SCHOOL OF GRADUATE STUDIES

MSc. Senior paper

The involvement of Adiponectinin Type 2 Diabetes:A systematic review of findings onhuman.

By: YohannesAbere

June 2011

Addis Ababa

A Systemic Review presented to the Department of Biochemistry in partial Fulfillment of the Requirements for the Degree of Master ofBiochemistry

Advisor:

Daniel Seifu (PhD)

June, 2011

ADDIS ABABA

TABLE OF CONTENT

Table of contents……..……..I
List of tables……II
List of Figures……III
Acronyms……...……IV
Abstract……...……..v

1. Introduction ……..……..1
2. **Literature review**…….……...3
2.1 Adiponectin……..3
2.2 Adiponectin and insulin sensitivity 7
2.3 Insulin sensitizing action of adiponectin (Mode of action)…….....9
3. **Objective**……...15
3.1 General objective…….....15
3.2 Specific objective…….....15
4. Methods……..16
3.1 Literature search strategy…….....16
3.2 Eligibility Criteria…….....16
3.3 Data extraction…….....16
5. Result……..17
6. Discussion…….....21
7. Conclusion……..23
8. Recommendation…….....24
9. Reference…….....25

ACKNOWLEGEMENT

I am thankful to my family and my helpful advisor, Dr. Daniel Siefu and everyone who helped me in making this review worthwhile.

LIST OF TABLES: PAGE No.

Table 5.1Characteristics of the identified prospective studies (N = 10) of ……19
adiponectin levels and risk of type 2 diabetes
Table 5.2 Adiponectin level in diabetes vs. non-diabetes with adjustment…….21
for covariant and ascertainment of type 2 diabetes with
adiponectin assay

LIST OF FIGURES: PAGE No.

Figure 2.1 Primary structure of adiponectin…….4

Figure 2.2 Multimeric structure of adiponectin. HMW, Middle molecular weight and Low molecular weight…….……..…5

Figure 2.3 Schematic representations of adiponectinoligomeric forms…….5

Figure 2.4 Adiponectin mRNA levels during human preadipocyte……....7

Figure 2.5 Structure of adiponectin receptors…….11

Figure 2.6 A model of adiponectin-stimulated AMPK activation in muscle cells……..13

Figure 2.7 Signal transduction by adiponectin receptor…….……....14

Figure 2.8 Hypothetical model for the actions of adiponectin……15

ACRONYM

Acrp30	Adipose Complement-Related Protein of 30 kDa
AdipoR1	Adiponectin Receptor 1
AdipoR2	Adiponectin Receptor 2
AdipoQ	Adiponectin, C1Q and collagen domain containing
AMPK	AMP activated protein Kinase
ApM1	Adipose Most abundant gene transcript 1
APPL	Adaptor protein containing Pleckstrin homology domain, Phosphotyrosine-binding domain and Leucine zipper motif)
CaMKK	$Ca2^{+}$/calmodulin-dependent protein kinase
DM	Diabetes Mellitus
ELISA	Enzyme-Linked Immunosorbent Assay
GBP28	Gelatine Binding Protein of 28 kDa
HbA1c	Hemoglobin A1C
HMW	High Molecular Weight form
HOMA-IR	Homeostasis Model Assessment-Insulin Resistance index
IGT	Impaired Glucose Tolerance
IP3	Inositol triphosphate

LMW	Low-Molecular Weight
MMW	Medium Molecular Weight
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test;
PLC	Phospholipase C
PPAR	Peroxisome Proliferator Activated Receptor
RIA	Radio Immuno Assay
SD	Standard Deviation
TNFα	Tumor Necrosis Factor α

ABSTRACT

Background: *The association of obesity with development of type 2 diabetes may be partly mediated by altered secretion of adipokines by adipose tissue. Greater adiposity down regulates secretion of adiponectin, an adipokine with anti-inflammatory and insulin sensitizing properties. The strength and consistency of the relation between plasma adiponectin and risk of type 2 diabetes is unclear.*

Objective: *To review prospective studies of the involvement of adiponectin in type 2diabetes.*

Methods: *A review search of the pub med, hinari and Google scholar search engine using different name of adiponectin and type 2 diabetes mellitus. This systemic review included prospective studies with plasma adiponectin levels as the exposure and incidence of type 2 diabetes.*

Results: *Ten prospective studies with a total of 7018 participants and 1343 incident cases of type2 diabetes were included in the review. Higher adiponectin levels were monotonically associated with a lower risk of type 2 diabetes. This inverse association was consistently observed in whites, Middle East Asians, East Asians, Asian Indians, African Americans, Japan Americans and Native Americans and the inverse relationships are not differ by adiponectin assay, method of diabetes ascertainment, duration of follow-up.*

Conclusion: *Higher adiponectin levels are associated with a lower risk of type 2 diabetes across diverse populations.*

Key words: *adiponectin, adipose tissue, type 2 diabetes*

1. INTRODUCTION

In recent years, the perception of the adipose tissue being solely an energy storage organ has extended to include an endocrine organ that plays a pivotal role in relation to energy homeostasis and metabolism (Rabe *et al.,* 2008). Adipose tissue has been traditionally considered to represent an inactive storage for energy in the form of triglycerides. However, the discovery of leptin in 1994 showed that in fact, the adipose tissue is an active endocrine gland that secretes several bio-active mediators, collectively known as adipokines. These are produced by adipocytes and other cells resident in the adipose tissue, i.e. macrophages and pre adipocytes. Adipokines are, in their majority, pro-inflammatory and contribute to atherogenesis (Lau *et al.,* 2005). A major exception to that rule is adiponectin, which has insulin sensitizing and anti-inflammatory properties (ouchi & Walsh 2007; Berg *et al.,* 2002). Furthermore, adiponectin differs from other adipokines in being secreted solely by the adipose tissue, being abundant in the circulation, and found at reduced levels in the presence of obesity (Arita *et al.,* 1999).

An increasing body of evidence indicates that some of these adipose-tissue-derived molecules are involved in the pathophysiology of obesity related insulin resistance (Kubota *et al.,* 2002). Insulin resistance is considered one of the hallmarks of pre diabetes, but also defects in insulin secretion are regarded as a key pathophysiological characteristic of type 2 diabetes. It is characterized by chronically elevated blood glucose concentrations, resulting from both defects in insulin production and insulin action (Cornier *et al.,* 2008).

Findings from animal studies and metabolic studies in humans suggest several mechanisms through which adiponectin may decrease the risk of type 2 diabetes, including suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of fatty acid oxidation and glucose uptake in skeletal muscle, and stimulation of insulin secretion.

These effects may be partly mediated by stimulatory effects of adiponectin on signaling pathways for 5-adenosine monophosphate activated protein kinase and peroxisome proliferator activated receptor (Kadowaki *et al.,* 2006; Rabe *et al.,* 2008).

Currently, the prevalence of type 2 diabetes in the United States and many other countries in the world has reached epidemic proportions (Zimmet *et al.,* 2010). In the present review, the recently discovered adipose tissue derived protein, adiponectin, will be discussed with focus on its action and sensitivity.

2. LITRATURE REVIEW

2.1 Adiponectin

Adiponectin is a secreted protein of 247 amino acids, produced exclusively by adipocytes, plays an important role in regulating glucose and lipid metabolism and controlling energy homeostasis in insulin-sensitive tissues (Scherer *et al.,* 2006). Adiponectin was independently identified by four laboratories; hence the multiple names (Scherer *et al.,* 2006; Hu *et al.,* 2002). The Lodish laboratory first discovered adiponectin in 1995 as a protein synthesized and secreted by differentiated murine 3T3-L1 adipocytes. It was named "Adipocyte Complement Related Protein of 30 kDa" (ACRP30) because of homology to Complement C1q (Scherer *et al.,* 2006). The same protein was identified independently by the Spiegelman laboratory and named (Adiponectin, C1Q and Collagen domain containing) adipoQ (Hu *et al.,* 2002). Both studies found high levels of murine leptin in plasma, suggesting an endocrine role (Scherer *et al.,* 2006; Hu *et al.,* 2002). Adiponectin was found to be highly expressed in human adipose tissue and, thus, given the name "Adipose Most abundant gene transcript 1" (APM1) (Maeda *et al.,* 1996). Independently, the protein was purified and shown to have a high affinity for gelatin cellulose resins and was named "Gelatin-Binding Protein of 28 kDa" (GBP28) (Nakano *et al.,* 1996).

The primary sequence of adiponectin contains a signal peptide at the N terminus, a variable region with no homology among different species, a collagenous region containing 22 Gly-X-Pro or Gly-X-Y repeats, and a globular domain with sequence homology to C1q in the C terminus (Figure 2.1). This sequence of adiponectin is highly conserved among mammals.

Adiponectin shares a similar modular structure with C1q and other proteins, e.g., saccular collagen of the inner ear, Hibernation-related proteins (HP-20), 25, and 27 and type VIII

and type X collagens. Moreover, the crystal structure of the C-terminal globular domain forms ahomotrimeric structure that is structurally similar to the Tumor Necrosis Factor α (TNF) super family, despite a lack of sequence homology (Berg *et al.,* 2002). Collagen-like parts of three adiponectin molecules can interact forming triple coiled coil structure much alike to that in collagen (Pajvani 2003).

