ADIPONECTIN AS A CLINICAL INDICATOR AND AS A THERAPEUTIC AGENT

ALI IBRAHIM AL SAMAWI1, SAMAL HAKEEM KAREEM AL-JAFF, NOOR AL-HUDA A.H. SAEED

1Mustansiriyah University, College of Science, Biology Department, Baghdad. Iraq. 2 Mustansiriyah University, College of Science, Biology Department, Baghdad. Iraq. *Biology Department, College of Science, Mustansirya University, Iraq.

Email: nooral-huda@uommustansiriyah.edu.iq

Received - 29.06.2019; Reviewed and accepted - 31.07.2019

ABSTRACT

Objective: Worldwide, there are several biologically active proteins known as adipokines, which were secreted from adipose tissues. Adiponectin is the most important one of them, which plays a major role in pathogenesis. Adiponectin recently acts as a modulation in many syndrome and metabolism, like inflammation, obesity which is the major cause of the cardiovascular disease is hypertension it also leads to mortality and morbidity. Conclusion: The correlation between hypertensive people have lower Adiponectin levels than normal adults and the levels increase when reducing risk of hypertension, in human, adipose tissue is the largest metabolic active compartment, which regulates many biological functions.

Keywords: adiponectin, adipose tissue, risk factors, diabetes, cardiovascular, metabolism, obesity, atherosclerosis.

INTRODUCTION

Adiponectin classified as a protein hormone of 244 amino acids that regulate glucose levels and fatty acid breakdown [1]. In human it produced by adipose tissue and encoded by the ADIPOQ gene as well as it is known as adipocyte complement-related protein of 30 kDa. Adiponectin is widely recognized because of its anti-diabetic, anti-inflammatory, antiatherogenic and cardioprotective effects [2 - 4]. It suffices for insulin promoting and ameliorates insulin resistance also it can exert pro-inflammatory activities in some of the contexts [5] Adiponectin also can promote secretion of anti-inflammatory cytokine IL10 by culture human monocytes-derived macrophages and Stromal Vascular Cells which prepared from adipose tissue [6], sexual dimorphism observed that males showing lower level in Adiponectin expression than females [7]. The levels of Adiponectin among these people are lower than those with normal weight, the low levels are associated with lipid abnormalities, and inflammation increased risk of diabetes resistance of insulin, coronary heart disease, and cancer. A recent study has shown that adipose tissues are not simply an inert storage depot of lipids, it's also the important endocrine organ which plays a major role for integration endothelial inflammatory signal of control energy homeostasis, so as metabolic. Adipocyte secretes a variety of bioactive proteins are collectively named adipocytokines [8] including leptin, tumor necrosis factor, plasminogen activator inhibitor type 1, Adipin, Resistin and Adiponectin [9-14]. Many diseases with unclear rezone may be related to Adiponectin and some diseases simply be treated by Adiponectin.

Adiponectin actions in Inflammation

Now it's well known that adipokines which are a number of biologically active proteins were secreted from adipose tissue [15], the most important one is Adiponectin which is act as a major role in the pathogenesis of metabolic syndrome in a few years ago, its play a role in modulation of inflammation which become increasingly apparent [16] it exhibits a protective activity in many inflammatory diseases include atherosclerosis, cardiovascular disease and insulin resistance [17,18]. Studies of in vitro showed that Adiponectin attenuates inflammation in endothelial, epithelial cells, muscles, macrophages by Adiponectin mediated protein kinase A activation [19], on the other hand, the Adiponectin mechanisms may be directly action on inflammation cells suppression reaction oxygen and stimulating the expression of anti-inflammatory IL10 cytokine downregulated of inflammatory responses which involve TNF-alpha and expression of NF-KB inflammatory signaling pathway [19,20], Adiponectin can also inhibit myelomonocytic progenitors growth and mature macrophages function [21] and suppressing macrophage to foam cell transformation [22] Figure (1).

Fig. 1: The anti-inflammatory and anti-atherogenic role of adiponectin [23]

In adipose tissue, adiponectin inhibits the manufacture of CRP and TNF-α; in dissimilarity, TNF-α inhibits the manufacture of adiponectin. In the vasculature, adiponectin suppresses monocyte adhesion to ECs, foam cell formation of Ms and VSMC immigration and increase. In ECs, adiponectin prompts NO product and adjust vasodilation or angiogenesis.

