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ADIPONECTIN VERSUS THIAZOLIDINEDIONES AND ANGIOTENSIN RECEPTOR BLOCKERS

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Abstract

Adipose tissue has gained great attention during the last decade. It represents not only a depot for energy stores, but also releases adipocytokines regulating energy disposal and can therefore be considered from therapeutic point of view. Hypoadiponectemia is an independent threat for development of metabolic syndrome. When subjects treated with antidiabetic (Thiazolidinediones) and antihypertensive (angiotensin receptor blocker) agents , the plasma concentration of adiponectin, the only component of adipocytokines, directly proportional to plasma values of these drugs. The prevalance of hypertension and T2DM is mounting with unprecedented degree in both developing and advanced countries, therefore, there is a dire need to find safer and economical therapeutic regimes for the treatment of these ailments, and intensive research is also

underway for this purpose. PPARγ serves as a common link in the actions of ADN, TZDs and ARBs when exerting their effects, and it is responsible for stimulation of adiponectin receptors, thus ultimately enhancing the levels of adiponectin in plasma. This review aims to elucidate the role, link and use of ARBs, ADN and TZDs as a safer and convenient approach for the treatment of these co-morbidities as a unanimous or single remedy from comparative point of view.

Keywords: Adiponectin (ADN), Thiazolidinediones (TZD), Angiotensin receptor blocker (ARB), Peroxisome proliferator–activated receptor (PPAR), Type 2 diabetes mellitus (T2DM)

1.1 Introduction

During the last ten years, adipose tissue has entered into the sphere of cardiology. Adiponectin, an adipocytokine, is involved in regulating different physiological mechanisms in body. Consequently, the idea of considering the adipose tissue only as a metabolic storehouse for energy is outdated. In reality, it should be recognised as a vitally important endocrine organ which produces biologically active compounds, together known as adipokines. The interaction between biological systems and adipose tissue is attained through expression of bioactive mediators, known as adipocytokines. Adiponectin, resistin, leptin, interleukin 6, tumour necrosis factor and the inhibitor of plasmainogen activator-1 constitute the major components of adipocytokines.

Adiponectin is now regarded as not only the secretory factor from adipose tissue , but as an adipokine which has several beneficial effects on body. Adipose complement is a related protein of 30 kDa, with 247-amino acids having four differentiable domains. It was identified through cDNA cloning of the adipocyte mouse cell line 3T3-L1 and was referred to as Acrp30 by Scherer (*Scherer et al., 1995), meanwhile in* 1996, while using the adipocyte cell line, 3T3-F442A , isolated this protein and named it AdipoQ (Hu, Liang *et al*. 1996). The other names used for adiponectin are *apM1* (Maeda *et al*., 1996) and GBP28 (*Nakano et al.,1996).* Thus this protein was identified by different research groups as a protein exclusively and abundantly formed in adipose tissue.

The insulin-sensitizing adipokine, adiponectin is composed of N-terminal collagenous and C-terminal globular domain. It exists in three isoforms, globular, multimeric, and full length (Fantuzzi 2005). It has also been known as a 'fat burning molecule', because of its ability to mobilise fatty acids to muscle for their oxidation. This is of enormous concern, as entry of fatty acids in to the liver will decrease and therefore total

triglyceride content will also fall, which ultimately lead to an insulin-sensitivit state (Garaulet, *et al*., 2007).

Plasma concentration of AND ranges from 5 to 30 µg/µl, which makes 0.01% of total plasma protein ***(***Gil-Campos, *et al*, 2004***).*** It exists as full-length AND or globular domain ADN in plasma (Fruebis, *et al*., 2001 and Yamauchi, *et al*., 2001, Kadowaki *et al*.,2005, Kadowaki, *et al*., 2006) The most active form of ADN is the high-molecular-weight form, and it is related to insulin sensitivity. Both hexamers and high-molecular-weight oligomers circulate in blood with high concentrations of nearly 10 µg/ml (Waki H *et al.*, 2003), with half- life in plasma up to 2.5 hrs (Hoffstedt, *et al*., 2004). It is apparent that for these structures to have different actions and properties, and the ratio between high molecular and low molecular weight structures, as compared to their respective concentrations, establish ADN physiological activity (Pajvani *et al*., 2004). There is good evidence that ADN increases fatty acid oxidation in skeletal muscle and hepatic insulin action, thus decreasing glucose levels, as revealed from previous studies (Berg, *et al*., 2001 and Tomas, *et al*., 2002). Production of ADN takes place robustly by differentiated adipocytes, liver cells, and cardiomyocytes (Staiger *et al*., 2003, Piñeiro, *et al*., 2005 and Ding *et al*., 2007), thus regulating glucose and lipid breakdown through increases in fatty acid oxidation and glucose uptake with decrease of hepatic gluconeogenesis (and Yamauchi *et al*., 2002 and Kadowaki *et al.*, 2005)

