

Reference:

[1] Spiegelmen BM, Choy L, Hotamisligil GS, et al. Regulation of adipocyte gene expression in differentation and syndromes of obesity/diabetes. *J Biol Chem* 1993;268:6823.

[2] Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: Contribution of adipocyte-derived bioactive substances. *Ann NY Acad Sci* 1999;892:146.

[3] Friedman JM. Obesity in the new millenium. *Nature* 2000;404:632.

[4] Hotamisligil GS. The role of TNF-a and TNG receptors in obesity and insulin resistance. *J Intern Med* 1999;245:621.

[5] Shimomura I, Funahashi T, Takahashi M, et al. Enhanced expression of PAI-1 in visceral fat. Possible contributor to vascular disease in obesity. *Nat Med* 1996;2:800.

[6] White RT, Damm D, Hancock N, et al. Human adipsin is identical to complement factor D and is expressed in high levels in adipose tissue. *J Biol Chem* 1992;267:9210.

[7] Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature* 2001;409:307.

[8] Maeda K, Okubo K, Shimomura I, et al. cDNA cloning and expression of novel adipose specific collogen like factor apM1 (adipose most abundant gene transcript 1). *Biochem Biophys Res Commun* 1996;221:286.

[9] Linton MF, Fazio S. A practical approach to risk assessment to prevent coronary artery disease and its complications. Am J Cardiol 2003;92:19i– 26i.

[10] Scott CL. Diagnosis, prevention, and intervention for the metabolic syndrome. Am J Cardiol 2003;92:35i – 42i.

[11] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications: Part 1. Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539– 53.

[12] Expert panel on detection evaluation and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486– 97.

[13] Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intraabdominal fat accumulation to the impairment of glucose and lipid metabolism. *Metabolism*. 1987;36:54–59.

[14] Despres JP, Moorjani M, Ferland M, Tremblay A, Lupien PJ, Nadeau A, Pinault S, Theriault G, Bouchard C. Adipose tissue distribution and plasma lipoprotein levels in obese women: importance of intraabdominal fat. *Arteriosclerosis*. 1989;9:203–210.

[16] Despres JP, Nadeau A, Tremblay A, Ferland M, Moorjani S, Lupien PJ, Theriault G, Pinault S, Bouchard C. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes*. 1989;38:304–309.

[17] Calle EC, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;341:1097.

[18] The World Health Report 2002. Reducing Risks, Promoting Healthy Life. Geneva, Switzerland: World Health Organization; 2002.

[19] Reaven GM. Role of insulin resistance in human disease. *Diabetes*. 1988; 37:1595–1607.

[20] Kaplan NM. The deadly quartet: upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension. *Arch Intern Med*. 1989;149: 1514–1520.

[21] Matsuzawa YM. Pathophysiology and molecular mechanism of visceral fat syndrome: the Japanese case. *Diabetes Metab Rev*. 1997;13:3–13.

[22] Adiponectin and Adiponectin Receptors, Takashi Kadowaki and Toshimasa Yamauchi, 2005.

[23] Role of adiponectin in human skeletal muscle bioenergetics, Anthony E. Civitarese,1 Barbara Ukropcova,1 Stacy Carling,1 Matthew Hulver,1 Ralph A. DeFronzo,2 Lawrence Mandarino,2,3 Eric Ravussin,1,* and Steve R. Smith12006.

[24] Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q produced exclusively in adipocytes. *J Biol Chem* 1995;270:26746.

[25] Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF: A novel serum protein similar to C1q produced exclusively in adipocytes. J Biol Chem270:26746–26749, 1995.

[26] Berg AH, Combs TP, Scherer PE: Acrp30/adiponectin: an adipocytokine regulating glucose and lipid metabolism. Trends Endocrinol Metabolism13:84–89, 2002.
[27] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257:79–83, 1999.
[28] Saito K, Tobe T, Minoshima S, et al. Organization of the gene for gelatin-binding protein (GBP 28). *Gene* 1999;229:67.
[29] Takahashi M, Arita Y, Yamagata K, et al. Genomic structure and mutations in adipose-spesific gene, adiponectin. I*nt J Obes Relat Metab Disord* 2000;24:861.
[30] Yamauchi T, Kamon J, Ito Y, et al. Clonning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003;423:762.
[31] Berg AH, Combs TP, Scherer PE. Acrp 30/adiponectin: An adipocytokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab* 2002;13:84.
[32] Shimada K, Miyazaki T, Daida H. Adiponectin and atherosclerotic disease. *Clin Chim Acta* 2004;344:1.
[33] Halleux CM, Takahashi M, Delporte MI, et al. Secretion of adiponectin and regulation of apM1 gene expression in human visceral adipose tissue. *Biochem Biophys Res Commun* 2001;288:1102.
[34] Moore GB, Chapman H, Holder JG, et al. Differential regulation of adipocytokine mRNAs by risiglitazone in db/db mice. *Biochem Biophys Res Commun* 2001;286:735.
[35] Chen H, Montagnani M, Funahashi T,et al. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003;278(45):45021.
[36] Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K. et al. The fat derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001; 7: 941–6.
[37] Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T: Adiponectin stimulates glucose utilization and fatty acid oxidation by activating AMP-activated protein kinase. Nat Med 8:1288–1295, 2002.
[38] Chandran M, Ciaraldi T, Phillips SA, Henry RR. Adiponectin: More than just another fat cell hormone. *Diabetes Care* 2003;26(8):2442.
[39] Szmitko PE, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S. New markers of inflammation and endothelial cell activation. *Circulation* 108: 1917–1923, 2003.
[40] Verma S, Szmitko PE, Ridker PM. C-reactive protein comes of age. *Nat Clin Pract Cardiovasc Med* 2: 29–36,2005.
[41] Matsubara M, Namioka K, Katayose S. Decreased plasma adiponectin concentrations in women with low grade C-reactive protein elevation. *Eur J Endocrinol* 148: 657–662, 2003.
[42] Okamoto Y, Arita Y, Nishida M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injures vascular walls. *Horm Metab Res* 2000;32:47.
[43] Ouchi N, Kihara S, Arita Y, et al. Novel modulator for endothelial adhesion molecules: Adipocyte-derived plasma protein adiponectin. *Circulation* 1999;100:2473.
[44] Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NFkappa B signalling yhrough a cAMP-dependent pathway. *Circulation* 2000;102:1296.
[45] Matsuda M, Shimomura I, Sata M, et al. Role of adiponectin in preventing vascular stenosis: The missing link of adipo-vascular axis. *J Biol Chem* 2002;277:37487.
[46] Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. *Circulation* 105: 546–549,2002.
[47] Szmitko PE, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S. New markers of inflammation and endothelial cell activation. *Circulation* 108: 1917–1923, 2003.
[48] Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitricoxide in vascular endothelial cells. *J Biol Chem* 278: 45021–45026, 2003.
[49] Hattori Y, Suzuki M, Hattori S, Kasai K. Globular adiponectin upregulates nitric oxide production in vascular endothelial cells. *Diabetologia* 46: 1543–1549, 2003.