International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 401-417www.ijdmsrjournal.com ISSN: 2582-6018

"The Emerging Role of Adiponectin as Potential Biomarker and Therapeutic Target in Type 2 Diabetes Mellitus" Running title:"Adiponectin in Diabetes"

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Submitted: 01-06-2021 Revised: 16-06-2021 Accepted: 18-06-2021

ABSTRACT
The increasing prevalence of diabetes and its complications heralds an alarming situation globally. Adiponectin is a secretory protein predominantly expressed by adipocytes, released at a high rate into circulation and is developed as an appreciated biomarker for insulin sensitivity, cardiovascular risk, inflammation. Adipose tissue is now considered as a link between obesity and insulin resistance. Adiponectin levels through its receptor signaling, in bloodstream play a key role in reflecting its metabolic action on adipocytes and adipose tissue. Adiponectin exerts insulin-sensitizing effects through binding to its receptors, leading to activation of AMPK, PPAR-α and potentially other unknown molecular pathways. Adiponectin is a viable therapeutic protein that is beneficial effects on cardiovascular cells through its antidiabetic, anti-inflammatory, antioxidant, antiapoptotic, antiatherogenic, vasodilatory, antithrombotic activity and consequently has a favorable effect on cardiac and vascular health. Thus, there is biological and clinical importance of adiponectin in vascular health, identification of its receptors, post-receptor signaling is useful understanding potential use as a target for therapeutic interventions in vascular diseases. The main purpose of review the current knowledge regarding the molecular structure and protective properties of adiponectin as well as its relationship with metabolic complications in type 2 diabetes mellitus and in its therapeutic management.

Keywords: Adiponectin; Diabetes; Disease; Health; Human; Obesity

I. INTRODUCTION

Diabetes has quickly become a serious public health problem in developing countries and its economic burden is very high, especially in developing countries and even more so in the lower economic groups, which spend from 25 to 34% of their income in diabetes care.[1,2,]The cost of treatment increases substantially when complications occur or when hospitalization, surgery or insulin treatment is needed.

Adipose tissue is a specialized connective tissue that functions as an important energy storage site. this tissue performs additional physiological functionsas an active endocrine organ with a central role in energy homeostasis and is directly involved in the metabolism of carbohydrates and lipids. Adipocytes, the resident cells of adipose tissue, produce and secrete biologically active protein molecules into the bloodstream that can affect the function and structural integrity of the target tissues. This function is obtained by modulating a series of signaling cascades through specific receptors.[3] These bioactive molecules, collectively referred to as "adipocytokines", include adiponectin, leptin, resistin, Tumor Necrosis Factor (TNF-a), Plasminogen Activator Inhibitor (PAI-1), angiotensin II, interleukin-6 (IL-6) and soluble preadipocyte factor.[4,5]Adiponectin, also known as AdipoQ[6,] Acrp30[7,] GBP28 and apM1[8].Adiponectin has a molecular weight of about 30 kDa, is very abundant compared to other adipocytokines in human plasma and has several roles in pathogenesis of human diseases.

Circulating plasma adiponectin plays an important role in protecting against the development of various pathophysiological disorders, including metabolic and vascular diseases. Adiponectin has insulin sensitizing,

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Volume 3, Issue 3, May - June 2021 pp 401-417www.ijdmsrjournal.com ISSN: 2582-6018

antidiabetic, anti-inflammatory and anti-atherosclerotic properties[9]. Mice with adiponectin deficiency are prone to insulin resistance and therefore adiponectin supplementation improves insulin sensitivity in insulin resistance by stimulating the use of glucose and oxidation of fatty acids[10]. Phosphorylation and activation of theAMP-activated protein kinase (AMPK), which is found downstream of the adiponectin 1 receptor (AdipoR1) both in skeletal muscle and in liver tissue[11]. AdipoR2 is mainly expressed in the liver and can activate the peroxisome proliferator activated alpha receptor (PPARα) to stimulate oxidation of fatty acids and insulin sensitivity when it binds to adiponectin[12].Adiponectin negatively regulates the expression of adhesion molecules and cytokines associated with inflammatory processes and atherosclerosis by suppressing inflammatory transcription factors and TNFα-induced nuclear factor (NF-κB)[13]. Plasma adiponectin has been shown to be a beneficial effector for human health. The low level of plasma adiponectin, a condition known as hypoadiponectinemia, is related to numerous adverse outcomes in patients with a variety of deadly diseases, such as obesity, diabetes, stroke,coronary artery disease, cardiovascular disease, athero-sclerosis, myocardial infarction, hypertension and hyperlipidemia.Routine changes in life style associated with profitable transition, urbanization, industrialization and globalization have been key causes in the growing burden of non-communicable diseases (NCD) and low class of nutritional food, reduced physical activity and an increase in sedentary behaviors are reflected in the growing prevalence of type 2 diabetes and related risk factors in the region.An increasing percentage of children, adolescents and women are overweight or obese, which increases the risk of T2D.Physiological role and identification of the receptor and post-receptor signaling and clinical significance of adiponectin in vascular health related to the protective effects of the adiponectin system on vascular compartments and presents the available therapeutic uses of adiponectin and other potential interventions to overcome hypoadiponectinemia-related complications[14].

ADIPOSE TISSUE

The adipose tissue was considered metabolically inactive, dedicated exclusively to the storage of fats and most abundant as well as and most widely studied form of adipose tissue in the human body [15]. Adipose tissue consists mainly of adipocytes, but also macrophages, fibroblasts, endothelial cells, pre-adipocytes and other cell types. There are also stem cells from which pre-adipocytes come which have the potential to generate new adipocytes throughout human life[16].Adipocytes release stored energy mainly in the form of free fatty acids that can satisfy the body's energy needs during a state of increased physical activity. The accumulation of fat, adipose tissue has many other important functions as an active endocrine organ in both physiological and pathophysiological conditions, playing one of the central roles in energy homeostasis and insulin sensitivity[17].