Adiponectin has type 1 and type 2 receptors. In 2007, *Yamauchi* isolated these two related receptors by expression cloning from human skeletal muscle, and they share 67% of the gene sequencing. These receptors are activated by full length and globular ADN, and stimulate enhanced adenosine monophosphate (AMP) kinase, leading to gluconeogenesis, PPAR-alpha ligand activity and β-oxidation with searching for reactive oxygen species (*Yamauchi et al*., 2007). It is noteworthy that AdipoR1 binds to globular adiponectin, whereas AdipoR2 has affinity for full-length adiponectin (Kharroubi, *et al*., 2003 and Peake *et al*., 2005. The expression of AdipoR1 is greater in skeletal muscles, whereas liver is enriched with AdipoR2 (Kadowaki and Ymauchi., 2005) as shown in Fig 1. Among these tissues, AdipoR1 is important for the anti-inflammatory effects of ADN on the walls of blood vessels and the cells lining. Several studies also revealed that ADN acts as a powerful anti-inflammatory adipocytokine (Yokota, *et al*. 2000, Yamaguchi, *et al*. 2005 and Thakur, *et al*., 2006) which also has anti-atherogenic and anti-diabetic properties (Trujillo *et al*., 2005), whereas the increased expression of AdipoR2 is believed to increase sensitivity of liver cells to ADN and thus augment the anti-diabetic activity of ADN (Sun, *et al*., 2006). In humans, the probability of acquiring insulin resistance, hyperinsulinaemia with an increased risk for type 2 diabetes is

related to the low serum concentration of adiponectin (Weyer, *et al*., 2001 and Lindsay, *et al*., 2002). These receptors are up-regulated in fasting, whereas down regulation takes place following insulin administration (Tsuchida, *et al*., 2004). In addition, skeletal muscle and adipose tissue levels of AdipoR1 and AdipoR2 were found to be less in congenitally obese Lep^{Ob} mice and humans where the chances of heart attack are elevated (Ouchi, Kihara *et al*. 2000). Inukai and coleagues confirmed the inhibitory effect on obesity and found that AdipoR1 expression was suppressed in genetically diabetic obese and obese mice (Inukai, *et al*., 2005). Plasma adiponectin concentrations are decreased in obese individuals (Hotta *et al*., 2000, Okamoto, *et al*., 2002 and Ouchi *et al*., 2007), in coronary artery disease (Kumada, *et al*., 2003) and in hypertensive individuals (Iwashima *et al*., 2004). By contrast, high ADN levels have been found in patients with essential hypertension, chronic and congestive heart failure (Kistorp *et al*., 2005 and George, *et al*., 2006)**.** Its levels are positively related to insulin sensitization, β-oxidation, and cardiovascular safety (*Kadowaki etal., 2006 and Scherer 2006 and), whereas* hypoadiponectinemia, a risk for hypertension is independent of insulin resistance and diabetes *(Chow et al., 2007).* Male subjects have less of the HMW form as compared to females and in obese, insulin-resistant subjects as opposed to lean subjects and insulin-sensitive individuals. Human serum has generally the more abundant trimer form as compared to mouse adiponectin and the quantity of HMW form selectively decreases in the circulation when obesity reduces adiponectin concentration (Schraw, *et al*., 2008)

It is also considered that hypoadiponectemia is an independent threat for development of metabolic syndrome (Renaldi *et al*.,2009) and Diabetes mellitus (Hara K *et al*.,2005). In addition, the genomic locus encircling human Acrp30 gene, 3q27, has been recognized as a vulnerable locus for diabetes and metabolic syndrome X (Comuzzie, *et al*., 2001). Studies in rhesus monkeys demonstrate that Acrp30 levels were inversely related to body weight, fat content and resting levels of insulin, and declined with progression toward the diabetic state (Hotta *et al*., 2001). Apart from these observations, treatment with ADN is responsible for reducing extent of insulin resistance in lipoatrophic/obese mice (Yamauchi *et al*., 2001).

