

## **Chapter (6)**

# **ADIPONECTIN**

*Author*

*Samir Naim Assaad, MD, FRCP(Edin)*

- Introduction
- Structure
- Origin
- Secretion
- Adiponectin Receptors
- Metabolic & Vascular Effects
- Mechanism of Action
- Adiponectin and Disease States
- Nonpharmacologic & Pharmacologic Treatment of Hypoadiponectinemia

## SUMMARY

Adiponectin is a protein specifically secreted from adipose tissue. It circulates to influence other organs as the liver, skeletal muscles, and blood vessels. An auto/paracrine effect on adipose tissue also exists. It has antidiabetic (by promoting insulin sensitivity), anti-inflammatory and anti-atherogenic effects. Its secretion is influenced by different hormones and cytokines. Hypoadiponectinemia is observed in obesity, type 2 diabetes, hypertension, and coronary artery disease.

## AIM

A short review on the physiology of adiponectin, and its relation to different disease states.

## INTRODUCTION

- Adiponectin is exclusively and abundantly expressed in white adipose tissue (1). It was identified in 1995-6 by 4 different groups (2, 3).
- Most of the information concerning the physiological role of adiponectin was gained by transgenic and Knock-Out mouse models (4).
- It has anti-diabetic, anti-inflammatory and anti-atherogenic effects (5). It correlates negatively with percent body fat, waist/hip ratio and plasma insulin, and positively with insulin sensitivity (6, 7). In various mouse models, injection of recombinant adiponectin caused a transient decrease in blood glucose levels (8).

## STRUCTURE

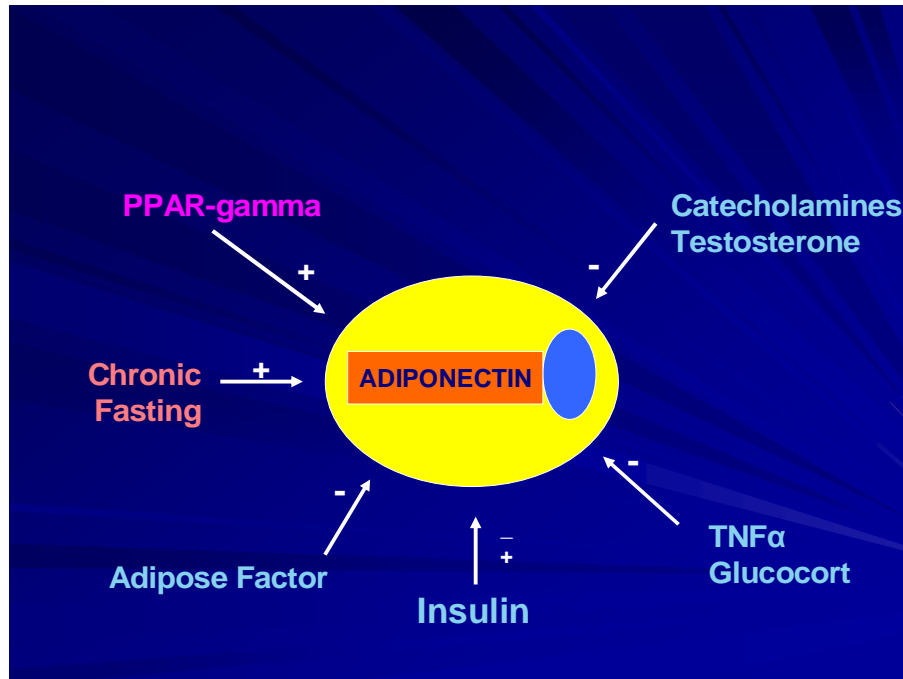
- Adiponectin is 244 amino acid 30 Kd protein, with high homology to collagen III, collagen X and complement C1q. The mature protein consists of an amino-terminal collagen-like domain and a carboxyterminal head domain (1,5).
- It circulates in 2 forms:
  - A full length protein (fAd) [High Molecular Weight (HMW) multimer and Low Molecular Weight (LMW)hexamer] (9, 10); HMW form appears to be more active in insulin sensitivity and diabetes protection (11).
  - A proteolytic cleavage globular C-terminal domain (gAd) which has potent pharmacologic activity (12).