Adipose tissue plays a central role in the regulation of energy throughout the body and in the homeostasis of glucose through both its organic and systemic functions [18,19].Adipose tissue an endocrine organ and produces several bioactive features such as adipokines which connect with other organs and control a series of metabolic paths [20].Dysregulation of adipokine secretion plays a pivotal role in the development and progression of insulin resistance in adults as well as in children [21].The regulation of energy expenditure, insulin sensitivity and inflammation, adipokines are promising molecular targets for the treatment of diabetes patients [22].This family of cytokines includes molecules with high biological activity, such as adiponectin, resistin, leptin and PAI-1 (plasminogen activator inhibitor-1). These factors derived from adipose tissue show paracrine activity and which are involved in glucose metabolism (adiponectin, resistin), inflammation (tumor necrosis factor-α, interleukin-6), coagulation (inhibitor of plasminogen activator-1), blood pressure regulation (angiotensinogen, angiotensin II) and eating behavior (leptin), thus communicating with other central and peripheral organs and tissues, such as muscles, liver, nervous and vascular systems, and influencing their metabolism and the function [23]. Therefore, tumor necrosis factor-α and interleukin-6, which are not secreted exclusively by adipocytes, have a pro-inflammatory effect and are closely related to insulin resistance [24].

ADIPONECTIN

Adiponectin a protein hormone that is abundantly expressed in adipose tissue plays an important role in glucose regulation, lipid metabolism insulin resistance potent insulin-sensitizing effect through binding to its receptors. Decreased adiponectin levels are believed to play a central role in the development of T2D, obesity and cardiovascular disease in humans. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are downregulated, leading to activation

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Volume 3, Issue 3, May - June 2021 pp 401-417www.ijdmsrjournal.com ISSN: 2582-6018

of signaling pathways involved in metabolism regulation [25]. Adiponectin, which is mainly produced by adipocytes, is a multimeric protein found in several biologically active isoforms. The basic 30 kD monomeric subunits consist of an N-terminal collagen domain and a globular head which is structurally related to the complement factor C1q/proteins of the Tumor Necrosis Factor (TNF)[26]Adiponectin production is induced by insulin, angiotensin II and inflammatory cytokines, TNF-a, IL-6, IL1b andIFN-c and certain pathological conditions[27]. Adiponectin is composed of several complexes are formed by a form of low molecular weight trimer (LMW), with medium molecular weight hexamers (MMW) consisting of two trimers, with forms of high molecular weight (HMW) which they consist of a maximum of 18 molecules [28]. Adiponectin globular is proteolytic cleavage of full-length adiponectin, which has greater role in binding skeletal muscle membranes and myocytes, but reduces binding in liver membranes and hepatocytes. High molecular weight adiponectin (HMW) is believed to be the most physiologically relevant marker for disease associated adipocyte dysfunction[29].Plasma levels are inversely related to the degree of insulin resistance [30]. Hypoadiponectinemia is also associated with dyslipidemia, hypertension, oxidative stress and carbohydrate-rich diet and adiponectin levels are predictive of steatosis and are inversely related to liver fat content and insulin resistance in the liver [31].

ADIPONECTIN RECEPTORS, STRUCTURE AND FUNCTIONS

The main effector receptors for adiponectin are adiponectin receptor. Although they have seven transmembrane domains, they do not belong to the G protein-coupled receptors (GPCR) family. The biggest and the most obvious difference is absence of G protein in downstream signaling of AdipoRs. Moreover, the orientation of N- and C-terminus is opposite to this seen in GPCRs.Three types of adiponectin receptors can be distinguished: AdipoR1, AdipoR2 and T-cadherin (Table 1). AdipoR1 is found in many tissues, being particularly abundant in skeletal muscles, while AdipoR2 is most commonly found in the liver (Fig.1). The expression of these receptors in insulin target organs, such as skeletal muscles and liver, increases significantly in fasting mice and decreases in refed mice, the expression of AdipoR1/R2 is reduced by insulin through phosphoinositide 3-kinase/FoxO1dependent pathway. AdipoR1 and AdipoR2 levels decrease significantly in muscle and insulin resistant adipose tissue [32].T-cadherin binds adiponectin with relatively high affinity, yet this, interaction is not responsible for adiponectin physiological effects. The precise function of T-cadherin as adiponectin receptor still remains unknown, however it is supposed to be helpful in keeping the adiponectin within its effector tissues.

Two types of adiponectin receptors with different binding affinities for globular or integral adiponectin known as AdipoR1 and AdipoR2 exert downstream potential signal mechanisms are which collectively lead to pleiotropic biological actions; including adiponectin expressions to control additional and complex pathways, such as ceramide and S1P downstream of AdipoR1 and AdipoR2, in addition to those originally identified, such as AMPK, Ca2þ and PPARa [33]. Human and mouse AdipoR1 is found on chromosome 1p36.13-q41 and 1 E4 and AdipoR2 is found on chromosome 12p13.31 and 6 F1. AdipoR1 and AdipoR2 are part of the progesterone and adiponectin Q receptor (PAQR) family, with sequence homology with alkaline ceramidase [34]. AdipoR1 and AdipoR2 have been revealed to be hyper insulin and glucose intolerant, AdipoR1 and AdipoR2 specify to as that for help regulate insulin sensitivity and normal glucose metabolism and these specific tissues with hepatic AdipoR1 involved in activating AMPK, while AdipoR2 is involved in the activation of PPARa, which increases sensitivity to insulin. Structure of human adiponectin (trimer, hexamer, multimer and globular) (Fig.2). AdipoR1 and AdipoR2 act as receptors for globular and integral adiponectin and mediate the major activities of AMPK, PPARa ligands, oxidation of fatty acids and absorption of adiponectin glucose [35].