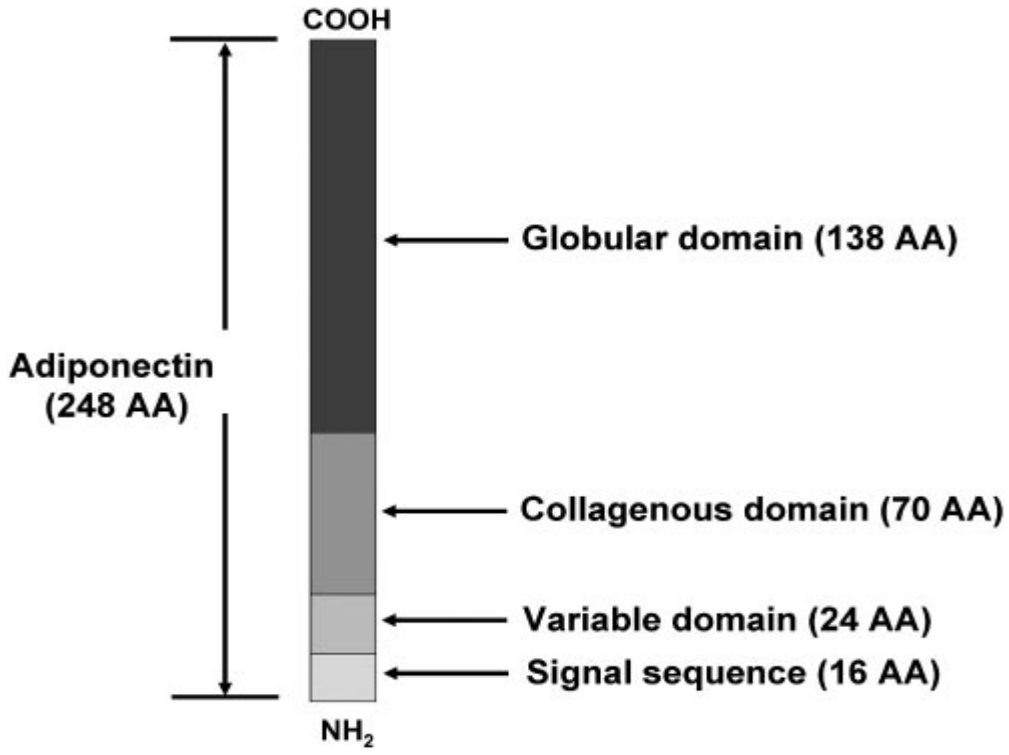

Figure 2.1 *Primary structure of adiponectin (Schraw et al., 2008)*

C1q-like domains form a "head" of adiponectin globular (Figure 2.2) and share a great degree of structural similarity to complement component C1q. Several oligomer forms of native adiponectin circulating in the blood are described in literature: trimers (Low-Molecular Weight form, LMW), hexamers (Medium Molecular Weight form, MMW) and higher order multimers (High Molecular Weight form, HMW (12 to 36 mer) (Wang *et al.,* 2002).

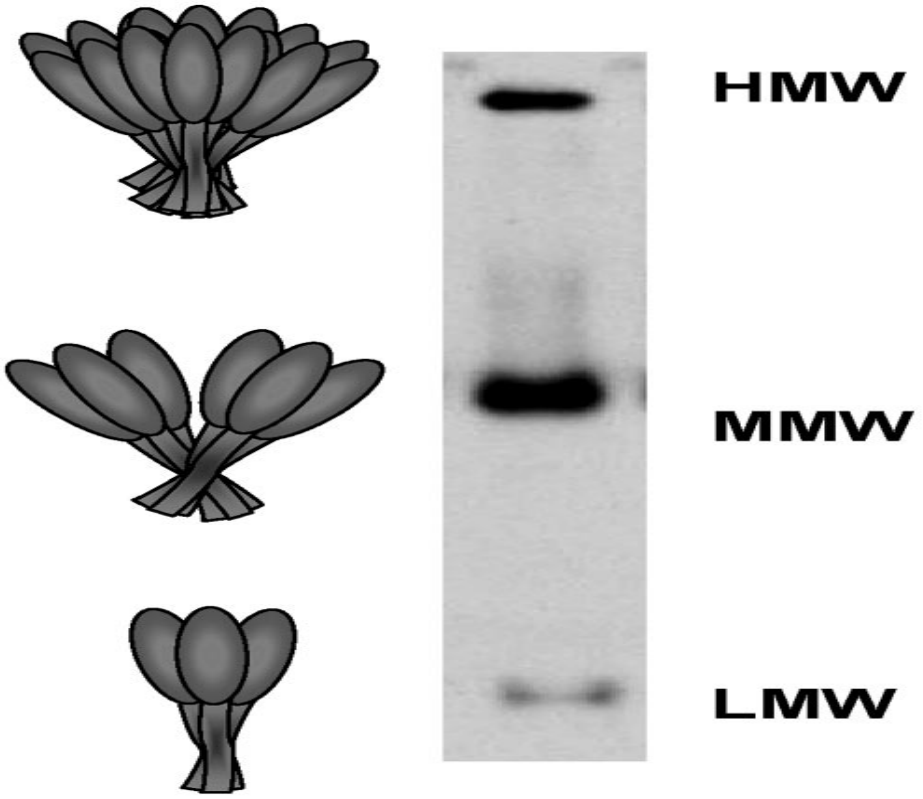

Figure 2.2*Multimeric structure of adiponectin. High molecular weight, Middle molecular weight and Low molecular weight (Schraw et al., 2008)*

Three monomers of adiponectin form a trimer. Trimers linked by disulfide bond form a hexamer (Figure 2.3). The exact structure of the high-molecular weight form of adiponectin is not yet known. Most likely several combined hexamers and/or trimers constitute high-molecular weight form of adiponectin. It is generally believed that disulfide bonds as well as some bonds withparticipation of modified amino acid residues in collagen domain of adiponectin, take part in holding subunits of high-molecular weight form of adiponectin together. It is also believed thatthose oligomeric forms exist in the blood stream as separate moieties and do not convert into each other (Wang *et al.,* 2002).

The adiponectin protein can undergo proteolytic cleavage, leading to the formation of a globular form of adiponectin containing only the globular head domain (Scherer *et al.,* 1995). The pharmacological effect of this globular fragment of adiponectin appears to be

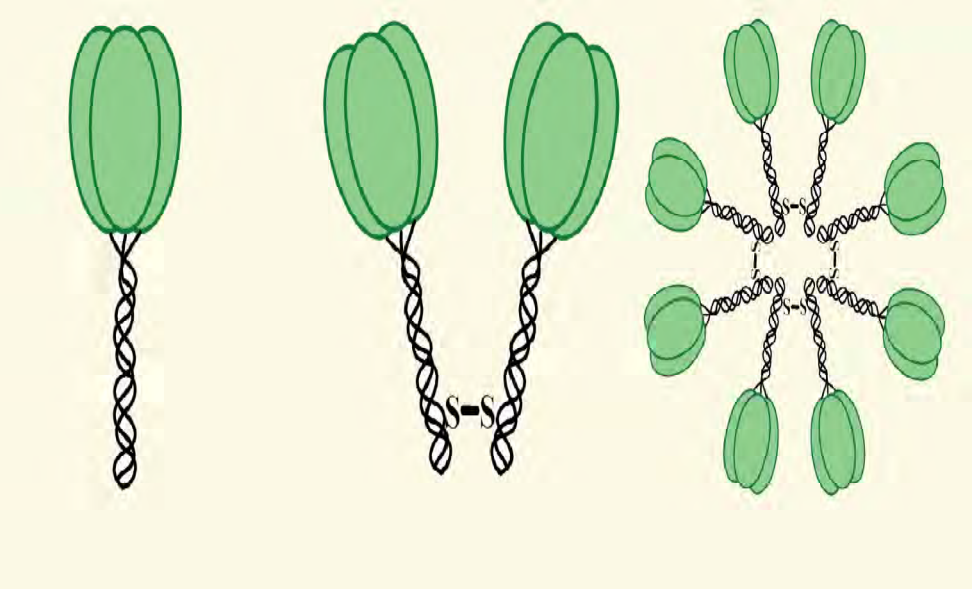

Figure 2.3 *Schematic representations of adiponectin oligomeric forms(Wang et al., 2002).*

stimulation of β-oxidation in skeletal muscle, whereas full-length adiponectin decreases hepatic glucose output (Schraw *et al.,* 2008). Thus, the primary site of action as well as the mode of action seems to be different for globular and full length adiponectin. Furthermore, the protein undergoes post-translational modification including hydroxylation and glycosylation (Yamauchi *et al.,* 2002).

The adiponectin gene is located on chromosome 3q27, and consists of three exons and two introns. This region of the chromosome has also been found to be the locus for other candidate genes with phenotypes related to features of the metabolic syndrome (Schraw *et al.,* 2008). Various conditions affect the gene expression of adiponectin in adipose

tissue. For example adiponectin gene expression is increased 50–100 fold during differentiation of 3T3-L1 adipocytes indicating that adiponectin is a marker of mature adipocytes (Yamauchi *et al.,* 2002). In accordance with these data obtained with clonal preadipocytes, we found the expression of adiponectin Messenger Ribonucleic Acid (mRNA) to be induced nearly 100- fold during differentiation of human preadipocytes in primary culture. After 13–16 day of culture, about 70– 80% of the cells were differentiated into mature adipocytes, and already after 5 day of differentiation the adiponectin messenger ribonucleic acid level was substantially increased (P<0.05, n=6) (Figure 2.4).