## ORIGIN

- An adipose tissue specific protein (5).
- Adiponectin is synthesized more from visceral adipose tissue (VAT) than subcutaneous adipose tissue (SAT) (13). Serum adiponectin correlates positively with SAT, and negatively with VAT (2, 9). VAT accumulation was found to be the only independent predictor of adiponectin levels (14). In obesity, adiponectin secretion from adipose tissue is reduced (6); therefore hypoadiponectinemia is more pronounced in visceral obesity.

## SECRETION

- It is 2-3 times more in healthy women (6, 10). In boys, serum adiponectin declines with pubertal development, with significant reduced levels in adolescent boys versus girls. In adults, levels tend to increase with age (7,9).
- It circulates in high concentration (2-10 ug/mL)(9,15), 1000 times the concentration of insulin or leptin (7). Its half life is about two and half hours (13).
- Different factors influence its plasma levels (see figure 1) (15 ,16). Obesity is an important association with hypoadiponectinemia. Insulin might increase (short term) or diminish adiponectin expression (long term) (15). There is no acute effect of nutrient excess or deprivation on adiponectin; but chronic caloric restriction increases serum adiponectin levels (17). In addition, genetic polymorphism at chromosomal loci can be responsible for altered levels (3,10).



**Figure 1: Factors influencing adiponectin secretion**

## ADIPONECTIN RECEPTORS

Cell surface receptors for adiponectin have been cloned. They initiate signal transduction through phosphorylation and activation of AMP activated PK (18), which has pivotal role in regulating cholesterol synthesis, lipogenesis, lipid oxidation and glucose transport and oxidation.

- Two receptors were discovered: R1 has higher affinity to gAd, while R2 has equal affinity to both gAd and fAd (12).
- In skeletal muscles, R1 is abundantly expressed, while in the liver R2 is more predominant. In the endothelium, both receptor types are expressed (R1>R2) (4).
- Adiponectin receptors were also observed in adipocytes and macrophages (19).

## METABOLIC EFFECTS

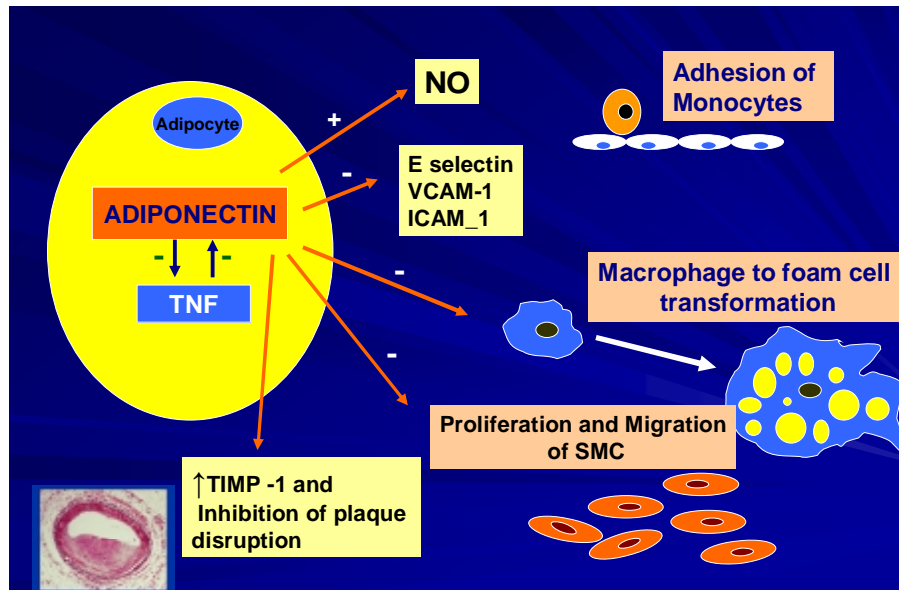
- In the adipose tissue: It promotes cell proliferation and differentiation from preadipocytes to adipocytes. It improves insulin sensitivity with stimulation of glucose uptake (by increasing GLUT4 expression) in adipocytes (autocrine effect) (4).