Adiponectin action in Obesity

Today the major health problem is obesity which is increasing risk of cardiovascular disease, respiratory disorder, cancer, and diabetic retinopathy, fat of visceral body may affect health conditions in obese patients within an abnormal Adipokines production [24], when Adiponectin playing a pivotal role in metabolism, the concentration of total Adiponectin and high molecular weight decreases in obesity and then increases after weight loss [25], abdominal obesity leads to endothelial dysfunction and insulin resistance due to metabolic products formation which derived from cytokines, lipids, and hormones. Recently, clinical studies have shown that the strategies of non-pharmacological and pharmacological to combat insulin resistance and obesity can improve endothelial dysfunction, also mild inflammation which can see in these conditions. These findings have added a new dimension of association with obesity,

Review Article
endothelial dysfunction and insulin resistance, which is become the main target to the prevention of type 2 diabetes mellitus and disease of cardiovascular [26].

**Adiponectin with Hypertension.**

In worldwide the major risk factor of cardiovascular disease is hypertension, which constitutes the main cause of morbidity and mortality [27], relationship between hypertension and obesity is well established and related with many other factors like sympathetic nervous system activation and endothelial dysfunction [28], lower level of Adiponectin is detected in hypertension adults whereas total level of Adiponectin was found to be lower in obesity-associated hypertension than in rest hypertension or rest normotension[29,30]. Many previous studies evidenced that hypertensive adults have lower levels of Adiponectin than normotensive adults, and the increased level of Adiponectin associated with reduced hypertension risk [31], more than 25% of population affected with hypertension, two-third of those patients reside in developing countries [32], in vitro study shows that Adiponectin can inhibit the expression and biological effect of TNF-alpha, also the macrophage of foam cell transformation. Adiponectin anti-atherogenic properties are directly according to the production on the endothelial cell when using phosphorylinsolot 3-kinase-dependents pathway, so as Adiponectin mediated protein kinase pathway [31], on physiological condition if reduce production, exert anti-inflammation relaxes vessels and vascular wall antithrombotic effects [33].

**Adiponectin and Atherosclerosis.**

Atherosclerosis has been demonstrated as an inflammatory disease. The first discovered atherosclerosis lesion was consisting of T-lymphocyte and monocyte/macrophage [34].

There are many mechanisms link obesity with cardiovascular disease [35], previous studies have showed that Adiponectin has a beneficial role in cardiovascular disease and atherosclerosis, so any altered releases of adipokines can induce a prothrombotic state which contributes with atherosclerosis and cardiovascular disease [36]. Adiponectin serum levels inversely correlated with a marker of carotid atherosclerosis, some researchers have been reported that no significant correlation between Adiponectin serum levels and the risk of coronary heart disease, whereas, other researchers have been showed high levels of Adiponectin as a predictor of adverse outcome in acute coronary syndrome patients [37].

The expression of the adhesion molecule acts a major role in the regulation of inflammatory reaction in several types of cells if the Adiponectin can neutralize the excess inflammatory response than it may be possible to prevent the process of atherosclerosis [38].

Environmental agents, such as overnutrition and physical inactivity, encourage visceral fat gathering may cause a decrease in plasma adiponectin (hypo adiponectinemia). Genetic agents, for example, I164T SNP, also correlates with hypo adiponectinemia. Hypoadiponectinemia boasts a cluster of hypertension, diabetes mellitus, and dyslipidemia, and eventually causes atherosclerosis. Besides, hypo adiponectinemia raises atherosclerosis by decrease the detrimental interaction between arteries and adiponectin.

5) **Adiponectin and Diabetes.**

Recent study has showed that the adipose tissue not as simply as inert storage depot for lipids, but also it is important endocrine organ which plays a major role in the integration of endocrine inflammatory and metabolism [39], also it plays a key role in the modulation of lipid and glucose in insulin-sensitive tissues in human and animals, recently, adipose tissue is considered to be large one metabolically active compartment which involved to regulate several biological function [40].