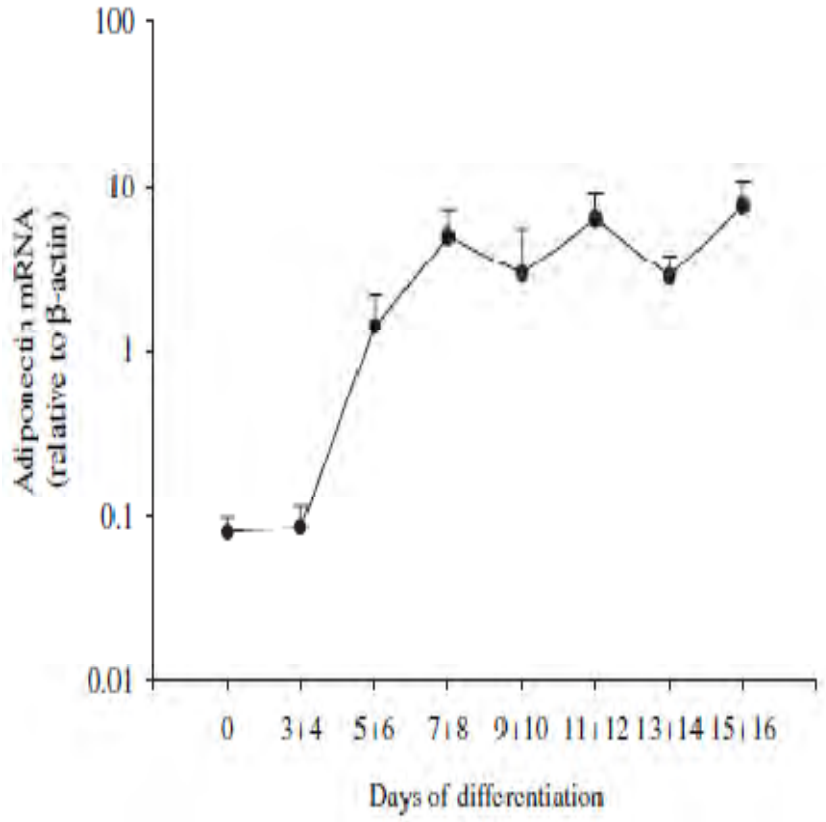

Figure 2.4*Adiponectin Messenger Ribonucleic Acid* (*mRNA) levels during human pre adipocyte differentiation (Lihn et al., 2002).*

In contrast to what is the case for most adipose-tissue produced proteins, plasma adiponectin levels are found to be lower in obese subjects than in lean subjects, and strong negative correlations between plasma adiponectin levels and body mass index (BMI) have been shown both in humans and in animals (Berg *et al.,* 2001). In accordance with these findings, the adiponectin messenger ribonucleic acid levels are also lower in adipose tissue from obese as compared with lean subjects (Nishizawa *et al.,* 2002).

Furthermore, adiponectin gene expression and protein levels are higher in subcutaneous than in intra-abdominal adipose tissue (Cnop *et al.,* 2003), albeit this has not been a consistent finding (Arita *et al.,* 1999). Preferential accumulation of Adipose Tissue (AT) in the gluteofemoral region ('gynoid obesity') has been associated with protective effects especially with respect to cardiovascular disease risk (Nishizawa *et al.,* 2002). Interestingly, adiponectin messenger ribonucleic acid levels do not seem to differ between abdominal and gluteo/femoral subcutaneous adipose tissue (Berg *et al.,* 2001). Differences in adiponectin gene expression in relation to various adipose tissue depots is, however, still not fully elucidated (Weyer *et al.,* 2001).

Adiponectin concentration in plasma is two to three orders of magnitude higher than other polypeptide hormones (Berg *et al.,* 2001). In human plasma concentrations between 2 - 30 µg mL-1, accounting for up to 0.05% of total serum protein (Berg *et al.,* 2001; Pajvani 2003, Arita *et al.,* 1999). As mentioned, plasma adiponectin levels are lower in obese subjects as compared with lean subjects (Arita *et al.,* 1999; Cnop *et al.,* 2003; Weyer *et al.,* 2001). Women have about 40% higher circulating levels of adiponectin than men (Arita *et al.,* 1999; Cnop *et al.,* 2003). The level of androgens may play a role for these gender differences because androgen appears to have an inhibitory effect on adiponectin (Nishizawa *et al.,* 2002). In addition, women display higher serum proportions of High molecular weight adiponectin as compared to men (Berg *et al.,* 2001).

Furthermore, plasma adiponectin is negatively correlated with plasma triglycerides, Low-Density Lipoprotein (LDL)-cholesterol, and positively correlated with High Density Lipoprotein (HDL)-cholesterol (Cnop *et al.,* 2003; Yamamoto *et al.,* 2002).

2.2 Adiponectin and insulin sensitivity

In rhesus monkeys genetically predisposed to develop insulin resistance showed that circulating adiponectin levels decrease in parallel with the development of insulin resistance, and thus prior to the onset of diabetes (Hotta *et al*., 2000) . In a group of First-Degree Relatives (FDR) to patients with type 2 diabetesfound that first-degree relatives were characterized by being more insulin resistant, and they had significantly lower adiponectin messenger ribonucleic acid levels in adipose tissue. Adiponectin gene expression was found to correlate positively with insulin sensitivity in control subjects, but not in first-degree relatives. These results suggest that adiponectin gene expression is dysregulated in relation to insulin resistance prior to the development of type 2 diabetes (Lihn *et al.,* 2003).

Not only obesity, where fat mass is increased, but also lipodystrophy, where fat is lost partially or totally, is associated with the development of insulin resistance (Carr *et al.,* 1998). Both lipodystrophy and the so-called HIV-associated lipodystrophy syndrome (HALS), which is a syndrome characterized by body fat redistribution and metabolic abnormalities including insulin resistance are associated with low plasma adiponectin and low expression of adiponectin in the adipose tissue (Phillips *et al.,* 2003). These data indicate that reduced plasma adiponectin levels might play a role for lipodystrophy related insulin resistance. Using a mouse model with lipodystrophy and insulin resistance found that these mice were hyperinsulinemic, hyperglycaemic, and they had no adiponectin in serum. Systemic infusion of physiological doses of recombinant adiponectin, alone or in combination with leptin, ameliorated hyperglycaemia and

hyperinsulinaemia, suggesting that insulin resistance of lipoatrophic mice be caused at least partially by a deficiency in adipocytokines such as adiponectin and leptin (Yamauchi *et al*., 2003) .

Injection of recombinant adiponectin to wild-type mice as well as to various models of insulin resistant mice resulted in a significant acute decrease in plasma glucose levels (Berg *et al.,* 2001). This glucose lowering effect was independent of plasma insulin levels, and was also observed in mice with insulin secretion deficiency, indicating that the effect most likely was mediated by enhancing insulin action. Importantly, only full-length adiponectin lowered plasma glucose levels in the study. In contrast, injection of globular but not full-length adiponectin reduced plasma glucose levels. Different approaches for the production of the recombinant proteins as well as for the post-translational modification were used in the two studies, which might explain the different findings (Fruebis *et al*., 2005).

Apart from affecting blood glucose levels, it has been suggested that adiponectin plays a role in reducing the plasma concentration of Free Fatty Acid (FFA) (Fruebis *et al*., 2005; Maeda *et al.,* 2002). This effect has been indicated by data from both adiponectin treatment and adiponectin knockout studies and it might be important for the insulin sensitizing effects of adiponectin. Interestingly, adiponectin knockout (KO) mice on normal chow displayed normal fasting plasma levels of glucose, insulin and free fatty acid; however, when fed a high-fat/high-sucrose diet, these mice developed severe insulin resistance and increased plasma free fatty acid concentrations. When subjected to adenoviral overproduction of adiponectin, the diet treated adiponectin mice displayed improved insulin sensitivity and decreased plasma levels of free fatty acid concentrations, glucose and insulin. Based on these adiponectin knockout studies, Maeda and colleagues suggested that hypoadiponectinaemia caused by over nutrition is linked to the development of insulin resistance and diabetes (Maeda *et al.,* 2002).

Recently, demonstrated that adiponectin might also decrease the hepatic fat content. They administered adiponectin to mice with fatty liver diseases and this resulted in alleviation of both steatosis and hepatomegaly. These effects were at least in part attributed to enhanced hepatic fatty acid oxidation and decreased hepatic fatty acid synthesis. The increase in hepatic lipid oxidation by adiponectin might also play a role for the beneficial effect of adiponectin on hepatic glucose metabolism (Xu *et al.,* 2003).

Recently, two reports have described mouse models with transgenic-induced hyperadiponectinaemia, albeit two different approaches were used (Yamauchi *et al.,* 2003; Combs *et al.,* 2004). First, investigated the effects of over expressing adiponectin by analyzing globular adiponectin transgenic mice with leptin deficiency. They found that these mice showed amelioration of insulin resistance and diabetes. Concomitantly, they observed increased expression of molecules involved in fatty acid oxidation in skeletal muscles. This hyperadiponectinaemia was found to increase lipid clearance, improve hepatic insulin sensitivity, and improve oral glucose tolerance. Moreover, they found increased Adenosine Mono Phosphate activated protein kinase (AMPK) activity in the liver. Thus, consistent with the results of the pharmacological studies, these two studies suggest that the effects and mechanism of action differ between globular and full-length adiponectin. The results of adiponectin knockout mice studies are, however, conflicting, and were not able to demonstrate insulin resistance either of knockout mice on normal chow or after 7 months of feeding with a high-fat diet (Ma *et al.,* 2002). In contrast, observed mild insulin resistance in heterozygousadiponectin deficient mice and moderate insulin resistance in homozygous adiponectin deficient mice. The observed differences in the phenotypes of the knockout mice might be caused by different knockout methods and the genetic background of the animals. However, taken together, the adiponectin deficiency studies indicate that adiponectin plays a protective role against the development to insulin resistance (Kubota *et al.,* 2002).

2.3 Insulin sensitizing action of adiponectin

Adiponectin has various biological functions including insulin sensitizing, anti-atherogenic, anti-inflammatory, anti-angiogenic and anti-tumour functions. The recent discovery of adiponectin receptors has helped in elucidating the more specific intracellular pathways involved in the action of adiponectin. The Adiponectin Receptor 1 (AdipoR1) was found to be predominantly expressed in skeletal muscle, but may be ubiquitously presented, whereas the expression of Adiponectin Receptor 2 (AdipoR2) was most abundant in the liver. Both receptors are related to G protein-coupled seven transmembrane domain receptors; however, the sequence homology of both AdipoR1 and AdipoR2 (Figure 2.5) with this type of receptors is low. Furthermore, the N terminal is intracellular and the C terminus is extracellular, which is opposite to the topology of classical G protein-coupled receptors (Yamauchi *et al.,* 2003).