- In the liver: Reduction of hepatic glucose output (20), decreased free fatty acids (FFA) influx to the liver, increased fatty acid oxidation, and promotion of insulin sensitivity (21). Injection of fAd in mice resulted in decreased gluconeogenesis and lipid accumulation (10).
- In skeletal muscles: Augmentation of lipid oxidation, with increased glucose uptake (10, 21, 22). This results in prevention of postprandial elevation of FFA. gAd administration improved insulin sensitivity in muscle by increasing fatty acid oxidation with a reduction in myocellular lipid accumulation (10).
- Serum adiponectin correlates positively with HDL (9, 14), negatively with TGs (14, 23) independent of obesity. This might be due to the relation of adiponectin to insulin sensitivity or due to the activation of PPAR- $\alpha$  (14). Adiponectin injection in mice results in decrease in plasma FFA and triglycerides (22).
- It also increases uncoupling protein expression in adipose tissue (24).

## **VASCULAR AND ANTI-INFLAMMATORY EFFECTS**

In Apolipoprotein E deficient mice, adiponectin treatment reduced the atherosclerotic lesions by 30% (25). Adiponectin inhibits the inflammatory response and atherogenesis by suppressing the migration of monocytes/macrophages and their transformation into foam cells (26, 27). It inhibits tumor necrosis factor (TNF) – $\alpha$  induced cell adhesion in human aortic endothelial cells (28). These effects are demonstrated in figure 2 (12, 24, 25 ).

Recently, adiponectin was reported to be a novel humoral vasodilator that relaxes aortic and mesenteric rings by opening K (v) channels (29). Adiponectin induces the production of the anti-inflammatory mediator IL-10, while it inhibits the production of the pro-inflammatory cytokine TNF- $\alpha$  (30).



**Figure 2: Protective effects of adiponectin on atherothrombosis.**

### MECHANISM OF ACTION

- Endocrine (as a circulating hormone acting on blood vessels, liver and skeletal muscles).
- Auto/Paracrine (differentiation preadipocytes to adipocytes).
  - Adiponectin inhibits endothelial NF- $\kappa$ B signaling by c-AMP-protein kinase A dependent pathway; this facilitates the anti-inflammatory effects of adiponectin (26).
  - AMP kinase mediates the metabolic effects of adiponectin on the liver, skeletal muscles, and adipose tissue (12). Blocking AMPK activation inhibited these effects.
  - Activation of the NO synthetase, and suppression of the NADPH oxidation pathway (which is involved in superoxide generation in the endothelial cells) (12) are involved in the vasculoprotective effects of adiponectin.
  - The insulin sensitizing effect occurs through increasing insulin receptor substrate -1 and PI<sub>3</sub> kinase activity (15).

## **ADIPONECTIN AND DISEASE STATES**

- Serum adiponectin was observed to be low in individuals with obesity (even in children), dyslipidemia, hypertension and type 2 diabetes mellitus due to decreased adiponectin gene expression (6, 31-34). In obesity the gender difference is preserved (10), while it is equal in both sexes if type 2 diabetes is present (35).
- The mechanism of reduced adiponectin levels in obesity is not known, a negative feed back was postulated. Prospective studies have reported that hypoadiponectinemia is an independent predictor of type 2 diabetes (36).
- Weight reduction (by 21%) by gastric partition surgery was associated with 40% increase in circulating adiponectin (37).

### ***Adiponectin and CAD***

- An inverse association has been found between serum adiponectin and prevalence of CAD in cross sectional studies (38,39).
- Prospective studies have demonstrated low circulating adiponectin to be an independent predictor of CVD events in diabetic subjects (40,41).
- Low adiponectin levels are associated with higher risk of myocardial infarction (42). Adiponectin can improve lipid profile, lower C- reactive protein, inhibits transformation of macrophages to foam cells, and improves plaque stability (42).
- However, in the British Women Heart and Health Study (7), and in the Strong Heart Study (43) serum adiponectin failed to predict CHD events.

## **NONPHARMACOLOGIC & PHARMACOLOGIC TREATMENT OF HYPOADIPONECTINEMIA**

- Weight reduction: Diet, Exercise, Gastric partition surgery (37).
- Agents to increase adiponectin:
  - Thiazolidinediones especially increase the HMW form of adiponectin (3,44).
  - Endocannabinoid receptor-1 blockers (see chapter 17).