T-CADHERIN STIMULATING ON TISSUE ACCUMULATION OF ADIPONECTIN AND ITS IMPORTANT

The T-cadherin genotype has a significant impact on plasma adiponectin concentrations and the hazard ratio of total mortality decrease after adjustments by the T-cadherin genotype, suggesting that the “adiponectin paradox” reflects “adiponectin resistance” [36]. The adiponectin protein has been detected in the aorta, heart tissues, and skeletal muscle, while adiponectin mRNA was not present in these non-adipose tissues. T-cadherin plays a crucial role in the tissue accumulation of adiponectin [37]. The localization of adiponectin and T-cadherin, even in mice lacking AdipoR1 or AdipoR2 [38]. The adiponectin protein disappeared in these tissues in T-cadherin knockout mice or with the administration of the T-cadherin

International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 401-417www.ijdmsrjournal.com ISSN: 2582-6018

cleavage enzyme, phosphatidylinositol-specific phospholipase C (PI-PLC), to wild-type mice, indicatingthat T-cadherin is a key molecule for the tissue accumulation of adiponectin [39].

T-cadherin-dependent muscle regenerative effects have also been demonstrated in a cardiotoxin-induced muscle damage model and in humans, T-cadherin is also abundantly expressed in skeletal muscle [40]. Circulating adiponectin levels were found to be increased in subjects with myotonic dystrophy type 1 associated with insulin resistance [41]. Skeletal muscle may also be one of the organs in humans that accumulate adiponectin. The role of the adiponectin/T-cadherin system in skeletal muscle may be important from the aspect of insulin resistance. A genome-wide association study (GWAS) indicated a strong relationship between the T-cadherin gene and circulating adiponectin levels, metabolic syndrome, and cardiovascular diseases by several independent groups [42], while this relationship has not been reported for AdipoR1 or R2. These clinical GWAS data also suggest the significance of T-cadherin as a hysiological binding partner of adiponectin in humans. The regulation of T-cadherin remains unclear. T-cadherin protein levels were shown to be markedly reduced in adiponectin knockout mice, but T-cadherin mRNA levels were similar in adiponectin knockout and wild-type mice [43].

MAIN FACTORS RESPONSIBLE FOR T2DM

Environmental and Lifestyle Factors

In addition to obesity, sedentary lifestyle, poor nutrition and smoking, physical environmental factors contribute to the pathogenesis of T2D. The role of these factors, including air and water pollution, sleep disturbances, traffic noise and exposure to chemicals that are harmful to the endocrine system are poorly understood [44]. Diabetes is a risk factor for vascular and respiratory diseases, research has explored the association between these results in people with diabetes and positive exposure to air pollution, the positive association between air pollutants increases the risk of T2D [45]. The potential endocrine disrupting chemicals, including pesticides and industrial solvents, as the use of chemical contaminants is likely to be more widespread and the potential role of exposure to chemicals in the environment, including in the workplace and development of T2D progression is unclear. Chemical exposure during pregnancy and predisposition to gestational diabetes due to hypersensitivity to chemical insults to the fetus during this phase of life [46]. Smoking is known as the leading preventable cause of disease worldwide and, together with smokeless tobacco and betel quid chewing, is particularly problematic in developing countries [47]. The association between smoking and diabetes risk is causal, significant public health efforts to reduce smoking are likely to have implications for reducing the overall burden of diabetes. The physical environment, working conditions, including shift work, sleep interruption or irregular sleep play a crucial role in metabolic functioning, social pressures, including long hours of work, n including long work hours, nocturnal light exposure, unusual timing of food intake and work-related stress, might have important implications for the endocrine system, all impact normal physiological functioning [48].

Overweight and Obesity

Overweight and obesity are the main risk factors for the development of T2D and the prevalence of the disease has increased in conjunction with the growing trends of overweight and obesity in recent decades [49]. The standardized prevalence for age of overweight and obesity in adults is consistently higher in women than in men in all South Asian countries[50]. Lifestyle factors, such as poor nutrition, low levels of physical activity and an increase in sedentary behaviors have also contributed to increasing overweight and obesity in children and adolescents, obesity in this age group is associated with a number of health complications and an increased risk of early onset T2D and cardiovascular disease and the prevention of childhood obesity are a great opportunity in primary prevention of NCD [51]. Women who become pregnant with an unhealthy body composition contribute to short and long term negative outcomes for the health of the mother and offspring, with maternal obesity associated with intergenerational cycles of increasing obesity and diabetes [52]. The positive energy balance has been linked to a greater exposure to non-traditional and unhealthy foods, even a surplus of local foods above the energy requirement is problematic[53].

Contribution of Nutrition and Dietary Patterns

Improvements in socioeconomic conditions contributed to the transitions in nutrition and lifestyle in the Asian country and physical inactivity is estimated to cause 6 to 10% of cases of CKD, T2D, breast cancer and colon cancer [54]. The growth and aging of the population, in addition to a more proactive and worldwide survey, the increase in the aging of the population will see that the number of adults aged 65 and over will double in 2050 to about 2 billion and the socioeconomic disparities contribute to a worsening of the

incidence and outcomes of NCD, including T2D, often aggravated by insufficient absorption of health promoting behaviors, including among the poorest members of society [55]. The dietary patterns of Indians have changed dramatically and there has been an increasing prevalence of obesity and T2D along with the nutritional transition, along with decreasing levels of habitual physical activity and energy expenditure [56]. The increased consumption of non-traditional food is associated with an increased availability of fast food [57]. The incidence of diabetes doubles when the consumption of refined carbohydrates, including added sugar, reaches 330 gm per day [58]. A major challenge across the Asian country is the consumption of foods cooked in fats and oils and desi ghee (clarified butter), coconut oil (saturated fat), partially hydrogenated vegetable oils that contain trans fats (Vanaspati and high saturated fat palm oil) dairy sources(Saturated fat) and the main problem is related to the common practice of repeated or prolonged heating and overheating of cooking oil [59]. Five dietary models distributed regionally, with rice-based models in the south and wheat-based models in the northwest, but diversity within and between countries based on geographic location and religion. Many Indians are vegetarians, most Pakistanis have a wide range of meat that is consumed, mainly chicken because it is cheap, easy to process, eats beef, lamb, but not pork and fish consumption is more common in non-Hindu environments, particularly in the coastal areas of Sri Lanka, Bangladesh and West Bengal [60]. Coconut milk and coconut oil are widely used in southern India and Sri Lanka, improving the quality of carbohydrates and fats in the diet, as well as an increase in protein intake to improve blood sugar, serum insulin, lipids, inflammatory markers and liver fat [61].