The receptors have also been shown to be markedly expressed in pancreatic b-cells, macrophages and atherosclerotic lesions as well as in the brain (Chinetti *et al.,* 2004). Adiponectin Receptor 1 appears to be a high affinity receptor for globular adiponectin, as well as a low-affinity receptor for full length adiponectin, and it mediates Adenosine Mono Phosphate activated protein kinase activation increase in glucose uptake and fatty acid oxidation in skeletal muscle (Yamauchi *et al.,* 2003).

Adenosine mono Phosphate activated protein kinase is a multisubstrate heterotrimer that contains a catalytic α-subunit and two regulatory (β and γ) subunits which play an important role in determining substrate specificity and protein stability (Hardie 2004). Adenosine Mono Phosphate kinase is allosterically activated by increases in the ratio of Adenosine Mono Phosphate (AMP): Adenosine Tri Phosphate (ATP) or creatine: phosphocreatine, and by phosphorylation on Thr-172. It regulates a series of responses that act to restore energy balance in cells, switching of adenosine tri phosphate consuming pathways and switching on adenosine tri phosphate generating pathways which, as shown here, include increased glucose uptake and fatty acid oxidation in

muscle. Adenosine mono phosphate activated protein kinase is an energy sensor within the cells, as it activates the cellular processes that produce energy, e.g. fatty acid oxidation and glucose uptake in skeletal muscle. The C-terminal extracellular domain of

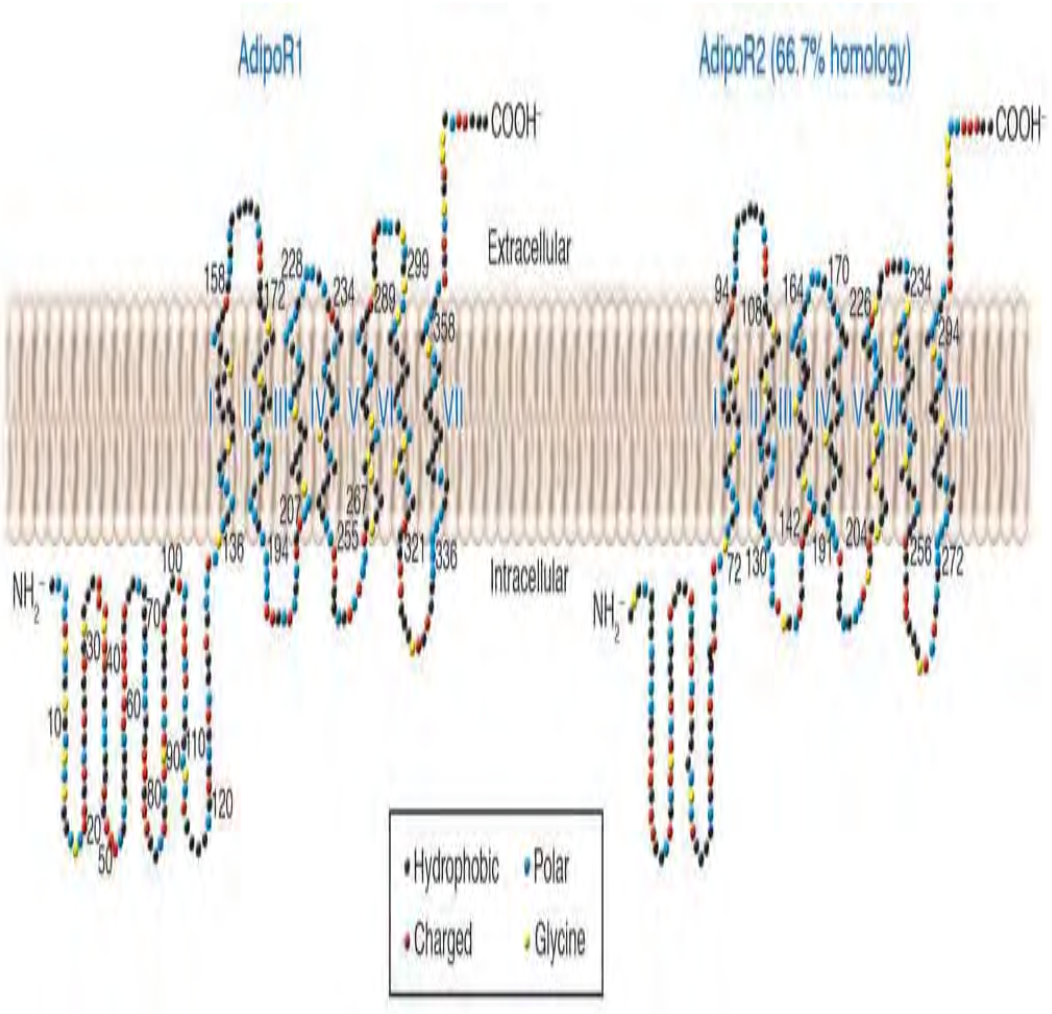

Figure 2.5*Structure of adiponectin receptors, AdipoR1 and AdipoR2 (66.7% amino acid identity with AdipoR1) are predicted to contain 7 transmembrane domains but are structurally and topologically distinct from GPCRs (Kadowaki et al., 2005)*

adiponectin receptor 1 interacted with adiponectin, whereas the N-terminal cytoplasmic domain of adiponectin receptor 1 interacted with APPL (Adaptor protein containing Pleckstrin homology domain, Phosphotyrosine-binding domain, and Leucine zipper motif) (Carling & Hardie 1999).

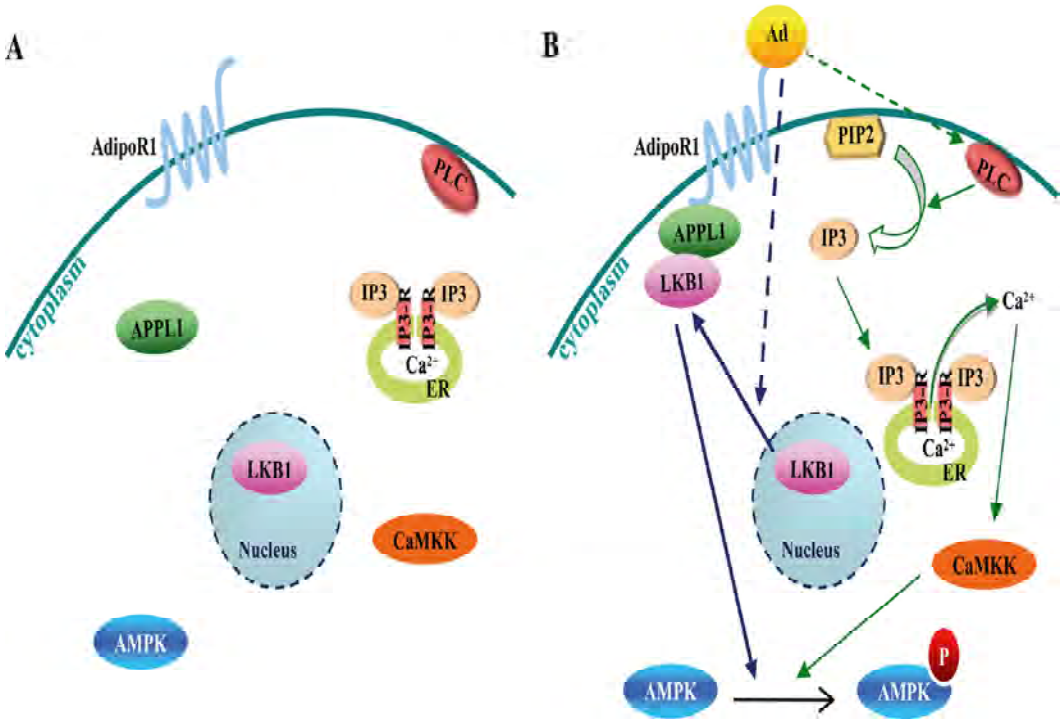

Figure 2.6*A model of adiponectin-stimulated AMPK activation in muscle cells. A, under basal conditions, LKB1 is localized in the nucleus and APPL1, CaMKK, and inactive AMPK in the cytosol. B, adiponectin stimulation induces LKB1 translocation from the nucleus into cytosol, associates with APPL1, and phosphorylates AMPK. Adiponectin also activates PLC, which subsequently produces IP3 and stimulates IP3 receptor on the ER membrane. The release of* Ca^{2+} *from the ER leads to the stimulation of CaMKK, which activates AMPK in an APPLl-independent manner (Lijun et al., 2009).*

APPL1 is the first identified protein that interacts directly with adiponectin receptors. The phosphotyrosine binding domain of APPL1 interacts directly with the intracellular region of adiponectin receptors. Through this interaction, APPL1 mediates adiponectin signaling and its effects on metabolism. APPL1 is the "missing link" in the adiponectin-signaling cascade, transmitting signals from adiponectin receptors to downstream targets by directly interacting with the NH2-terminal intracellular region of AdipoR1 (Mao *et al.,* 2006).

The binding of the adaptor protein APPL1 to adiponectin receptors is necessary for adiponectin induced adenosine mono phosphate activated protein kinase activation in muscle; however the underlying molecular mechanism remains unknown. In muscle cells adiponectin and metform in induce adenosine mono phosphate kinase activation by promoting APPL1-dependent LKB1 cytosolic translocation. APPL1 mediates adiponectin signaling by directly interacting with adiponectin receptors and enhances LKB1 cytosolic localization by anchoring this kinase in the cytosol (Lijun *et al.,* 2009).

Adiponectin also activates another adenosine mono phosphate kinase upstream kinase Ca^{2+}/calmodulin-dependent protein kinase by activating phospholipase C and subsequently inducing calcium ion release from the endoplasmic reticulum, which plays a minor role in adenosine mono phosphate kinase activation (Lijun*et al.,* 2009).