## References

- 1- Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem.*1995; 270: 26746–9.
- 2- Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and Metabolic syndrome. *Arterioscl Thromb Vasc Biol* 2004 , 24: 29- 34.
- 3- Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J clin Invest* 2006, 116: 1784-92.
- 4- Fu Y, Luo N, Klein RL, Garvey WT. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. *J Lipid Res* 2005; 46: 1369-79.
- 5- Trujillo ME, Scherer PE. Adiponectin– journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005, 257:167–75.
- 6- Wyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni AP. Hypoadiponectinemia in Obesity and Type 2 Diabetes: Close Association with Insulin Resistance and Hyperinsulinemia. *J Clin Endocrinol Metab* 2001; 86: 1930- 5.
- 7- Lawlor DA, Smith GD, Ebrahim S, Thompson C, Sattar N. Plasma Adiponectin Levels Are Associated with Insulin Resistance, But Do Not Predict Future Risk of Coronary Heart Disease in Women. *J Clin Endocrinol Metab* 2005, 90: 5677-83.
- 8- Berg AH, Combs T, Du X.. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001, 7: 947–53.
- 9- Hanley AJG, Bowden D, Wagenknecht LE, Balasubramanyam A, Langfeld C, Saad MF, Rotter JI, Guo X, Chen Y-D I, Bryer-Ash M, Norris JM, Haffner SM. Associations of Adiponectin with Body Fat Distribution and Insulin Sensitivity in Nondiabetic Hispanics and African-Americans. *J Clin Endocrinol Metab* 2007, 92: 2665-71.
- 10- Rajala RW and Scherer PE. Minireview: The Adipocyte—At the Crossroads of Energy Homeostasis, Inflammation, and Atherosclerosis. *Endocrinology* 2003, 144: 3765-73.
- 11- Fisher FF, Trujillo ME, Hanif W, Barnett AH, McTernan PG, Scherer PE, Kumar S. Serum high molecular weight complex of adiponectin correlates better with glucose tolerance than total serum adiponectin in Indo-Asian males. *Diabetologia* 2005, 48: 1084–7.
- 12- Goldstein BJ, Scalia R. Adiponectin: A Novel Adipokine Linking Adipocytes and Vascular Function. *J Clin Endocrinol Metab* 2004, 89: 2563-8.
- 13- Hoffstedt J, Arvidsson E, Sjölin E, Wåhlén K, Arner P. Adipose Tissue Adiponectin Production and Adiponectin Serum Concentration in Human Obesity and Insulin Resistance. *J Clin Endocrinol* 2004, 89: 1391-6.
- 14- Côté M, Mauriège P, Bergeron J, Alméras N, Tremblay A, Lemieux I, Després J-P. Adiponectinemia in Visceral Obesity: Impact on Glucose Tolerance and Plasma Lipoprotein and Lipid Levels in Men. *J Clin Endocrinol Metab* 2005, 90: 1434-9.
- 15- Haluzik M, Parizkova J, Haluzik MM. Adiponectin and its role in the obesity-related insulin resistance and related complications. *Physiol Res* 2004, 53: 123-9.
- 16- Sutton BS, Weinert S, Langefeld CD, Williams AH, Campbell JK, Saad MF, Haffner SM, Norris JM, Bowden DW. Genetic analysis of adiponectin and obesity in Hispanic families: the IRAS Family Study. *Hum Genet* 2005, 117: 107–18.