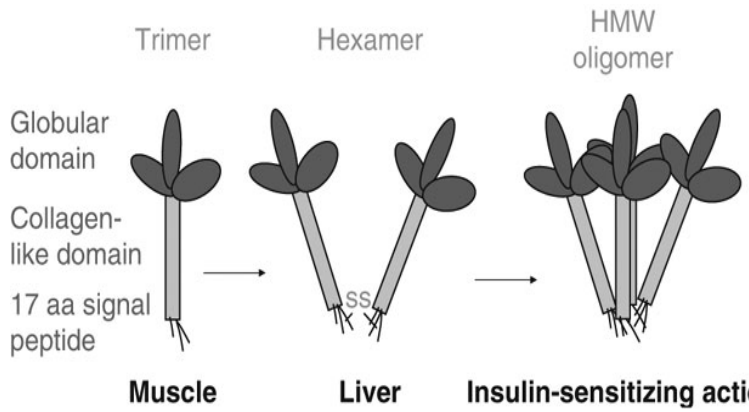

Fig.1 (Drawn from Marta Garaulet *et al*., 2007) Configurations of adiponectin

1.2 Mode Of Acton Of Adiponectin

There are perplexing observations regarding the function and mode of action of ADN, in relation to inflammation and insulin resistance (Garaulet, *et al*. 2007). In adipose tissue, ADN and TNF-α jointly slow down each other's production (Maeda *et al*., 2001, 2002, Fasshauer, *et al*., 2002 and Tomas, *et al*., 2002) through activation of its specific receptors, AdipoR1 and AdipoR2 (Yamauchi, K *et al*. 2003). For the insulin-sensitizing action of ADN, Yamauchi observed that full-length ADN stimulated AMP-activated protein kinase (AMPK) phosphorylation in hepatocytes, whereas globular adiponectin did same in skeletal muscle and liver. The blockade of AMPK activation repressed the effects of globular and full-length ADN, indicating that stimulation of fatty acid consumption and glucose utilization occured through an antidiabetic hormone known as AND (Berg *et al*., 2001 and Yamauchi *et al*., 2002 and). In another study Lodish and colleagues observed that the ADN globular domain improved glucose transport and muscle fat oxidation by using acetyl-CoA carboxylase inhibition and AMPK activation (Tomas *et al*., 2002). It was also observed that ADN increased energy consumption and fatty-acid combustion (fat burning molecule), through peroxisome proliferator activated receptor (PPARα) activation, which resulted in a decreased triglyceride content in skeletal muscle and liver, and enhanced insulin sensitivity (Yamauchi *et al*. 2003). It has also been proposed that two pathways are involved in improving insulin resistance stimulated by PPARγ agonists thiazolidinediones (TZDs), rosiglitazone and pioglitazone. TZDs increase ADN levels, thereby improving insulin resistance, decreasing gluconeogenesis in liver while increasing the AMPK activation (dependant pathway). Whereas, independent of ADN, TZDs reduce serum FFA levels, adipocyte size, as well as expression of resistin and TNF-α, which ultimately alters the insulin resistance of skeletal muscle (Yamauchi *et al*., 2001, Waki

et al., 2003, and Kubota *et al.*, 2006). Adiponectin modulates intracellular signaling pathways and stimulates PPARγ, AMPK and MAPK in skeletal muscle and liver(Kelesidis *et al*., 2006). Even if ADN activates AMPK, there is also evidence which proves that activation of AMPK through the AMP - mimetic and 5 – aminoimidazole – 4 - carboxamide ribonucleoside (AICAR) enhances ADN gene expression (Lihn *et al*., 2004) signifying a feedback circle between AMPK and ADN in adipose tissue. Studies using spontaneously hypertensive rats revealed an overexpression of ADN receptors (AdipoR1 and R2) and an impaired downstream signalling of ADN via the AMPK-ACC-CPT1 pathway in liver and skeletal muscle (Rodríguez, *et al*. 2008). Although adiponectin activates both AMPK and PPAR-α pathways and increase the expression of AdipoR1 expression in coronary artery disease, nonetheless, in spite of increased muscle and circulating adiponectin levels, the PPAR-α/AMPK pathway is deactivated, resulting in decreased AdipoR1 expression for glucose metabolism and fatty acid, which favors a state of adiponectin resistance in coronary artery disease (Berendoncks *et al*., 2010).

1.3 Peroxisome Proliferator - Activatedreceptor And Adiponectin

Peroxisome proliferator–activated receptor (PPARs), is a subgroup of a superfamily of receptors which are closely related to thyroid hormone (Rios-Vazquez *et al*., 2006). They are present in adipose tissue, vascular smooth cells, macrophages, vascular endothelial and renal glomerular cells (Tontonoz *et al*., 1994, Sarafidis P.A *et al*., 2006 and Sarafidis *et al*., 2008), skeletal muscle (Norris *et al*., 2003) and at high level in adipose tissue. So far three PPAR isoforms have been recognized as PPAR-α, PPAR-β (orδ) and PPAR-γ (Abbott *et al*., 2009). The nuclear hormone receptor peroxisome proliferator–activated receptor-γ (PPARγ) serves as a factor in the regulation of insulin sensitivity. PPARγ functions through activation of its ligands such as prostaglandins and thiazolidinediones/glitazones, as a transcriptional regulator of genes involved in glucose and lipid metabolism, and through this means may ameliorate type 2 diabetes (Picard *et al*., 2002). The master regulator of adipogenesis, adipose PPARγ, is activated by thiazolidinediones (TZDs) which are used clinically to stimulate the action of insulin (Evans *et al*., 2004). PPARγ is highly expressed in adipose tissue, and its activation with TZDs changes the fat landscape and adipocyte phenotype besides up-regulating the genes responsible for fatty acid metabolism and triglyceride storage (Nedergaard *et al*., 2005, Sharma and Staels 2007). PPARγ enhances adipose tissue modification besides fat mass accumulation brought about with an enhanced adipocyte differentiation by genes involved in lipid metabolism. Hydrolysis of triglyceride-rich lipoproteins results in fatty acids which are forwarded towards adipose tissue, hence glucose metabolism in the muscle increases, and it is linked