In contrast, Adiponectin receptor 2 is an intermediate- affinity receptor for both globular and full-length adiponectin, which seems to be predominantly responsible for mediating the effects of full-length adiponectin in the liver presumably also through activation of Peroxisome proliferator activated receptor or adenosine mono phosphate kinase (Yamauchi *et al.,* 2002). Adiponectin infusion decreases expression of hepatic gluconeogenic enzymes, inhibits glucose production (Figure 2.7) and enhances the hepatic effect of insulin (Combs *et al.,* 2001). Suppression of Adiponectin receptor 1 by ribonucleic acid interference markedly reduces globular adiponectin binding, whereas

suppression of Adiponectin receptor 2 by RNA interference largely reduces full length adiponectin specific binding (Kadowaki *et al.,* 2001; Yamauchi *et al.,* 2003).

In myocytes over expressing AdipoR1/R2, adiponectin stimulates PPAR, AMPK, and p38 MAPK activation, glucose uptake, and fatty-acid oxidation. Suppression of AMPK or PPAR partially reduces adiponectin-stimulated fatty acid oxidation, and suppression of AMPK of

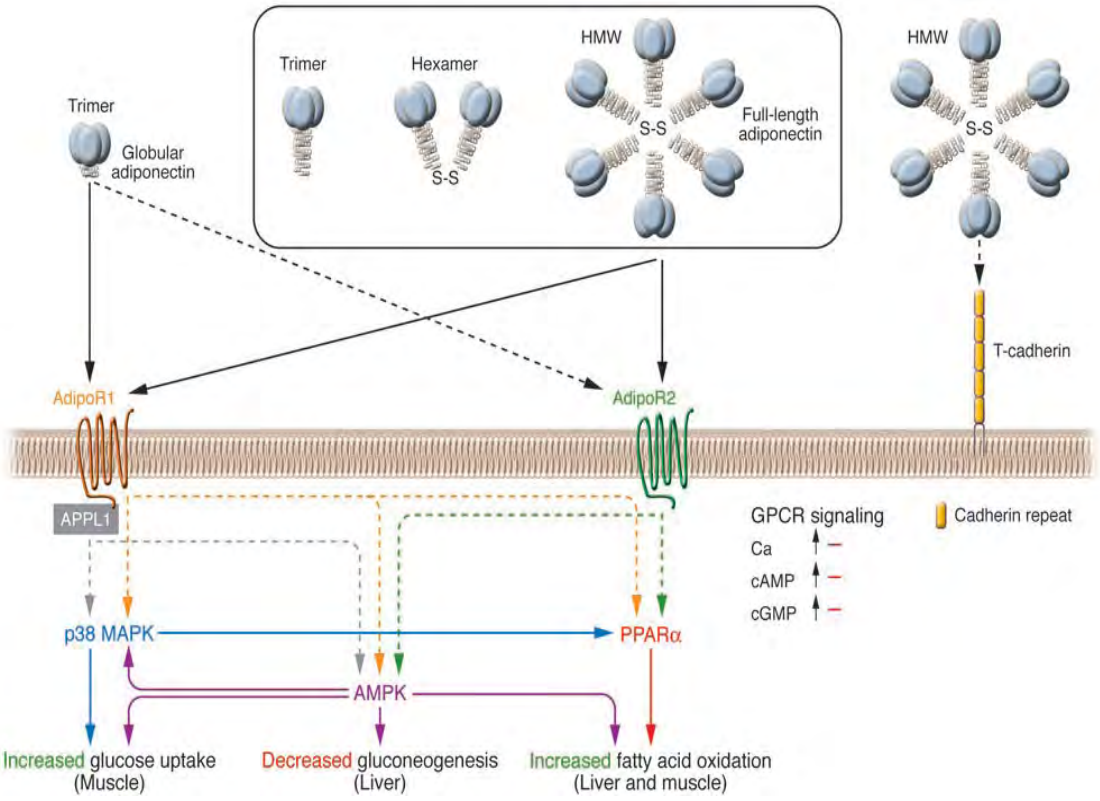

Figure 2.7 *Signal transduction by adiponectin receptors (Kadowaki et al., 2005).*

p38 mitogen-activated protein kinase (MAPK) partially reduces adiponectin-stimulated glucose uptake. In hepatocytes over expressing AdipoR1/R2, adiponectin stimulates PPAR or AMPK and fatty acid oxidation (Yamauchi *et al.,* 2003). Suppression of AMPK or PPAR in these hepatocytes partially reduces adiponectin stimulated fattyacid

oxidation. Moreover, treatment with adiponectin reduces plasma glucose levels and molecules involved in gluconeogenesis in the liver, and dominant negative AMPK partly reduces these effects. T-cadherin is capable of binding adiponectin but is thought to have no effect on adiponectin cellular signaling, since T-cadherin lacks an intracellular domain (Hug 2004).

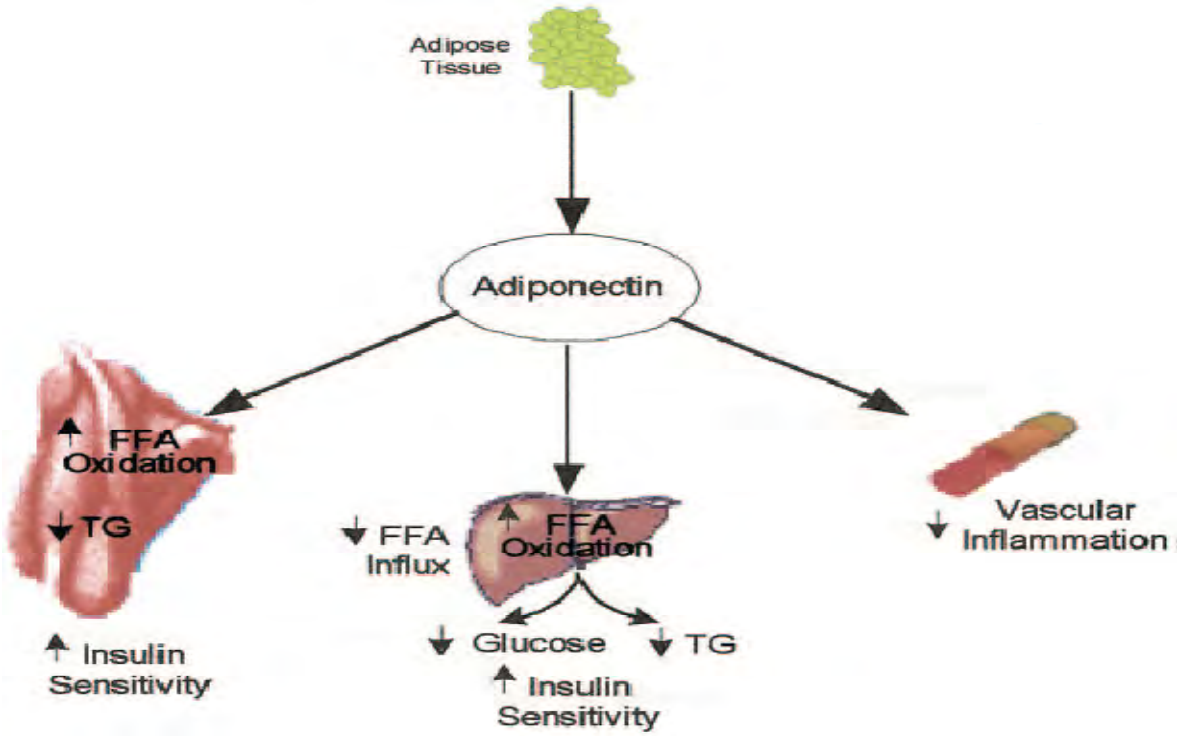

Figure 2.8 *hypothetical models for the actions of adiponectin. In skeletal muscle, adiponectin increases tyrosine phosphorylation of the insulin receptor. This effect may contribute to increased insulin sensitivity. It also increases fatty acid oxidation, probably by activation of 5AMP kinase, with resultant decreased intramyocellularsteatosis. In the liver, the decreased free fatty acid influx and increased fatty acid oxidation contribute to reduced hepatic glucose output and VLDL triglyceride synthesis(Chinetti et al., 2004).*

3. OBJECTIVE

3.1 General objective

To review prospective studies of the involvement of adiponectin levels in type 2 diabetes.

3.2 Specific objectives

To review

1. The association of adiponectin and type 2 diabetes.
2. The association between sex, obesity and adiponectin.
3. Mechanism of action of adiponectin to insulin sensitivity.

4. METHODS

4.1 Literature search strategy

The information which was searched for literatures used Pubmed central, Hinari, Google scholar search engine. The following terms were used for search**:** *adiponectin* OR *ADIPOQ* OR *ACDC* OR *ACRP30* OR *APM1* OR *GBP28* OR *C1q* and *type 2 diabetes mellitus.* Only English language was applied for searching and review inclusion.

4.2 Inclusion Criteria

In this review only included prospective studies (Case-control, Cohort, Case- cohort) of plasma adiponectin concentrations and type 2 diabetes (i.e., studies with adiponectin levels measured in blood collected before and after the onset of diabetes) in humans with a minimum follow-up duration of 1 year. In order to be in the review, studies had to individual level and to be published after 2003 and also included three studies were reported separately for diabetes and Impaired Glucose Tolerance (IGT).

4.3 Data Extraction

For each included article, The information extracted on the title, authors, publication year, name of the study, sample size, number of diabetes cases, study design, mean (standard deviation) 99% CI and OR of 95%CI for the adiponectin level, duration of follow-up, mean age, country, race/ethnicity, proportion of women, assay for measuring adiponectin levels and adjustment for covariant.

5. RESULTS

The review contain 10 prospective studies (Cohort studies, Case-control and Case cohort studies) that met in the inclusion criteria, all studies could be used in the review of adiponectin levels in type 2 diabetes mellitus expressed in μg/mL. Table 5.1 shows the characteristics of the identified prospective studies of adiponectin levels and risk of type 2 diabetes. The studies included 7 cohort studies and 3 case cohort study and also studies included largely white, a mixture of whites and African Americans, Asian Indians, a mixture of white Japan Americans, Mexico children & African American peoples. Type 2 diabetes was ascertained using an oral glucose tolerance test in 7studies, self-monitoring report in 2 studies and self-monitoring or fasting or non –fasting glucose test in 1 study. Table 5.2 shows the results of the individual studies for adiponectin levels and risk of type 2 diabetes.