Adiponectin with Type 1 Diabetes. Diabetes type 1 is an insulin deficiency disease, characterized as insulin resistance [41], the Profane secreted from adipose tissue is Adiponectin and so like many adipocytokines, it makes the connection between different organs [42], in autoimmune disorders and type 1 diabetes are associated with increased adiponectin, whereas in non-autoimmune, the obesity, circulating levels are fat-derived protein and type 2 diabetes are decreased and insulin resistance correlated with decrease Adiponectin [43-45].

The levels of Adiponectin are varying among adults and children and it is higher in type 1 diabetes and it has been seen that the level is decreased in boys with both healthy controls as well as type 1 diabetes [46,47].

Adiponectin with Type 2 Diabetes. Type 2 Diabetes (T2D) classifies as a combination of impaired insulin which secreted from pancreatic beta cells and insulin resistance on the peripheral target tissue, T2D mostly affected older age, previous history of gestational diabetes, diabetes family history and obesity [48]. Adiponectin plays a major role in the suppression of metabolic derangement which causes insulin resistance as well T2D [49], there is some relation between Adiponectin and T2D Figure (3).

![Fig. 3: The effects of adipocytes on the pathogenesis of Type 2 diabetes. [49]](image)

The intra-abdominal fat class is the main fat depot determining plasma adiponectin levels and insulin sensitivity, while leptin levels are determined by the subcutaneous fat mass. Rising the intra-abdominal fat depot will elevate adiponectin and increase NEFA (‘FFA’) levels, which will antagonize insulin effects in liver and muscle, leading to increased gluconeogenesis. In the existence of increased intra-abdominal adiposity, with low adiponectin and consequent hepatic insulin resistance, the activity of hepatic lipase will increase, causing a decrease in
HDL cholesterol and an increase in small dense LDL particles, as seen in the metabolic syndrome. Insulin resistance correlates with intra-abdominal fat aggregation and will also favor the development of glucose intolerance. The loss in β-cell function and mass may also result from exposure to NEFAs, lipoproteins, and adipokines.

Adiponectin as a therapeutic agent

Adiponectin roles in metabolism

According to Adiponectin antidiabetic and anti-atherogenic activity plays an important role in the therapeutic of type 2 diabetes mellitus as well as metabolic syndrome [50]. The reduction in levels of serum Adiponectin can lead to reducing insulin sensitivity in the prediabetic state [51]. The low levels of plasma Adiponectin predict the development of type 2 diabetes and insulin resistance [52], previous studies suggests that higher concentration of Adiponectin acts a major protective role against T2DM as well as MetS, whereas, the normal concentration as considered to be beneficial [53], any defects in secretion of adipocytokine by abdominal or visceral adipocytes can lead to MetS [54]. Correlation between the concentration of Adiponectin and arterial blood pressure has also been reported. Some researchers found that hypoadiponectinemia is a good indicator of hypertension development [55], the accumulations of Adiponectin in the wall of damaged vascular and modulated the response of endothelial inflammatory to vascular injury by its anti-atherogenic and anti-inflammatory properties [56]. Increased the concentration of Adiponectin levels associated with an increased cardiovascular mortality in type 1 diabetes [57], lower concentration levels of Adiponectin were found to be lower in cardiovascular patients, many reports indicate the association between endothelial dysfunction and serum Adiponectin levels, these findings reports suggested that was a close relationship between cardiovascular disease with Adiponectin.

Therapeutic obesity by Adiponectin

By mean of diet or Body Weight loss, hypoadiponectinemia comes from the visceral fat accumulation, particularly. Body Weight loss in the form of visceral fat achieved by a combination of suitable diet as well as exercise. Central obesity may act an important role in adipocytokines secretion [58]. Body Weight reduction in obese person shows an increased concentration of plasma adiponectin, which suggested that obesity-associated hypoadiponectinemia in reversible. Previous studies showed that reduce body weight may cause a significant increase in Adiponectin plasma levels for both diabetic and non-diabetic subjects [59]. In obese, the moderate body loss weight increased Adiponectin plasma levels significantly by increase HMW oligomer concentration, which is known as vasculoprotective activities [51].

Adiponectin as an anti-atherosclerotic.