with an enhanced expression of genes responsible for glucose uptake and insulin signaling in adipose tissue and muscles, which ultimately could influence glucose processing. Therefore, PPARγ seems to care for cells against intracellular triglyceride buildup which is connected with type II diabetes (Picard *et al*., 2002). The direct effect of PPAR-γ on adiponectin transcription is through PPAR-γ activation (Iwaki *et al*. 2003). The insulin-sensitising activities of PPARγ agonists causes the decrease of circulating levels of free fatty acids by inhibiting adipocyte lipolysis, apart from regulation of proteins which modulates insulin sensitivity and lipid metabolism (Berger 2002, Desvergne, *et al*. 2004, Li and Glass 2004). The increased expression of AdipoR2 leads to an enhanced sensitivity of liver cells to adiponectin and thus improvement in anti-diabetic activity of AND. (Sun, *et al*. 2006) The use of PPAR-γ agonists results in an improvement in glycaemia in diabetic mice and is linked with an increase in circulating adiponectin levels (Berg, *et al*. 2001 and Bruce, *et al*. 2005). PPARγ activation has been shown to stimulate adiponectin expression in adipocytes and to up-regulate ADN plasma levels in animals and humans *(Combs et al., 2002* and *Fasshauer et al., 2004)* Therefore, PPARγ-activating ligands improve adipose tissue function and thus help in averting the development of insulin resistance to diabetes along with endothelial dysfunction in atherosclerosis (Sharma and Staels 2007). Activation of PPARγ promotes the transcription of ADN and AdipoR1 (Chinetti *et al*., 2004 and Choi *et al*., 2005), whereas activation of AND receptors have the potential for the treatment of endothelial dysfunction related to diabetes, obesity, and atherosclerosis (Zhang *et al*., 2009)

1.4 Adiponectin And Thiazolidinediones

"Diabetes mellitus" is defined by high blood glucose level. There is a failure of β-cells to produce insulin togather with a resistance of target tissues to the action of insulin. Impaired insulin secretion by the pancreas and insulin resistance in peripheral tissues are the characteristics of Type II diabetes, which has increased dramaticaly over the last 50 years. There are about 285 million people worldwide in 2010 with this disease (Smyth and Heron., 2006). The increased blood glucose level results in a range of serious complications which arises from the persistently elevated blood glucose levels. The major organ for glucose homeostasis is liver, in which insulin stops gluconeogenesis and stimulate glycogen synthesis whereas in muscle, insulin is responsible for glucose uptake and synthesis of glycogen; and at white adipose tissue (WAT), where glucose uptake is stimulated by insulin (Chao *et al*., 2000)

Thiazolidinediones (TZDs) are currently being used for the treatment of T2DM (Bowen *et al*., 1991, Nolan *et al*.,1994, Saltiel., 2001, Rangwala and Yki-Jarvinen 2004). They are categorized as antidiabetic drugs, with

numerous effects on CVD and lipid metabolism, through increasing levels of adiponectin**.**

Although adipose tissue only accounts for 10% of the uptake of insulin- stimulated glucose, yet it plays an important role in whole-body glucose homeostasis in adipose tissue, thus helping adipose differentiation besides enhancing small adipocytes which are insulin sensitive (Okuno etal.,1998, Olefsky 2000, Evans 2004 and Rangwala 2004). The understanding that a fatty acid sensor like PPAR-γ serves as an important regulator of glucose metabolism began from the finding that the insulin-sensitizing TZDs are potent agonists for PPAR, which are agonist ligands (Forman *et al*., 1995 and Lehmann *et al*., 1995), for the transcription factor and their antidiabetic effects are considered to be mediated through stimulation of certain type of nuclear receptor known as PPARγ (Sarafidis *et al*., 2008). Different studies have demonstrated that in mice and humans treatment with TZDs causes transcriptional up-regulation accompanied by increase endogenous production and secretion of ADN from adipocytes *(Yu et al., 2002 and Maeda et al., 2002).* TZDs cause an increase in plasma ADN levels (Pajvani *et al*., 2004) and high molecular weight ADN is the principal form of ADN upregulated by TZDs (Karpichev *et al*., 2002). It is also evident that TZDs increase plasma adiponectin levels in obese and diabetic animal models, nondiabetic subjects as well as in patients with type 2 diabetes, by increasing glucose clearance in skeletal muscle by restraining gluconeogenesis in liver, and improving insulin sensitivity (Yamauchi *et al*., 2001, Combs *et al*., 2002 and Hirose *et al*., 2002). However, it is recognised that there are PPAR-γ-independent mechanisms by which TZDs improve insulin sensitivity. Activation of AMPK, which is an adipose-derived factor, ADN, mediates this effect (Kahn *et al*., 2005), and also imitates the metabolic and vascular actions of insulin (Han, *et al*., 2007)