Table 5.1*Characteristics of the identified prospective studies (N = 10) of adiponectin levels and risk of type 2 diabetes.*

Source and country	**Population character**	**Study Design**	**Follow up, Y**	**Age, Mean (SD), y**	**Number of women(men)**	**Diabetes Number Yes No**
Snehalatha *et al.,* 2003 India	Participants with IGT in a lifestyle intervention study	Cohort	1	45 (5)	91 38(53)	25 66
Cruz *et al.,* 2004 Mexico	Mexican children	Case-Cohort	6	13(2)	113 63(50)	40 73
Duncan *et al.,* 2004 United state	Black and white residents of US communities	Case-cohort	8.9	53(6)	767 697(70)	581 572
Osei *et al.,* 2005 USA	African Americans	Case-cohort	7	47(2)	41	14 27
Snijder *et al.,* 2006 Netherlands	Residents of the town of Hoorn	Cohort	6.4	60(7)	1264 680(584)	118 1136

Nakashima *et al.,* 2006 United States	Japanese Americans	Cohort	5.4	Diabetes 64(12) Non diabetes: 61(15)	766 445(32)	112 654
Koenig *et al.,* 2006 Germany	Residents of the Augsburg area (mixed urban/rural)	Cohort	18	54 (6)	887 0(887)	115 772
Taghi *et al.,* 2007 Iran	Postmenopausal Women	Case-Control	4	57(6)	70 70(0)	28 42
Wannamethee *et al.,*2007 United Kingdom	Men from general practices in 24 British towns	Cohort	5	67(5)	3599	108 3491
Zurawska *et al.,* 2009 Poland	Member of Medical University of Lodz, Poland & from diabetes outpatient medical clinic	Cohort	2	67(10)	96 52(44)	64 32

Table 5.2*Adiponectin level in diabetes vs. non-diabetes, adjustment for covariant, ascertainment of type 2 diabetes and adiponectin assay.*

Source	**Adiponetin assay**	**Ascertainment of Type 2 Diabetes**	**Adjustments for covariant**	**Adiponectin level in mean ± SD, µg/ml,in type2DM vs. non type2 DM (respectively)**
Snehalatha *et al.,* 2003	RIA	OGTT	-HbA1c	11.3 ± 5.5, 16.7 ± 7.6 P<0.0017
Cruz *et al.,* 2004	RIA	OGTT	- Sex, BMI, HOMA-IR, HbA1c, Fasting glucose, insulin	11.8 ±5.5, 17.6 ±6.6 P=0.001
Duncan *et al.,* 2004	RIA	Self-monitoring report, fasting or non-fasting glucose level	Age, BMI, waist-hip ratio, race, study center, family History of diabetes, hypertension, fasting glucose and insulin	10.2± 4.3 15.1± 2.2 P<0.05
Osei *et al.,* 2005	ELISA	OGTT	-Age, sex, BMI, HOMA-IR - fasting and 2-h glucose, fasting and 2-h insulin, ,HbA1c	6.74 ± 1.95 9.61 ± 5.09 P<0.01

Snijder *et al.,* 2006	RIA	OGTT	Age, waist-hip ratio, smoking, performance of sports, fasting and 2-h glucose, triglyceride	16.60 ±1.26 12.67 ±1.03 P<0.001 In women
Nakashima *et al.,* 2006	ELISA	OGTT	-Age, sex, BMI -waist-hip ratio, -HOMA-IR, -glucose tolerance Classification	9.47 ± 0.48 11.69 ±0.25 HMW 7.60 ±0.20 5.38 ± 0.35 P<0.001
Koenig *et al.,* 2006	ELISA	Self-monitoring report	Age, BMI, smoking, alcohol intake, physical activity, hypertension, history of myocardial infarction	5.0(3.5–7.8) 6.4 (4.6–9.2), p <0.001.
Taghi*et al.,* 2007	ELISA	OGTT	-Age -BMI -HbA1c	7.29±1.42 10.29±1.93 P<0.001
Wannamethee *et al.,* 2007	ELISA	Self-monitoring report	Age, BMI, social class, HOMA-IR, physical activity, smoking, alcohol intake, HDL-C	4.96(3.33-7.36) 7.04(4.49-11.41), P<0.0001
Zurawska *et al.,* 2009	ELISA	OGTT	-Age, BMI -waist circumference -WHR -fasting glucose	7.26 ± 4.42; 13.76 ± 5.90, P<0.001

6. DISCUSSION

Risk of type 2 diabetes appeared to decrease monotonically with increasing adiponectin levels. The association was Consistent for whites, East Asians, Asian Indians, African Americans, and Native Americans. The inverse relationships did not differ by adiponectin assay, method of diabetes ascertainment, study size, follow- up duration. As shown in Table 5.2 substantial associations between adiponectin levels and diabetes risk remained after adjustment for covariant (all covariates are baseline characteristics).

Data from studies suggested that associations between adiponectin levels and risk of type 2 diabetes were stronger in women than in men (Snijder *et al.,* 2006) and stronger in obese than in lean persons, P<0.001 (Wannamethee *et al.,* 2007). Women have about 40% higher circulating levels of adiponectin than men (Arita *et al.,* 1999; Cnop *et al.,* 2003). The level of androgens may play a role for these gender differences because androgen appears to have an inhibitory effect on adiponectin (Nishizawa *et al.,* 2002). In addition, women display higher serum proportions of high molecular weight adiponectin as compared to men (Berg *et al*., 2001). Adiponectin levels are significantly reduced among obese subjects in comparison with lean control subjects. Mean plasma adiponectin levels were 3.7 mg/ml in a group of obese patients, whereas in non-obese subjects these values reached a mean of 8.9 mg/ml (Arita *et al.,* 1999). In a recent longitudinal study, plasma adiponectin concentrations decreased with increasing adiposity in a group of children evaluated at 5 and 10 years of age (Cnop *et al.,* 2003). Recent evidence also suggests that weight loss induces an increase in adiponectin levels in obesity. In a group of 22 obese patients, who were treated by gastric partition surgery, a 46% increase in mean plasma adiponectin level was accompanied by a 21% reduction in mean body mass index (Kern *et al.,* 2001). Changes in plasma adiponectin were related to changes in body mass index, waist and hip circumferences. These data suggest the existence of a negative feedback mechanism between adipose mass and the production of adiponectin in humans.

Plasma adiponectin levels are reduced not only among obese patients but also among patients with some of the disease states frequently associated with obesity, such as type 2 DM and CAD. Because Tumor Necrosis Factor α (TNF α) expression is positively correlated with Body mass index (BMI), and several lines of evidence indicate a mutual negative regulation between tumor necrosis factor α and adiponectin, Tumor necrosis factor α could be the adipocytokine, which is suppressing adiponectin levels when fat mass is increased (Kubota *et al.,* 2002). However, other study did not report significant differences by sex and obesity (Duncan *et al.,* 2004).

Another Case-control study, performed on 28 diabetes and 42 healthy post-menopausal women, shown that plasma adiponectin is negatively correlated with total, LDL-cholesterol, TG and positively correlated to HDL-cholesterol with 95% CI (Taghi *et al.,* 2007). In a large number of non-diabetic women with dyslipidemia have shown that plasma adiponectin is negatively correlated with serum triglyceride and positively correlated with serum HDL-cholesterol (Matsubara *et al.,* 2003). These data suggest that low adiponectin concentrations are associated with some of the well-known risk factors for type 2 diabetes. However, a cohort study in 2003 did not report significant differences by total cholesterol and LDL-C (Snehalatha *et al.,* 2003).

Most of the study shows that plasma adiopnectin level has inverse relationship to insulin and calculated insulin resistance. In a group of non-diabetes Japan Americans, plasma adiponectin was negatively correlated with serum 2-hr and fasting insulin and calculated insulin resistance, $P< 0.001$ (Nakashima *et al.,* 2006). But a recent study performed on 64 diabetes patients and 32 healthy people, has shown that no significant correlation between adiponectin level and both insulin and calculated insulin resistance (Zurawska *et al.,* 2009).

From the review, the difference in adiponectin level between non-diabetic and diabetic patient higher in Pima Indians as compared with other racial/ethnic groups. Asian Indians have a high risk of diabetes and have an obesity phenotype characterized by lean Body

mass index, central obesity, and high body fat percentage. In addition, Asian Indians also have high degree of insulin resistance (Banerji *et al.,* 1999; Snehalatha & Ramachandran 1999).

This review focused on total adiponectin levels, because only the Nurses' Health Study (Nakashima *et al.,* 2006) reported associations for levels of high-molecular weight adiponectin and risk of type 2 diabetes. In the study, associations with diabetes risk were slightly stronger for high-molecular-weight adiponectin as compared with total adiponectin. Recently study showed that injection of high-molecular-weight adiponectin, but not Low-Molecular Weight (LMW) adiponectin, reduced plasma glucose levels, and that an increase in the proportion of high-molecular-weight adiponectin correlates with improved hepatic insulin sensitivity (Pajvani *et al.,* 2003). Increases in the ratio of plasma HMW adiponectin levels to total adiponectin levels correlate with improvement in insulin sensitivity during treatment with an insulin-sensitizing drug, TZD, in both mice and human diabetic patients, whereas increases in total serum adiponectin levels do not show good correlations with improvement in insulin sensitivity during treatment with TZD at the individual level. The level of plasma HMW adiponectin was reported to be associated with parameters related to glucose homeostasis in a cohort study. It is noteworthy that the ratio of plasma HMW adiponectin to total adiponectin correlated more significantly with glucose and insulin levels than did the total adiponectin level, suggesting that alterations in plasma HMW adiponectin level may be more relevant to the prediction of insulin resistance than are total plasma adiponectin alterations (Trujillo & Scherer 2005).