Physical Inactivity

Physical inactivity commonly contributes to energy imbalance and increases body fat, systemic inflammation, insulin resistance and over time, these characteristics are grouped together and significantly increase the risk of T2D, cardiovascular disease and some types of cancer, which leads to a decrease in life expectance[62]. Health benefits reduce the risk of NCD and the improved prognosis associated with a physically more active lifestyle is consistent in high-income, middle-income and low-income environments, this difference is observed in both men and women, with nearly 50% of women in high-income countries with insufficient physical activity and levels of physical inactivity in the region are increasing and women report a consistently higher prevalence of insufficient physical activity than men[63]. We must improve physical activity levels, health literacy related to a healthy lifestyle and reduce the risk and burden of T2D and other NCD[64]. If levels rise over time, physical inactivity will play a more important role in the expected developing country of NCD [65;66;67].

ADIPONECTIN AND INSULIN RESISTANCE IN TYPE 2 DIABETES

The expression and secretion of adiponectin are unique to the differentiated adipocytes. Unlike other adipokines, adiponectin exerts an anti-inflammatory effect and its plasma concentrations are decreased in obesity. Due to its complex influence on the liver and muscles, adiponectin greatly improves insulin sensitivity. Tumor necrosis factor-α and interleukin-6 are potent inhibitors of adiponectin expression and secretion.There is a process of "remodeling of the Adipose tissue" in obesity, which is characterized by adipocyte hypertrophy, macrophage and other immune cell infiltration, increased angiogenesis, and extracellular matrix overproduction [68]. Points out the existence of two types of macrophages in the adipose tissue, referred as M1 pro-inflammatory and M2anti-inflammatory, with the occurrence of a phenotypic change from M2 to M1 in the obese adipose tissue,overweight subjects the visceral adipose tissue is enriched by inflammation and oxidative stress related pathways, while subcutaneous adipose tissue is enriched by those related to insulin homeostasis [69].

Most of the insulin-mediated clearance of a glucose load is directed to the skeletal muscle, in addition to the response of insulin to food that stops glucose production in the liver Cellular defects, aided in part by the explosion of information, intracellular effects and insulin signaling pathways. The main muscle defect is the altered transport of glucose in the cell combined with a defective deposit such as glycogen, genetic defects would be found in glucose transport machinery or alternatively, the insulin receptor or its cascade of downstream factors[70].

Increasing age encourages an increase in the prevalence level of T2DM and fasting blood glucose. Glucose level intolerance also tends to increase with increasing age and some factors are particularly involved in the pathophysiology of impaired glucose intolerance in the elderly [71]. The predominant factor is that aging stimulates alteration, decreases insulin sensitivity and insufficiently compensates for beta cell functioning during increased insulin resistance. Insulin

International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 401-417www.ijdmsrjournal.com ISSN: 2582-6018

sensitivity is independent of changes in body composition, is not affected by the aging process. The main factors contributing to insulin resistance are the decrease in lean body mass and the increase in body fat, in particular "visceral adipocytes [72]. Age-associated mitochondrial function tends to contribute to insulin resistance in the elderly and relationship between the pathophysiological basis of sarcopenia with insulin-resistant state, reduced neuronal stimulation, oxidative stress and subclinical inflammation and diabetes mellitus in the elderly between the ages of 60 and 65 is gradually becoming a frequent and alarming public health problem in developing as well as developed countries [73].The prevalence and incidence of glucose intolerance (IGT) and T2D are more common in the elderly than in the young, these factors include reduced physical activity, an increase in adiposity, defects in insulin secretion that are associated with the aging process, to coexisting diseases and drugs, with advanced age, reduce the sensitivity of the liver to the action of insulin during the suppression of glucose production, it is likely that greater insensitivity to the actions of insulin [74].