Rosiglitazone enhances AMPK activity cell lines of skeletal muscle through an increase in the AMP/ATP ratio (Fryer, *et al*., 2002). In another study, rosiglitazone treatment re-established α2AMPK activity in skeletal muscle of insulin-resistant obese Zucker rats (Lessard, *et al*., 2006). Scherer's group observed that *ob/ob* mice exhibited a significant improvement in glucose tolerance with rosiglitazone, whereas *Adipo*$^{-/-}$ *ob/ob* mice remained glucose intolerant (Nawrocki *et al*., 2006) which suggested that rosiglitazone ameliorated glucose intolerance through ADN-independent and dependent pathways. In another trial performed in 64 type 2 diabetic patients, rosiglitazone treatement for 6 months resulted in twice the increase in plasma ADN level (Yang, *et al*., 2002) than observed in normal subjects , while comparable results have been reported for pioglitazone (Hirose *et al*., 2002). This synthetic PPAR-γ agonist, rosiglitazone, is reported to increase the serum ADN level in T2DM. The

activation of PPAR-γ by rosiglitazone increases adipocyte differentiation thereby increasing the number of small adipocytes which promote body weight apart from enhancing adiponectin gene transcription (Okuno *et al*., 1998). These effects potentially protect diabetic patients from macrovascular problems, and thus enable them to recover their insulin sensitivity as well as glycemic control (Yang *et al*., 2002). Expression of Acrp30 transgene results in modulation of lipogenesis and hepatic gluconeogenesis with a consequent reduction in expression of two key genes: *PEPCK* (phospho*enol*pyruvate carboxykinase) and *SREBP-1c* (sterol regulatory element-binding protein) in the liver (Shklyaev *et al*., 2003). Different studies also confirmed that rosiglitazone treatment decreased plasma concentrations of glucose, NEFA and triglyceride content, although body weight increased in obese Zucker rats (Cai *et al*., 2000, Finegood *et al*., 2001 and Reifel *et al*., 2005), whereas in animal models of metabolic syndrome, rosiglitazone recovered the metabolic profile and increased plasma levels of ADN and its gene expression. (Sharabi, *et al*., 2007).

The PPARreceptor-γ ligand, pioglitazone, is another oral agent used in the treatment of T2DM. Experimental studies have shown show that pioglitazone has beneficial effects on insulin resistance (*Yki et al.,2004),* hypertension (Iglarz *et al*.,2003) and atherosclerosis (Thorp *et al*., 2007). These beneficial effects of pioglitazone on glucose metabolism in patients with T2DM are associated with an increase in the plasma concentration of AND *(Miyazaki, et al., 2004). Therefore*, the pioglitazone-induced improvement in insulin resistance is dependent on ADN to improve insulin sensitivity *(Kubota, et al., 2006), and* this effect is self-regulating for reduction in food intake and body weight increase or activation of PPARγ in adipose tissue. (Zhao *et al*., 2011)

Troglitazone treatment is also associated with an increase in ADN levels in diabetic, obese and lean non-diabetic subjects (Yu, *et al*. 2002). In another study, subjects with glucose intolerance used troglitazone for 12 weeks which markedly increased plasma ADN levels in a dose-dependent manner (Maeda, *et al*., 2001).

These PPAR- agonists stimulate the production of adiponectin, which promotes fatty acid oxidation and insulin sensitivity in muscle and liver. As a result, hepatic glucose production is reduced and muscle glucose use is increased (Guan, *et al*., 2002). Current evidence suggests close relationship between activation of PPARγ and restoration of insulin sensitivity by reductions in the stimulation of PI3-K Pathway and also increase in ADN. (Tjokroprawiro 2006) Deficits in AND production lessen the capability of TZDs to recover glucose tolerance (*Nawrocki et al*., 2006) indicating the importance of ADN in the protective effects of TZDs against cardiovascular diseases. There are also different reports which confirm that the activation

of PPARγ or a PPARγ agonist, such as TZD, which induces adipocyte differentiation, improves insulin resistance (Tsuchida *et al*., 2004, Sharma 2007, Hunag *et al*., 2009 and DeFronzo 2010). Besides improving glycemic control in subjects with T2DM, several studies support the notion that TZDs have other important actions on metabolic syndrome, such as significant reduction in blood pressure (BP), elevation in high-density lipoprotein–cholesterol, reduction in triglycerides level (Lebovitz *et al*., 2001 and Stolar *et al*., 2003), improvement in endothelial function, reduction of intracellular Ca^{2+} content in vascular smooth muscle cells and attenuation of sympathetic overactivity (Sarafidis *et al*., 2006).

TZDs also have interactions with the renin–angiotensin system (RAAS), particularly, rosiglitazone decreases the production of angiotensins I and II from human subcutaneous adipose tissue (Harte *et al*., 2005), whereas in other studies TZDs have been observed to downregulate the expression of angiotensin AT1 receptor mRNA and AT1 receptor protein in vascular smooth muscle cells (Takeda *et al*., 2000 and Sugawara, *et al*., 2001). Such actions of TZDs could be attributed to reports describing their ability to blunt angiotensin II-induced vascular smooth muscle cells proliferation (Fukuda *et al*., 2002). Besides TZDs, which are effective exogenous agonists of PPAR-γ (Lehmann, Moore *et al*. 1995), the AT1 receptor antagonist telmisartan also acts as partial agonist of PPAR-γ and may potentially be useful in the treatment of diabetes and insulin resistance in times to come (Kurtz 2005).