A high adiponectin level was strongly associated with a lower risk of Impaired Glucose Tolerance (IGT)OR for IGT (95% CI) for highest compared with lowest adiponectin quartile were 0.28 (0.12– 0.68),(Snijder *et al.,* 2006). An expert committee sponsored by the American Diabetes Association (ADA) has identified an intermediate group of patients who have blood glucose values that are higher than the defined normal level but not high enough to meet the diagnostic criteria for diabetes (Genuth *et al.,* 2003). This group includes patients with impaired glucose tolerance. Impaired glucose tolerance is

defined as two-hour 75-g oral glucose tolerance test values of 140 to 199 mg per dL (7.8 to 11.0 mmol per L), normal values on this test are below 140 mg per dL. Impaired glucose tolerance is defined as fasting plasma glucose values of 100 to 125 mg per dL (5.6 to 6.9 mmol per L), normal fasting glucose values are below 100 mg per dL. Patients with impaired glucose tolerance or impaired fasting glucose are at significant risk for type 2 diabetes (Capes *et al.,* 2001) Recent studies of patients with impaired glucose tolerance have shown success for lifestyle interventions in delaying or preventing the development of diabetes (Knowler *et al.,* 2002). There is strong evidence that a structured program of diet and exercise can reduce the risk of progression to type 2 diabetes in patients with impaired glucose tolerance. Patients with impaired fasting glucose and impaired glucose tolerance should be advised on the benefits of modest weight loss, good dietary habits, and regular physical activity (Capes *et al.,* 2001). However, other studies shows the adiponectin level in control and impaired glucose tolerance are not significant and consider as similar (Snehalatha *et al.,* 2003; Osei *et al.,* 2005).

From the present review, an emerging paradigm of adiponectin as an insulin enhancer is evolving. The suggested mechanisms appear to depend on adiponectin isoforms. Full-length adiponectin seems to be the predominant form of endogenous adiponectin, and especially high-molecular-weight adiponectin oligomers have been related to metabolic effects. The primary site of action for full-length adipoenctin appears to be the liver, where it activates 5-adenosine monophosphate activated protein kinase. By still uncertain mechanisms, this leads to a decrease in hepatic glucose output. In contrast, globular adiponectin, which might be less important as a physiological molecule, but with pharmacological potential, seems to act predominantly in skeletal muscles through adipoR1 receptors causing increased glucose uptake and fatty acid oxidation (Yamauchi *et al.,* 2002).

Prior study demonstrates that expression of these receptors is decreased in mouse models of insulin resistance (Kadowaki *et al.,* 2006). Animal studies show that adiponectin receptor 1 knockout results in the abrogation of adiponectin-induced activation of 5-adenosine monophosphate activated protein kinase and increased glucose production and insulin resistance (Kadowaki *et al.,* 2006; Rabe *et al.,* 2008). Targeted disruption of adiponectin receptor 2 leads to decreased activity of peroxisome proliferator activated receptor signaling pathways and insulin resistance (Kadowaki *et al.,* 2006). Animal studies suggest increased susceptibility to diet-induced insulin resistance among adiponectin knockout mice, and injection of recombinant adiponectin dramatically improves hepatic insulin sensitivity (Kadowaki *et al.,* 2006; Rabe *et al.,* 2008). In rhesus monkeys, changes in adiponectin levels are closely associated with changes in insulin sensitivity in humans; higher adiponectin levels are associated with higher insulin sensitivity (Weyer *et al.,* 2003).

7. CONCLUSION

Adiponectin is a novel adipocyte-specific protein, which, it has been suggested, plays a role in the development of insulin resistance. Although it circulates in high concentrations, adiponectin levels are lower in obese subjects than in lean subjects.

Present systematic review show that higher adiponectin levels are consistently associated with a lower risk of type 2diabetes in prospective studies of diverse populations. Currently, adiponectin is among the strongest and most consistent biochemical predictors of type 2 diabetes (Sattar *et al.,* 2008). Although this review cannot establish causality, the consistency of the association across diverse populations and the supportive findings in mechanistic studies indicate that adiponectin is a promising target for the reduction of risk of type 2diabetes. Recent studies have shown that adiponectin levels can be increased through pharmaceutical and lifestyle interventions (Fargnoli *et al.,* 2008; Swarbrick *et al.,* 2008). In addition, adiponectin levels may be useful for identifying persons likely to benefit most from interventions to treat "dysfunctional adipose tissue" and its metabolic complications (Hajer *et al.,* 2008).

8. FUTURE PERSPECTIVES

Despite these issues, the anti-inflammatory and prediction of atherosclerosis properties of adiponectin are certainly of major interest as they may have potential therapeutic applications. Well designed studies using appropriate analytical methodologies and well characterized individuals are necessary and future studies to evaluate whether adiponectin is useful for prediction of type 2 diabetes in addition to established risk factors and to clarify the relationship of adiponectin with adiposity-related disorders. Future studies in the strength and consistency of the relation between plasma adiponectin and risk of type 2 diabetes.

9. REFERENCE

Adamczak M. **(2003)** Decreased plasma adiponectin concentration in patients with essential hypertension. *Am J Hypertens* 16:72–75.

Arita Y, Kihara S,Ouchi N. **(1999)** Paradoxical decrease of an adipose specific protein adiponectin, in obesity. *Biochem Biophys Res Commun* 257:79-83.

Banerji M, Faridi N, Atluri R, ChaikenR, Lebovitz H. **(1999)** Body composition, visceral fat, leptin and insulin resistance in Asian Indian Men. *J Clin Endocr Metab* 84:1137–1144.

Berg A, Combs T, Du X, Brownlee M, Scherer P. **(2001)** The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 7:947–953.

Brakenhielm E, Veitonmaki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, Funahashi T, Cao Y. **(2004)** Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proc Nat Acad Sci USA* 101:2476–2481.

Bruun J, Lihn A, Verdich C. **(2003)** Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. *Am J Physiol EndocrMetab* 285: 527-533.

Capes S, Anand S. (2001) What is type 2 diabetes? In: Gerstein HC, Haynes RB, eds. Evidence-based diabetes care. Hamilton Ont Decker 151–63.

Carling D, Hardie D. **(1989)** The substrate and sequence specificity of the AMP- activated protein kinase. Phosphorylation of glycogen synthase and phosphorylase kinase.*Biochem Biophys Acta* 1012:81–86.

Carling D. **(2005)** AMP-activated protein kinase: balancing the scales. *Biochem* 87:87–91.

Chinetti G, Zawadski C, Fruchart J, Staels B. **(2004)** Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPAR alpha, PPAR gamma, and LXR. *Biochem Biophys Res Commun* 314:151–158.

Cnop M, Havel P, Utzschneider K, Carr D, Sinha M, Boyko E, Retzlaff B, Knopp R, Brunzell J, Kahn S. **(2003)** Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diab* 46: 459–469.

Combs T. **(2003)** Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin.*Diab* 52:268–276.

Combs T, Berg A, Obici S, Scherer P, Rossetti L. **(2001)** Endogenous glucose production is inhibited by the adipose-derived proteinAcrp30. *J Clin Invest* 108:1875–1881.

Cornier M, Dabelea D, Hernandez T, Lindstrom R, Steig A, Stob N, Van Pelt R, Wang H, Eckel R**. (2008)** The metabolic syndrome. *Endocr Rev* 29:777–822.

Cruz M, Garcla-Macedo R, Garcla-valerlo Y, Gutierrez M, Media-Navarro R, Duran G, Wachera N, Kunate J. **(2004)** Low Adiponectin Levels Predict Type 2 Diabetes in Mexican Children. *Diab* 27:3567-3573.

Daimon M, Oizumi T, Saitoh T. **(2003)** Decreased serum levels of adiponectin are a risk factor for the progression to type 2diabetes in the Japanese Population: the Funagata study. *Diab* 26:2015-20.

Diez J, Iglesias P. **(2003)**The role of the novel adipocyte-derived adiponectin in human disease. *Eur J of Endocr* 148:293–300.

Duncan B, Schmidt M, Pankow J. **(2004)** Adiponectin and the development of type 2 diabetes: the Atherosclerosis Risk in Communities Study. *Diab* 53:2473-2478.

Fargnoli J, Fung T, Olenczuk D, Chamberland J, Hu F, Mantzoros C. **(2008)** Adherence to healthy eating patterns is associated with higher circulating total and high-molecular-weight adiponectin and lower resistin concentrations in women from the Nurses' Health Study. *Am J Clin Nutr* 88:1213-1224.

Fortson J, Howe L, Harmon C, Sherrill W**. (2008)** Targeting cardiovascular risks early identification of insulin resistance. *J Am Acad Nurse Pract* 20:319–325.

Fruebis J, Tsao T, Javorschi S, Ebbets-Reed D, Erickson M, Yen F, Bihain B, Lodish H. **(2005)** Proteolysis cleavage product of30-kDa adipocyte complement- related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 98:2005–2010.

Genuth S, Alberti K, Bennett P, Buse J, Defronzo R, Kahn R. (2003) Follow-up report on the diagnosis of diabetes mellitus. Diab 26:3160–7.

Hajer G, Haeften T, Visseren F. **(2008)** Adipose tissue dysfunction in obesity, diabetes and vascular diseases.*Eur Hea J* 29:2959-2971.

Hara K, Boutin P, Mori Y. **(2002)** Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diab* 51:536-40.

Hardie D. **(2004)** AMP-activated protein kinase: a key system mediating metabolic responses to exercise. *Med Sci Sports Exerc* 36:28–34.

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. **(2000)** Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Bio* 20:1595–1599.

Hotamisligil G. **(1999)** Mechanisms of TNF alpha induced insulin resistance. *Exp Clin Endocr Diab*107:119–125.

Hu E, Liang P, Spiegelman B. **(2005)** AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biochem* 271:10697–10703.