It’s well known that Adiponectin is a strong inhibitor to any expression of molecule adhesion, it is a direct anti-atherosclerotic effect [60,61], in men it suggested that low Adiponectin serum as an independent indicator of extent coronary atherosclerosis [62], hypoadiponectinemia can contribute with coronary plaque vulnerability, which acts an important role in pathophysiology of acute coronary syndrome. By inhibition of the atherogenesis, monocytes may adhere to the endothelial cells, then migration through subendothelial space to take an oxidized lipoproteins and transform through the foam cells and cause a plaque formation and atherosclerosis [63], some researchers found that the negative relation between levels of Adiponectin and CRP suggested that adequate of plasma Adiponectin levels played a protective agent against atherosclerosis development [64], whereas, the normal level of Adiponectin can restrain plaque formation as well as atherosclerosis by suppression the neo intimatal formation when inhibiting the expression of adhesion molecule, so as reduce cholesterol uptake by inhibiting the scavenger receptor-expressing [65].

Adiponectin as a disease risk marker

Diabetes risk of adiponectin

Adiponectin baseline concentration was strongly inversely associated with risk on the progression of type 2 diabetes in a diabetes prevention program, after adjustment of each age, sex as well as obesity and its traditional dysglycemic predictor risk of diabetes [66], quantitatively evaluation for uses of Adiponectin as a marker of diabetic risk. In many chines pieces of research by using some clinical predictors like [sex, age, smoking family history, physical activity and hypertension as well as fasting glucose] [67]. It will be suggested that the concentration of Adiponectin provides a useful surrogate of risk of the progression of diabetes type 2 that could be used in screening and also the intervention of prevention diabetes for a clinical population [68].

Cardiovascular risk of adiponectin

Most studies reveal the association between Adiponectin concentration and cardiovascular disease [69]. The adiponectin ratio is predictive of the incidence of cardiovascular [70]. On the other hand, high molecular weight/ not total Adiponectin concentration predicts the incidence of myocardial in non-diabetic men [71].

Adiponectin concentration with high molecular weight and total ratio Adiponectin are strongly correlating with severe angiographic determined coronary artery disease [72]. Many previous studies have shown Adiponectin concentration may increase with age, the relation between future cardiovascular disease and Adiponectin was complex. The researchers suggested that the complex mix of the relation between age and, which related to cardiovascular disease risk, and the relation between Adiponectin and obesity-associated cardiovascular disease risk [73].

It could be suggested that the observations are promising the applications of Adiponectin as adipokines as a measure of atherosclerosis heart disease risk.

Cancer, and Adiponectin

Prospective studies showed that the dysregulation of plasma level Adiponectin circulating may immediately be linked with development of obesity that related to malignancy[74] like leukemia [75], gastric cancer, colon cancer [76,77] prostate cancer and breast cancer [78,79], hypoadiponectinemia can induce insulin resistance as well as hyperinsulinemia and this can reduce the level of insulin-like growth factor-binding protein through the blood which directly increases the level of bioavailable (IGF1). The increasing on that levels signal through receptors of insulin also IGF1 receptor to facilitate the cellular proliferation, the inhibits apoptosis of many types of tissue and re-regulate vascular endothelial growth factor secretion, which contributed to any type of carcinogenesis [80].

Mortality risk related Adiponectin

The concentration of Adiponectin was associated directly with total mortality in coronary – artery disease subjects[81], previous study showed that the higher concentration of Adiponectin associated with greater mortality[82], in case with peripheral arterial disease, concentration of adiponectin was also associated with all-cause mortality[83] as well as, in congestive heart failure the concentration of Adiponectin related with mortality [84], in the other hand, the non-obese congestive heart failure total Adiponectin / not high molecular weight Adiponectin related mortality[85] Figure (4).
The important role of adipokines. Adipokines are created mostly by adipocytes and play essential roles in many major disorders such as obesity, insulin sensitivity, arthritic and cardiovascular disease [86].

Competing interests
The authors don't have any competing interests to declare.

Acknowledgment
The authors thank the Department of Biology, College of Sciences, The University of Mustansiriyah for their facilities to write this review.

REFERENCES


Vol 8 Suppl 3, July-Aug 2019 www.mintagejournals.com 15


© 2019 by the authors; licensee MJPMS, India. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).