Table 1 shows observations pertaining to their effect as reduction in blood pressure levels in animal studies conducted earlier.

Table 1: BP: Blood pressure, SHR: spontaneously hypertensive rats, TZD: thiazolidinedione.

Study	TZD treatment	Animal model	Duration	Effect on BP
Yoshioka *et al.1993*	Troglitazone	Obese Zucker rats	4 and 8 weeks	↓
Fujiwara *et al.* 2000	Troglitazone	Heminephrectomized Wistar fatty rats	24 weeks	↓
Yoshida *et al.* 2001	Troglitazone	5/6 nephrectomized SHR	12 weeks	↓
Khan *et al.* 2005	Rosiglitazone	Obese Zucker rats	12 weeks	↓
Buckinghamet al.*1998*	Rosiglitazone	Obese Zucker rats	4 and 9 months	↓

1.5 Adiponectin And Angiotensin Receptor Blockers

Essential hypertension, the major cause of mortality in developed countries (Ezzati *et al*., 2002), is linked to additional metabolic irregularities like obesity and dyslipidemia, glucose intolerance and insulin resistance, which are collectively classified as the metabolic syndrome (Eckel *et al., 2005*) It is considered that hypertension complicated with T2DM results in an increased incidence of CVD. Therefore, treatment of hypertension along with diabetes may be significant in reducing the risk of cardiovascular complications in subjects with T2DM (Hansson, Zanchetti *et al*. 1998). Metabolic syndrome relates to atherosclerosis and other cardiovascular diseases (Gustafson *et al*., 2007). The activation of rennin–angiotensin system (RAAS) is a general characteristic in patients with the metabolic syndrome (Prasad *et al*., 2004)

Angiotensin II apparently reduces adiponectin production. (Ran J *et al.,* 2006*).* However, the molecular mechanisms governing angiotensin II signaling reduction in adiponectin production is still not clear. There are also reports that ACEI and ARBs enhances plasma adiponectin concentration in hypertensive patients (Furuhashi *et al*., 2003 and Lely *et al*., 2007), whereas sympathetic activation restrains ADN expression through β adrenergic mechanisms (*Delporte et al., 2002, and* Imai *et al.*, 2006). One pathway underlying ADN reduction is that via inflammatory cytokines, eg, TNF-α, which causes transcriptional suppression and inhibition of adiponectin secretion (*Maeda et al., 2001).*

ARBs, are now considereed as first line of treatment for hypertensive individuals with T2DM. Apart from their antihypertensive activity, they also have metabolic actions and improve insulin resistance and enhance serum AND levels (Furuhashi *et al*., 2003 and Kurtz *et al.*, 2006) They play pivotal role in cardiovascular, metabolic abnormailities like hyperlipidemia, through AT_1 receptor-mediated signaling (Cooper *et al*., 2007 and Perkins *et al*., 2008). These receptor blockers are characterizsed as a class of orally active and effective antihypertensive drugs in diabetic and hypertensive individuals (Adler 2002*). They* also act as fractional PPARγ agonists (Drazen *et al*., 2007).

Adiponectin levels are higher in patients receiving long-term ARB therapy, indicating that ARBs decrease arterial stiffness by increasing serum ADN concentration and is independent of their effect on BP. One possible mechanism is that ARB can cause an increase in adipogenes which results in a larger capacity for ADN production, as in vitro studies have proved that angiotensin II distinctly slow down adipogenic differentiation of human adipocytes through angiotensin AT1 receptor (Sharma *et al.*, 2002). Studies in animlas established the function of angiotensin II signaling in diabetes and insulin resistance (Dahlof *et al.,* 2002), *whereas* Agata and colleagues

observed that long-term blockade of the (RAAS) could be appropriate treatment for averting increased arterial stiffness and lessening chances for cardiovascular complications, and this reduction in arterial stiffness after ARB treatment could be due to an increase in serum ADN concentration (Agata *et al*., 2004). The evaluation of antihypertensive drugs for their effect on regulation of ADN, ACE inhibitors and ARBs treatment has been shown to enhance ADN levels compared to other classes of antihypertensive drugs. RAAS blockers enhance plasma adiponectin levels to a greater extent than doxazocine, amlodipine and metoprolol regimens (Yilmaz *et al*., 2007) Eenhanced ADN levels recover endothelial function and insulin sensitivity through various mechanisms (Koh *et al*., 20005). Most common ARBs are not strong PPARγ activators which only occurs when given in high concentrations. There are also findings demonstrating that some AT_1 receptor blockers (ARBs) have an agonistic action on nuclear PPARγ receptors (Benson *et al*.,2004, Schupp, *et al*., 2004, Kurtz., 2006, Iwai, *et al* ., 2007 and Y. Tomono *et al*., 2008)