Hug C**. (2004)** T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Nat Acad Sci USA* 101:10308–10313.

Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. **(2006)** Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 116:1784-1792.

Kadowaki T, Yamauchi T. **(2001)** Adiponectin and adiponectin receptors.*Endocr Rev* 26:439–451.

Kern P, Ranganathan S, Li C, Wood L, Ranganathan G. **(2001)** Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol EndocrMetab* 280:E745–E751.

Kharroubi I, Rasschaert J, Eizirik D, Cnop M. **(2003)** Expression of adiponectin receptors in pancreatic beta cells. *Biochem Biophys Res Commun* 312:1118–1122.

Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda T. **(2002)** Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biochem* 277:25863–25866.

Knobler H, Benderly M, Boyko V, Behar S, Matas Z, Rubinstein A, Raz I, Wainstein J. **(2006)** Adiponectin and the development of diabetes in patients with coronary artery disease and impaired fasting glucose. *Eur J of Endocr* 154:87– 92.

Koenig W, Khuseyinova N, Baumert J, Meisinger C, Lowel H. **(2006)** Serum concentrations of adiponectin and risk of type 2 diabetes mellitus and coronary heart disease in apparently healthy middle-aged men: results from the 18-year follow-up of a large cohort from southern Germany. *J Am Coll Cardiol* 48:1369-1377.

Kumada M. **(2003)** Association of hypoadiponectinemia with coronary artery disease in men.*Arterioscler Thromb VascBio* 23:85–89.

Lau D, Dhillon B, Yan H. **(2005)** Adipokines: molecular links between obesity and atheroslcerosis. *Am J Physiol Hea Circ Physiol* 288:2031-2037.

Lihn A, Bruun J, He G, Pedersen S, Jensen P, Richelsen B. **(2004)** Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. *Mol Cell Endocr* 219:9–15.

Lijun Z, Sathyaseelan S, Julie C, Jiyoon R, Xuming M, Qichen F, Dianna D. L, Jesus M, Weiping J, James D, Feng L, Lily Q. **(2009)** Adiponectin Activates AMP-activated

Protein Kinase in Muscle Cells via APPL1/LKB1-dependent and phospholipase C/Ca^{2+}/Ca^{2}+/Calmodulin-dependent Protein Kinase Kinase- dependent path ways. *J Biochem USA* 284:22426–22435.

Lindsay R, Funahashi T, Hanson R, Matsuzawa Y, Tanaka S, Tataranni P, Knowler W, Krakoff J. **(2002)** Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360: 57–58.

Liu J, Yao F, Wu R, Morgan M, Thorburn A, Finley R, Chen Y. **(2002)** Mediation of the DCC apoptotic signal by DIP13. *J Biochem* 277:26281–26285.

Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. **(2002)** cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiposeMost abundant Gene transcript 1). *Biochem Biophys Res Commun* 221: 286–289.

Matsubara M, Katayose S, Maruoka S. **(2003)** Decreased plasma adiponectin concentrations in non-diabetic women with elevated homeostasis model assessment ratio. *Eur J Endocr* 148:343–350.

Ma K, Cabrero A, Saha P, Kojima H, Li L, Chang B, Paul A, Chan L. **(2002)** Increased beta-idation but no insulin resistance or glucose intolerance in mice lacking adiponectin. *J Biolchem* 277:34658–34661.

Mao X, Kikani C, Riojas R, Langlais P, Wang L, Ramos F, Fang Q, Christ-Roberts C, Hong J, Kim R, Liu F, Dong L. **(2006)** APPL1binds to adiponectin receptors and mediates adiponectin signaling and function. *Nat Cell Bio* 8:516–523.

Matsushita K. **(2006)** Comparison of circulating adiponectin and proinflammatory markers regarding their association with metabolic syndrome in Japanese men.*Arterioscler Thromb Vasc Biol* 26:871–876.

Nakamura Y, Shimada K, Fukuda D, Shimada Y, Ehara S, Hirose M, Kataoka T, Kamimori K, Shimodozono S, Kobayashi Y, Yoshiyama M, Takeuchi K, Yoshikawa J**. (2004)** Implications of plasma concentrations of adiponectin in patients with coronary artery disease. *Hea* 90:528–533.

Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. **(1996)** Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. *J Biochem* 120:803–812.

Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A, Kohno N. **(2006)** Decreased total and high molecular weight adiponectin are independent risk factor for the development of type 2 diabetes in Japanese-Americans. *J Clin Endocr Metab* 91:3873-3877.

Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, Matsuda M, Kondo H, Furuyama N, Kihara S, Nakamura T, Tochino Y, Funahashi T, Matsuzawa Y. **(2002)** Androgens decrease plasma adiponectin, an insulin-senitizing adipocyte derived protein. *Diab* 51:2734–2741.

Nishizawa H. **(2002)** Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte- derived protein. *Diab* 51:2734–2741.

Ouchi N, Walsh K. **(2007)** Adiponectin as an anti-inflammatory factor. *Clin Chim Acta* 380:24-30.

Osei K, Gaillard T, Schuster D. **(2005)** Plasma Adiponectin Levels in High Risk African Americans with Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes. *Obes Res* 13:179–185.

Ouch N. **(2003)** Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertens* 42:231–234.

Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. **(1999)** No modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circul* 100:2473–2476.

Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, Okamoto Y, Ohashi K, Nagaretani H, Kishida K, Nishizawa H, Maeda N, Kobayashi H, Hiraoka H, Matsuzawa Y**. (2003)** Reciprocal association of C-reactive protein with Aadiponectin blood stream and adipose tissue. *Circul* 107:671–674.

Pajvani U, Hawkins M, Combs T, Rajala M, Doebber T, Berger J, Wagner J, Wu M, Knopps A, Xiang A, Utzschneider K, Kahn S, Olefsky J, Buchanan T, Scherer P. **(2003)** Complex distribution, not absolute amount of adiponectin, correlates with Thiazolidinedione mediated improvement in insulin sensitivity. *J Biochem* 279:12152–12162.

Pajvani U. **(2003)** Structure-function studies of the adipocyte-secreted hormone Acrp30 adiponectin. *J B C* 278:9073-9085.

Pischon T, Girman C, Hotamisligil G, Rifai N, Hu F, Rimm E. **(2004)** Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 291:1730–1737.

Rabe K, LehrkeM, Parhofer K, Broedl U. **(2008)** Adipokines and insulin resistance. *Mol Med* 14:741-751.

Sattar N, Wannamethee S, Forouhi N. **(2008)** Novel biochemical risk factors for type 2 diabetes: pathogenic insights or prediction possibilities. *Diab* 51:926-940.

Scherer P, Williams S, Fogliano M, Baldini G, Lodish H. **(1995)** A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biochem* 270:26746–26749.

SchrawT, Wang Z, Halberg N, Hawkins M, Scherer P. **(2008)** Plasma adiponectin complexes have distinct biochemical characteristics. *Endocr* 149:2270-82.

Shapiro L, Scherer S. **(2004)**The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Curr Bio* 8:335–8.

Snehalatha C, Ramachandran A. (1999) Insulin resistance in Asian Indians. *Prac Diab Inter* 16:19–22.

Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner S, Ramachandran A. **(2003)** Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. *Diab* 26:3226-3229.

Snijder M, Heine R, Seidell J. **(2006)** Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the hoorn Study. *Diab* 29:2498-2503.

Spranger J, Kroke A, Mohlig M, Bergmann M, Ristow M, Boeing H, Pfeiffer A. **(2003)** Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–228.

Swarbrick M, Havel P. **(2008)** Physiological, pharmacological, and nutritional regulation of circulating adiponectin concentrations in humans. *Metab Syndr Relat Disord* 6:87-102.

Taghi M, Babaahmadi-Rezaei H, Kadkhodaei-Eliaderani M, Haddadinezhad S. **(2007)** Relationship of Serum Adiponectin with Blood Lipids, HbA1c, and hs-CRP in Type II Diabetic Postmenopausal Women. *J of Clin Lab Analy* 21:197–200.

Trujillo M, Scherer P. **(2005)** Adiponectin journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J of Inter Med* 257: 167–175.

Tuomilehto J, Lindstrom J, Eriksson J, Valle T, Hamalainen H, Ilanne-Parikka P, Keinanen- Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V. **(2001)** Diabetes Prevention Study Group Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 344: 1343–1350.

Vasseur F, Helbecque N, Dina C. **(2001)** Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet* 11:2607-14.

Wang Y, Xu A, Knight C, Xu L, Cooper G. **(2002)** Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity.*J Biochem* 277:19521–19529.

Wannamethee S, Lowe G, Rumley A, Cherry L, Whincup P, Sattar N. **(2007)** Adipokines and risk of type 2 diabetes in older men. *Diab* 30:1200-1205.

Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley R, Tataranni P. **(2003)** Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocr Metab* 86:1930–1935.

Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M, Matsubara K, Okazaki Y, Ishii T, Nishikai K, Saruta T. **(2002)** Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clin Sci Lond* 103:137–142.

Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. **(2003)** Cloning of adiponectin receptors that mediate anti diabetic metabolic effects. *Nat* 423:762–769.

Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R, Kadowaki T. **(2003)** Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biochem* 278:2461–2468.

Yamauchi T. **(2003)** Cloning of adiponectin receptors that mediate anti diabetic metabolic effects. *Nat* 423:762–769.

Yatagai T, Nagasaka S, Taniguchi A, Fukushima M, Nakamura T, Kuroe A, Ishibashi S. **(2003)** Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. *Metab* 52:1274–1278.

Zhang Y, Proenca R, Maffei M. **(1994)** Positional cloning of the mouse obese gene and its human homologue.*Nat* 372:425-32.

Zurawska-Klis M, Kasznicki J, Kosmalski M, Smigielski J, Drzewoski J. **(2009)** Adiponectin plasma concentration, type 2 diabetes mellitus, cardiovascular diseases and features of metabolic syndrome. *Diab Dosw Klin* 9:81–87.