- 17- Combs TP, Berg AH, Rajala MW. Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. *Diabetes* 2003; 52:268–76.
- 18- Yamauchi, T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002; 8: 1288–95.
- 19- Tsuchida, A, Yamauchi T, Ito Y, Hada Y, Maki T, Takekawa S, Kamon J, Kobayashi M, Suzuki R, Hara K. Insulin/foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. *J. Biol Chem* 2004, 279: 30817–22.
- 20- Combs, T P, Berg AH, Obici S, Scherer PE, Rossetti L.. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J. Clin Invest* 2001, 108: 1875–81.
- 21- Kershaw EE, Flier JS. Adipose Tissue as an Endocrine Organ. *J Clin Endocrinol Metab* 2004, 89: 2548-56.
- 22- Fruebis, J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 2001, 98: 2005–10.
- 23- Matsubara M, Maruoka S, Katayose S. Decreased Plasma Adiponectin Concentrations in Women with Dyslipidemia. *J Clin Endocrinol Metab* 2002, 87: 2764-9.
- 24- Masaki T, Chiba S, Yasuda T, Tsubone T, Kakuma T, Shimomura I, Funahashi T, Matsuzawa Y, Yoshimatsu H. Peripheral, But Not Central, Administration of Adiponectin Reduces Visceral Adiposity and Upregulates the Expression of Uncoupling Protein in Agouti Yellow ( $A^y/a$ ) Obese Mice. *Diabetes* 2003, 52: 2266-73.
- 25- Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, Ohashi K, Sakai N, Shimomura I, Kobayashi H, Terasaka N, Inaba T, Funahashi T, Matsuzawa Y. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002, 106: 2767-70.
- 26- Ouchi, N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF- $\kappa$ B signaling through a cAMP-dependent pathway. *Circulation* 2000, 102: 1296–301.
- 27- Ouchi, N., Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001, 103: 1057–63.
- 28- Ouchi N, Kihara S, Arita Y. Novel modulator of endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation*.1999; 100:2473–6.
- 29- Fésüs G, Dubrovská G, Gorzelnik K, Kluge R, Huang Y, Luft FC, Gollasch M. Adiponectin is a novel humoral vasodilator. *Cardiovasc Res* 2007, June Epub.
- 30- Guzik TJ, Mangalat D, Korb R. Adipocytokines – novel link between inflammation and vascular function? *J Physiol Pharmacol* 2006, 57: 505-28.
- 31- Böttner A, Kratzsch J, Müller G, Kapellen TM, Blüher S, Keller E, Blüher M, Kiess W. Gender Differences of Adiponectin Levels Develop during the Progression of Puberty and Are Related to Serum Androgen Levels. *J Clin Endocrinol Metab* 2004, 89: 4053-61.
- 32- Arita Y, Kihara S, Ouchi N. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999, 257: 79–83.
- 33- Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. *J Clin Endocrinol Metab* 2002, 87:2764–69.

- 34- Kazumi T, Kawaguchi A, Sakai K, Hirano T, Yoshino G. Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. *Diab Care* 2002, 25:971–6.
- 35- Putz DM, Goldner WS, Bar RS, Haynes WG, Sivitz WI. Adiponectin and C-reactive protein in obesity, type 2 diabetes and monodrug therapy. *Metabolism* 2004; 53: 1454-61.
- 36- Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000, 20: 1595–9
- 37- Yang W-S, Lee W-J, Funahashi T, Tanaka S, Matsuzawa Y, Chao C-L, Chen C-L, Tai T-Y, Lee-Ming Chuang L-M. Weight Reduction Increases Plasma Levels of an Adipose-Derived Anti-Inflammatory Protein, Adiponectin. *J Clin Endocrinol Metab* 2001; 86: 3815-9.
- 38- Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Matsuzawa Y. Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol.* 2003; 23: 85–89
- 39- Koz C, Uzun M, Yokusoglu M, Baysan O, Erinc K, Sag C, Hasimi A, Isik E. Evaluation of plasma adiponectin levels in young men with coronary artery disease. *Acta Cardiol* 2007, 62: 239-43.
- 40- Costacou T, Zgibor JC, Evans RW, Otvos J, Lopes-Virella MF, Tracy RP, Orchard TJ . The prospective association between adiponectin and coronary artery disease among individuals with type 1 diabetes. The Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia* 2005, 48:41–8.
- 41- Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB. Adiponectin and future coronary heart disease events among men with type 2 diabetes. *Diabetes* 2005, 54: 534–9.
- 42- Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004, 291:1730–7.
- 43- Lindsay R, Resnick H, Ruotolo G. Adiponectin and coronary heart disease: the Strong Heart Study. *Arterioscler Thromb Vasc Biol* 2005, 25: e15–6.
- 44- Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, Olefsky JM. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes* 2002, 51:2968–74.