Among ARBs, there is clear order of potency. Telmisartan is the most powerful and the only ARB to exhibit an effect at physiologically achievable plasma concentrations. Adiponectin is linked with glucose sensitisation and is modulated by activation of AT1, AT2 receptors and PPARγ agonists which are considered to stimulate adipocyte differentiation, as the breakdown of adipocyte differentiation is associated with T2DM **(**Kintscher and Unger 2005**).** In recent times, ARBs (irbesartan, telmisartan) have been shown to be ligands of the PPARγ receptor. Telmisartan also stimulates adiponectin protein expression, whereas the non-PPARγ-activating ARB like eprosartan does not express this effect. The PPARγ antagonist GW9662 significantly blocked irbesartan-induced AND expression (Clasen *et al*., 2005). Telmisartan, acts as an incomplete agonist of PPARγ and manipulates the expression of PPARγ target genes involved in lipid and carbohydrate metabolism, ultimately lowering insulin, triglyceride and glucose levels in rats on elevated carbohydrate and fat diets (Stephen *et al*., 2004). Irbesartan and telmisartan act as binding/dissociation discriminatory cofactors with a link between selective gene regulation and ligand-induced conformational changes of PPAR- γ at the molecular level, and thus may activate specific metabolic effects (Berger., 2003, Wang, *et al* .,2003 and Guan *et al*., 2005). Furthermore, the stimulatory effect of ARBs on PPARγ has been studied in a cell-free system, signifying the binding of blockers with PPARγ (*Erbe, et al*., 2006). The influence on the perfection of metabolic profile confirmed by telmisartan and the inverse correlation between ADN concentration and B.P could be partly due to its partial PPARγ agonistic activity (Negro *et al*., 2006). Analysis of PPARγ protein conformation using protease protection demostrated that irbesartan

and telmisartan interacted with the receptor, thereby producing conformational change which were different compared to those induced by pioglitazone (Schupp., 2005). In another recently conducted study by Shiota, this group also observed that telmisartan acted through a PPARgamma-independent pathway, but to some extent exerted its effects through a direct action on skeletal muscle AMPK/SIRT1 signalling pathways (Shiota, *et al*. 2012) .

In vivo, irbesartan administration increased the DNA-binding activity of PPARγ in white adipose tissue (WAT) of atherosclerotic mice. It increased adipocytes, and lessened WAT weight and increased mRNA expression of PPARγ in WAT. It can be assumed that a PPARγ agonist induces adipocyte differentiation, thereby, causing adipocytes of smaller size and increasing insulin sensitivity (Tsuchida *et al.*, 2005), whereas treatment with angiotensin II in rats decreased plasma ADN concentration via ATR1 receptor signalling *(Ran J et al*., 2006). These explanations suggest the possibility that ARBs show partial agonistic activity of PPARγ and through this mechanism could improve adipocyte differentiation. In addition, the ARBs losartan and candesartan enhance adiponectin plasma levels in essential hypertensive individuals *(Furuhashi, et al. 2003, Watanabe et al., 2006 and* Koh, Quon *et al*. 2004).

Apart from their role in the CVS, ARBs have been acknowledged as controller of lipid and glucose metabolism in adipose tissue. Clinicians have observed that AT1R antagonism lessen the risk for T2DM as compared to other antihypertensive therapies *(Scheen 2004).* Humans and rodents studies have shown an improvement in insulin sensitivity when treated with AT1 blockers (Benson *et al*., 2004, Negro *et al*., 2006, Aksnes, *et al*., 2007, Nishimura, *et al*., 2008 and Rong *et al*., 2010). Moreover, Ang II is believed to antagonize insulin signaling in liver and skeletal muscles (Olivare *et al*. 2009). Furthermore Ang II contributes to the pathogenesis of insulin resistance and myocardial remodeling in pioglitazone treated subjects through an ADN dependant mechanism (Li, *et al*., 2010).

The usefulness of Azilsartan in treatment of the metabolic syndrome, the insulin-sensitizing effect is self-regulating of increase in body weight and decreases in food intake or of the activation of adipose PPARγ in obese Koletsky rats (Zhao, *et al*. 2011**)**. In another study, Iwai, observed that in normotensive KK-Ay mice azilsartan was more effective as compared to candesartan in reducing plasma concentrations of fatty acids and glucose, enhancing adipose expression of PPAR-γ with its target AND genes, besides decreasing adipose tissue weight and size, without altering B.P or plasma insulin concentrations (Iwai, Chen *et al*. 2007). Other ARBs like efonidipine, ramipril and candesartan enhance ADN evels and insulin sensitivity in subjects without body mass index change (Koh *et al*., 2005,

Koh *et al*., 2006 and Koh, *et al*. 2007). Adding together ramipril and candesartan have direct effects to exhance insulin-stimulated glucose uptake and promote adipogenesis (Arya *et al*., 2002) and induce PPAR-γ activity which aides differentiation of adipocytes (Schupp *et al*., 2004). Agents which block RAAS, candesartan and temocapril, increased ADN levels with associated improvements in insulin sensitivity without affecting adiposity (Furuhashi , *et al*., 2003). The system, through which these drugs enhance ADN, is improvement in insulin sensitivity and modification in adipocyte differentiation whereas quinapril enhances the expression of ADN in T2DM patients (Hermann *et al*., 2006), and ramipril prevents the commencement of diabetes (Bosch *et al*., 2005).