INTERACTIONS BETWEEN THE AMPK AND INSULIN SIGNALING PATHWAYS

Adiponectin-induced AMPK activation of AdipoR1 and AdipoR2 is reduced in skeletal muscle of obese subject associated with insulin resistance [75]. Obesity not only reduces the plasma levels of adiponectin, but also the expression of AdipoR1/R20, which reduces the sensitivity to adiponectin and leads to insulin resistance, creating a "vicious circle" [76]. The insulin signaling pathway is activated when nutrients are available (Fig.3), while the AMPK pathway is activated when cells do not have a carbon source. Insulin promotes the synthesis of lipids, proteins and glycogen, while AMPK inhibits these biosynthetic pathways [77]. In some tissues, such as the heart, insulin inhibits AMPK and this action has been mediated by the activation of protein kinase B. The signaling pathways of insulin and AMPK work in the same direction, particularly in the processes that regulate plasma glucose levels (Fig.4). In skeletal muscle, the activation of insulin and AMPK favors the absorption of glucose by increasing the translocation of GLUT4 on the plasma membrane. Insulin, glucose, can be stored as glycogen (anabolic), while, in the case of AMPK, glucose can be fed into the oxidative (catabolic) pathway, insulin and AMPK act in the same direction in the liver, in which both repress the expression of gluconeogenesis enzymes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [78]. That insulin, a hormone released in response to an elevated blood glucose level, is expected to suppress glucose production in the liver, while in the case of AMPK it may have evolved among its anti-anabolic actions[79]. Type 1 diabetes are associated with high levels of adiponectin and adiponectin confers protective effects on podocytes through the AMPK pathway, angiotensin receptor blockers appear to increase serum adiponectin levels in hypertensive patients, T2D with metabolic syndrome, increased serum adiponectin levels [80]. Adiponectin also plays a central role in energy homeostasis through its action on the hypothalamus and a new role for adiponectin as a "hunger gene" and the transduction of adiponectin signals into different tissues and the role of APPL1 in mediating the effects of adiponectin [81].Adiponectin secreted from the adipose tissue sensitizes the insulin receptor signaling pathway, Anti-inflammatory, angiogenesis, lipid and glucagon secretion, promotes beta cell survival energy expenditure and hormones secretion. Adiponectin is a protein that modulates a number of metabolic diseases glucose intolerance, dyslipidemia, cardiovascular disease, Kidney diseases and hypertension and adiponectin actions in the maintenance of metabolic homeostasis (Fig.5) [82]

ADIPONECTIN AS A THERAPEUTIC TARGET

Hypoadiponectinemia has been demonstrated in human subjects with obesity, type 2 diabetes and CAD. Plasma adiponectin levels were increased by intervention therapies including body weight reduction, exercise training and drug administration. Body weight reduction increases plasma adiponectin levels in both diabetic and non-diabetic subjects in obese patients who received gastric partition surgery [83]and in premenopausal obese women [84].The peroxisome proliferator-activated receptor (PPAR)-r is the main regulator of adipocyte differentiation and adipocyte gene expression involved in fatty acid metabolism and insulin sensitization [85]. Third-generation of sulfonylurea hypoglycemic agent, not only improved insulin resistance but also increased plasma adiponectin levels in elderly patients with type 2 diabetes [86].The prevention and treatment of diabetes that deal with unhealthy dietary models and physical inactivity, as well as ensuring accessible access to good quality medical care and these approaches are related to the stage of life, sex, cultural and socioeconomic context of patients

and those at risk of developing T2D, metabolic syndrome, cardiovascular disease, cancer, kidney diseases and Alzheimer's disease are increasing in alarming proportions. Adiponectin activates numerous metabolic pathways to stimulate glucose and lipid metabolism and improve insulin sensitivity and has antidiabetic and anti-inflammatory activities [87]. The reduction of human health and the loss of body weight through exercise in combination with a regulated diet can be effective in restoring plasma adiponectin to normal levels [88]. Adiponectin shows these beneficial effects, a promising adiponectin based therapeutic drug is missing and the structure and functional relationships of this cytokine or complications in converting the integral adiponectin protein into a feasible drug are lacking. The recombinant adiponectin protein was active and exhibited insulin sensitizing properties, large-scale production and therapeutic use of the recombinant protein [89].The renin–angiotensin system (RAS) acts not only on the systemic endocrine system but also local tissue. In particular, angiotensin II exerts numerous effects on the pathogenesis of atherogenesis: (1) vasoconstriction, (2) migration and proliferation of smooth muscle cells, (3) production of extracellular matrix and matrix metalloproteinase (4) synthesis of inflammatory and/ or procoagulant mediators, such as IL-6, MCP-1, PDGF, and PAI-1 [90].Several mechanisms by which RAS inhibition leads to an increase of adiponectin includes (1) enhanced insulin sensitivity, (2) recruitment and differentiation of preadipocytes(3) increased transcription and/or translation of adiponectin. Indeed, RAS blockades have been reported to enhance insulin sensitivity, suppression of expression and secretion of TNF-a in adipocytes.

A fragment of adiponectin, including the C-terminal globular domain, exists in human blood stream, this globular domain adiponectin is pharmacologically active and regulates body weight and free acid oxidation in mice [91]. The C-terminal globular domain of adiponectin protects against atherosclerosis and globular adiponectin transgenic apoE-KO mice ameliorated the progression of atheroscleros.The globular adiponectin plays a protective role against atherosclerosis, globular adiponectin ameliorated insulin resistance and increased fatty-acid oxidation more effectively than the full-length adiponectin [92].The injection of recombinant adiponectin reduced basal glucose levels without increasing insulin levels. These effects derived from the suppression of glucose production in hepatocytes through increased ability of sub-physiological levels of insulin. Adiponectin acts as a ‘‘pleiotropic cytokine’’ linked not only to body fat, but also to the various cell-to-cell interactions, such as inflammation, hematopoiesis, and the immune system. Recombinant adiponectin may become beneficial in the treatment and prevention of cardiovascular disease[93].

II. FUTURE DIRECTION

Cell therapy, particularly with genetically modified stem cells that contain the adiponectin gene, offers a promising approach to overcome thinking problems, this method could be used for clinical applications. The discovery, development and registration of new drugs is an expensive and very long process. Natural products that improve AdipoR plasma levels can potentially mitigate adverse biological effects and adipocytokines minimize the natural production of adiponectin that needs to be expressed. The best adiponectin based therapeutic drugs include orally active small molecule AdipoR agonists that can mimic cellular activities mediated by adiponectin, including the activation of signaling cascades, AMPK and PPAR-α pathways and have anti-inflammatory, antidiabetics and insulin sensitizing properties without adverse biological effects.

The DNA chips, gene expression models, study in the white adipose tissue of the deficiency in which the adipocyte enlargement remains suppressed and the insulin sensitivity intact, even with a diet rich in fats and has found that adiponectin is abundantly expressed in small adipocytes, suggesting that adiponectin may represent a candidate insulin sensitization factor derived from adipocytes.

III. CONCLUSIONS

The fundamental relationship between innate and adaptive immune responses in the regulation of adipocyte, adipose tissue inflammation and insulin resistance. The temporal relationship between complement activation and accumulation of the different pro-inflammatory cell types warrants further investigation in order to delineate the key pathways contributing to adipose tissue inflammation and metabolic pathway mechanism.Role of adiponectin as an important physiological regulator of insulin sensitivity, glucose and lipid metabolism, as well as the potential role of adiponectin cardiovascular homeostasis and adiponectin receptors for these metabolic diseases. The therapeutic approach consists in using pharmacological or dietary interventions to restore the ability of adipose tissue in the secretion of adiponectin. This unique strategy

can probably serve as a possible new and innovative therapeutic approach to the treatment of metabolic diseases. Its full potential should be realized as effective options for the prevention and treatment of lifestyle-related diseases for which obesity is a common basis. Basic research is needed with innovative idea to provide information on feasible strategies for diabetes prevention and its complications.

In conclusion, more work is required to fully elucidate the molecular mechanisms of biosynthesis, molecular structures and two receptors of adiponectin, signaling of adiponectin and its potential therapeutic value. The biologically active forms of adiponectin or chemical entities that can become activated adiponectin receptors should be further investigated, applied in human studies to test their potential benefits in clinical settings and point to a new direction of future plan and clinical research.

Competing interest reposition: The authors declare that they have no competing interests

ACKNOWLEDGMENT

I am also grateful to Principal, Government Medical College, Haldwani, Nainital,Uttarakhand for given this opportunity. I appreciate the supporting staff of Multidisciplinary Research Unit and thankful to Department of Health and Research, New Delhi for given batter platform of research in Government Medical College, Haldwani Nainital, Uttarakhand.

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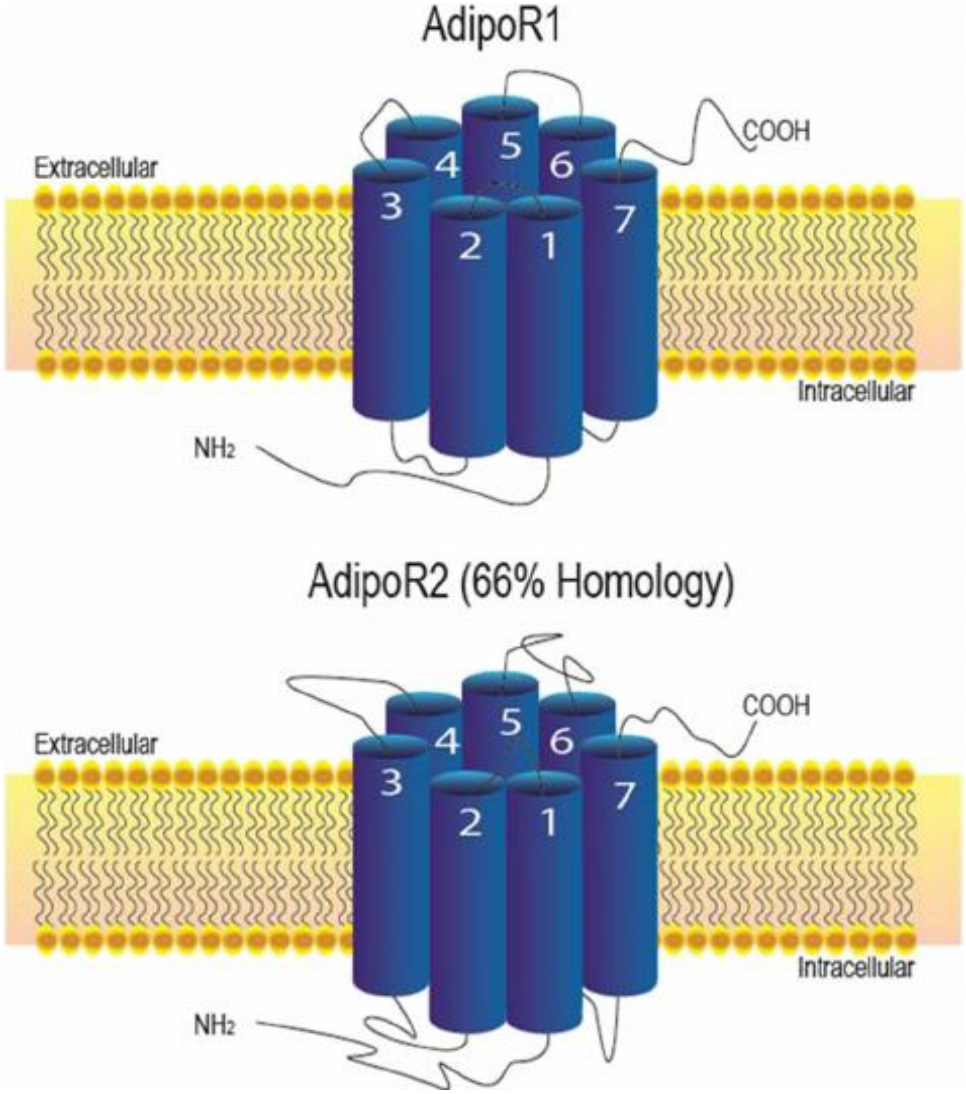