Kidneys secrete renin and mediate the production of angiotensin II from angiotensinogen.. Adiponectin production is inhibited by angiotensin II, whereas Angiotensin II receptor blockers exhibit antidiabetic like activity and B.P control via AND which stimulates the production of nitric oxide (NO), and regulates blood pressure (Wang and Scherer 2008)**.** In a recent observation, irbesartan activated PPARγ in WAT of atherosclerotic mice which was associated with an improvement of adipose tissue function in atherosclerosis and adipocyte differentiation (Iwai, *et al*. 2011). The role of ADN and mechanism of action of TZDs and ARBs through AND in diabetes and hypertension is shown in Fig 2.

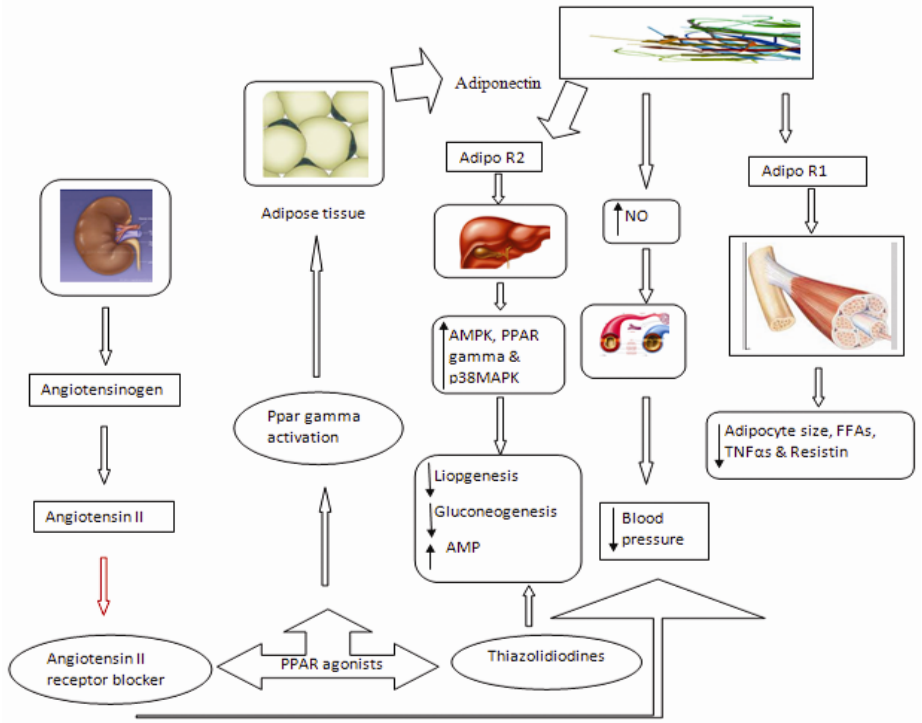

Fig 2: Role of adiponectin through ppar gamma in diabetes and hypertension Mechanism of action of TZDS and ARBs directly and through adiponectin

1.6 Conclusion And Future Directions

We are living in a world where the prevalence of T2DM and hypertension are increasing at a rapid pace and their alarming increase compels the scientists to make novel and effective remedies for both these diseases. There are reports which are providing us with the latest figures regarding these co-morbidities associated with metabolic syndrome from developed and third world countries. PPAR-γ is a universal pharmacological objective as it plays its significant role as a negotiator for both thiazolidinediones as well as ARBs, particularly in improving insulin sensitivity, thereby offering protection against T2DM and the reduction in blood pressure through an increase in adiponectin level. TZDs (antidiabetic therapeutic agents), whose primary target is PPARγ, require ADN as their mediator for the expression of their desired effects, but there are serious concerns regarding thier cardiovascular safety (Drazen JM *et al*., 2007). Several studies have proven that treatment with antihypertensive drugs like ARBs enhance ADN concentration with PPAR-γ as their mediator and thus exert multiple effects, like B.P control, antidiabetic activity, and cardioprotection. There is no doubt ADN, as a guardian angel, may have many beneficial effects to its credit, but there is another side of the coin that the cost effectiveness of the compound and its admistration as therapeutic agent, urges us to find alternate and safe therapeutic strategies. TZDs have their own limitations. Angiotensin receptor blockers (ARBs) only address the issue in an effective manner if the goal/purpose is only to activate PPAR-γ receptors and ultimately increase ADN concentrations in body, from bifunctional treatment point of view. Adiponectin has become an important potential focus for the development of therapeutic compounds, but the size of the molecule and its glycosylation requirement presents difficulty in the synthesis of this hormone. Different corporations have stopped their efforts for secretion and of ADN through adipose tissue (George L Blackburn., 2010). It is also controversial whether ADN bears a risk factor for cardiovascular diseases (CVD). However, there can be further exploration for the presence of ADN in natural sources, or for compounds which have ADN as part of their molecular structure. Further studies on these lines will help us gain a better perceptive of these findings and thus develop novel as well as safer therapeutic compounds.

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