Fig: 1 Structure of adiponectin receptors AdipoR1 and AdipoR2

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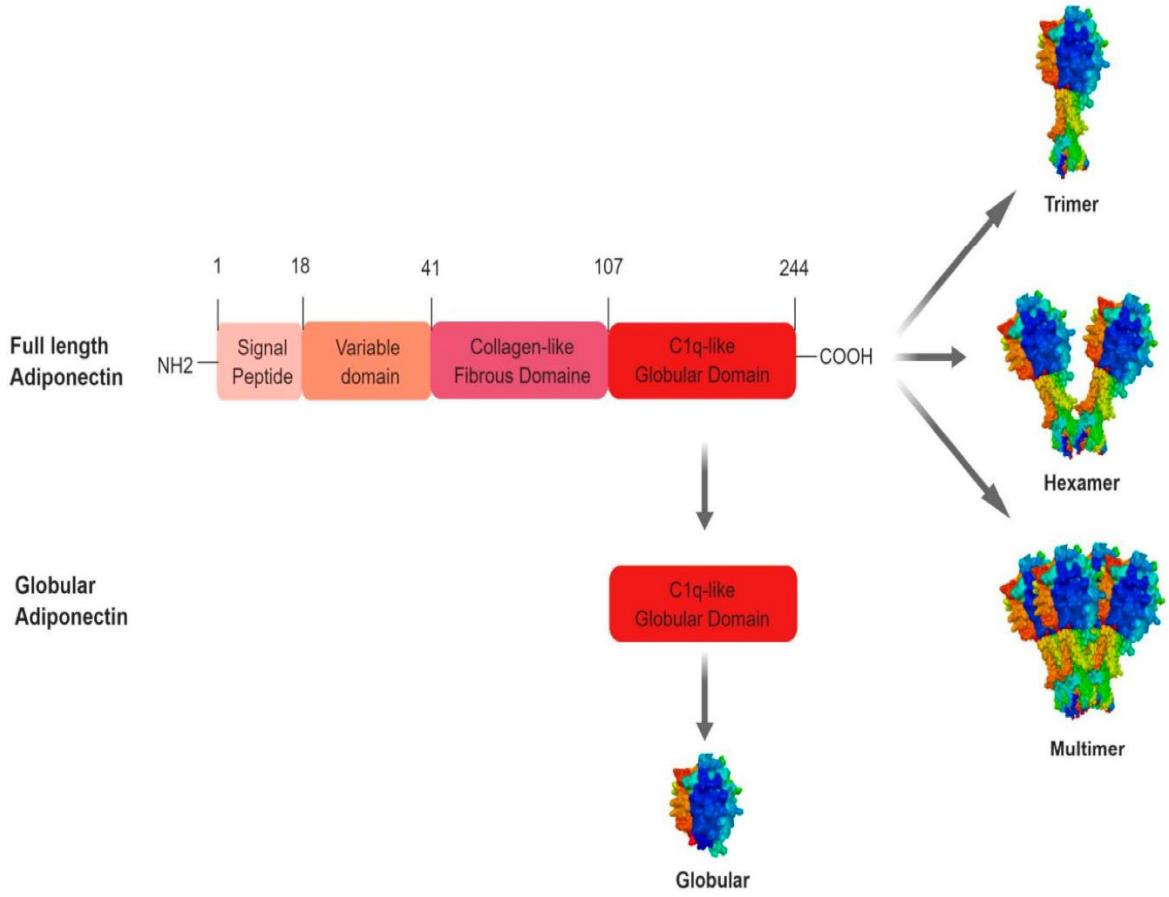

Fig: 2 Structure of human adiponectin (trimer, hexamer, multimer and globular).

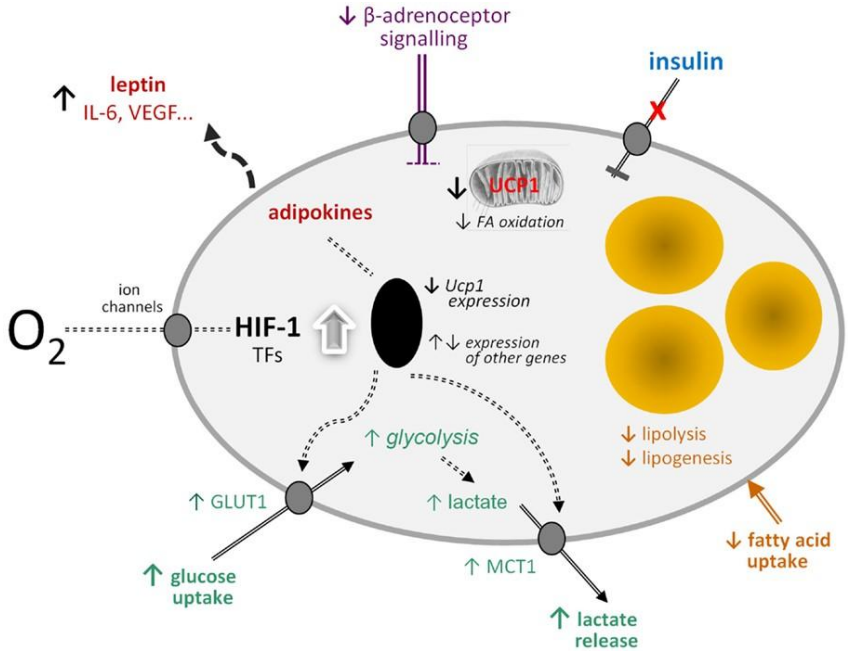

Fig: 3 β-Adrenoceptor signalling pathway

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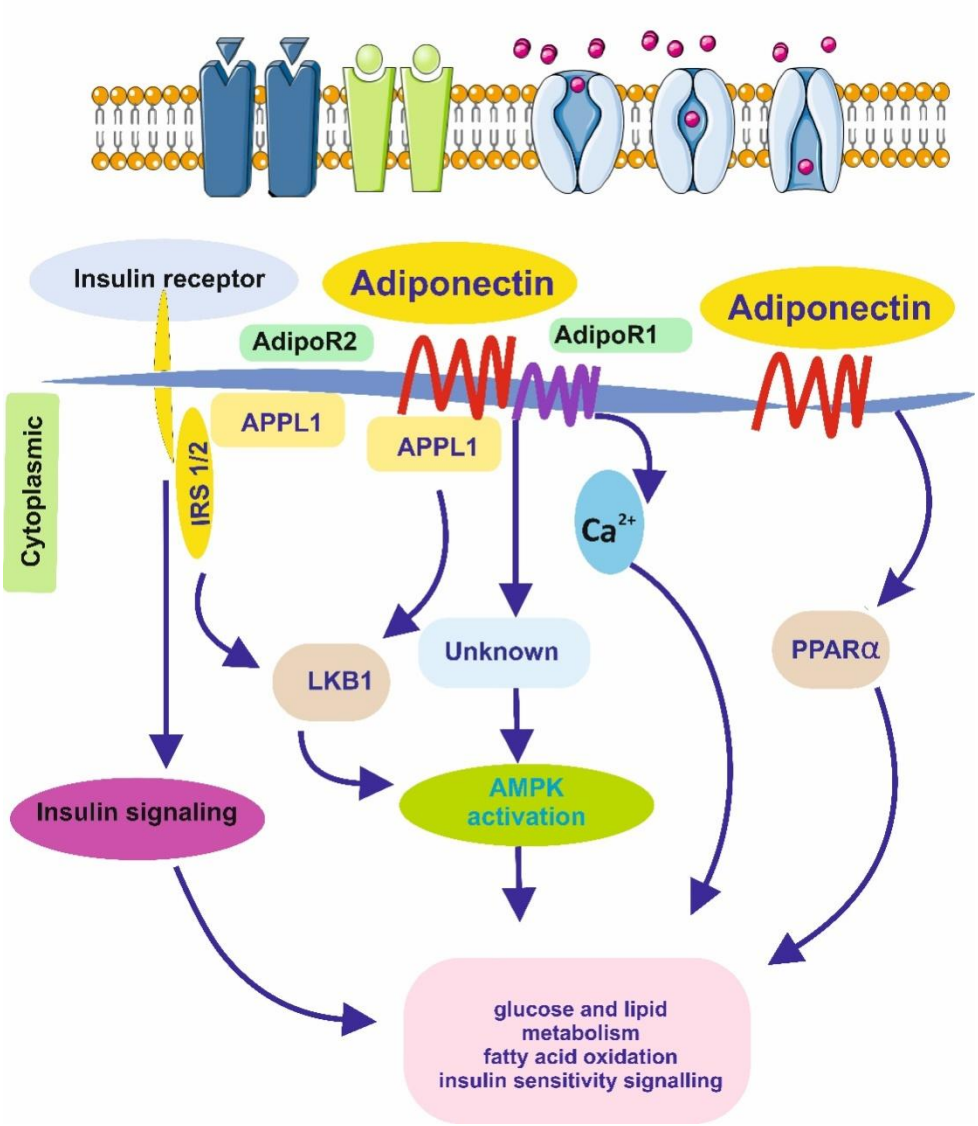

Fig:4 Interactions Between the AMPK and Insulin Signalling Pathways

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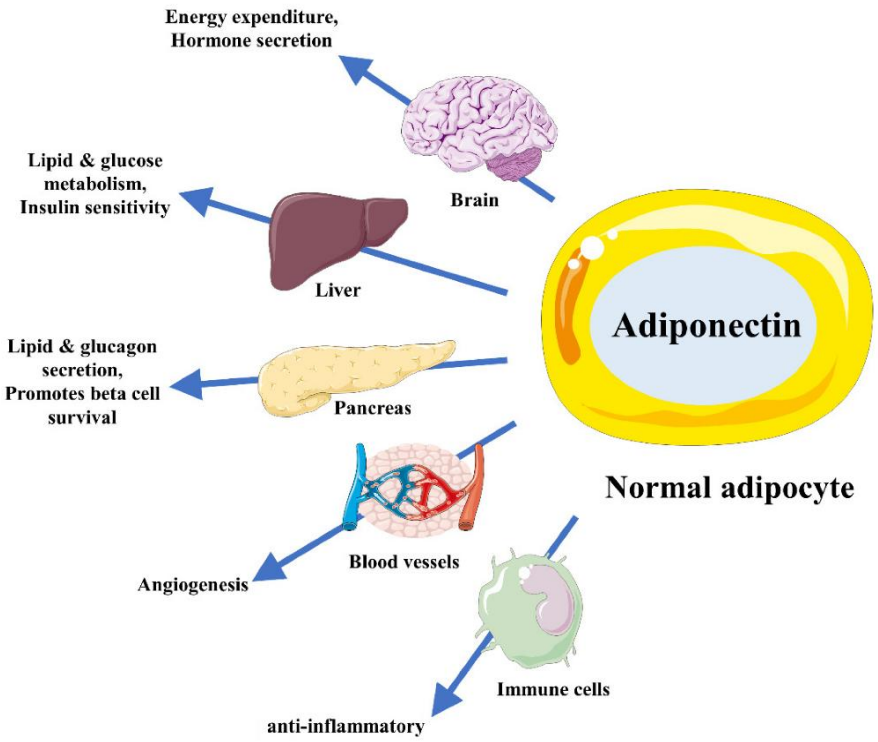

Fig: 5 Adiponectin actions in the maintenance of metabolic homeostasis

Table 1 The comparison of adiponectin receptors (Wang and Scherer, 2016)[94]

Feature \receptor	**AdipoR1**	**AdipoR2**	**T-cadherin**
Location	Widely distributed in the body. Most abundant expression in skeletal muscles. Present in other tissues like: liver, pancreas, bones, brain, heart, leukocytes and colon epithelium	Mainly liver	Endothelial and smooth muscle cells
Receptor affinity	High affinity to globular adiponectin	Intermediate affinity to both globular and full length adiponectin	• MMW • HMW
Intracellular signalling pathway	• AMPK pathway (preferred in AdipoR1) • PPARα pathway (preferred in AdipoR2) • Src/Ras • ERK1/2 pathway		None. T-cadherin is considered as a co-receptor for adiponectin