Association between serum levels of Adipokines and Polycystic Ovary Syndrome: Review article

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(Received 19 Dec, 2013 Accepted 12 Aug, 2014)

Review Article

Abstract

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder associated with metabolic disorders and infertility. Evidence suggests that the adipose tissue secreted products, adipokines, play an important role in the pathophysiology of PCOS. Reciprocally, PCOS influences on the adipokines serum content, also on gene or protein expression of some of them. Finding out of association between serum levels of adipokines and PCOS will help to understand the pathology of PCOS and identify treatment solutions of this syndrome. In this paper, we review the assosiation of several known adipokines with polycystic ovary syndrome.

Key words: Polycystic Ovary, Syndrome, Adiponectin, Omentin, Chemrine

Citation: Razavi A, Hashemi F, Emadi M, Saadati N, Haghighi S, Hedayati M. Association between serum levels of Adipokines and Polycystic Ovary Syndrome: Review article. Hormozgan Medical Journal 2016;19(5):315-322.

Introduction:

PCOS is a common endocrine disorder that leads to irregularities in the hypothalamic-pituitary-Adrenal axis and along with symptoms, such as polycystic ovaries, menstrual clutter, hyperandrogenism, anovulation, hirsutism and Acne (1,2). Racial and ethnic diversity is effective on the clinical signs in this syndrome (3). PCOS symptoms manifest during childbearing age, but can be rooted in childhood or fetus (1). This syndrome was observed in 5-10% of women during childbearing age and is the most common cause of infertility, approximately 75% due to anovulation (4,5). In most cases, PCOS also involves the metabolic changes such as insulin resistance (IR), hyperinsulinemia; dyslipidemia and obesity that these anomalies in the long term can be followed by consequences such as type 2 diabetes, cardiovascular disease, and endometrial cancer and breast cancer. In addition, a recent study found that PCOS causes metabolic changes such as increased glycolysis, inhibit the cycle of Teicarboxylic acids and change the basic level of amino acids (6,7).

About 50% of patients with PCOS are obese. Although obesity is a common and increasingly global problem, but the risk of overweight, obesity and central obesity is greater in women with PCOS that the issue is associated with insulin resistance and hyperandrogenism. On the other hand, obesity is considered a risk factor for developing PCOS (8).

Not only adipose tissue is a source of energy storage, but also it has a role in the regulation of many physiological processes such as fertility,

immune response and glucose and lipid metabolism as well. Adipose tissue plays its regulatory role through the secretion of Adipokines. Adipokines also includes cytokines that are specific for adipose tissue, such as, leptin, Resistin, adiponectin, Visfatin and omentin and includes cytokines that are not specific for adipose tissue, such as lipocalin-2, Chemerin, IL-6 and TNF-α (9). Fat tissue dysfunction in patients with PCOS will be observed in the form of an increase or decrease at the level of Adipokines.

In this review, the relation between Serum levels of adiponectin, omentin, Adipsin, Chemerin and TNF-α with polycystic ovary syndrome are reviewed.

Adiponectin

Adiponectin is the most abundant protein secreted by adipose tissue that is expressed exclusively in the tissue (10). There are three forms of adiponectin in the plasma: the trimmer form with low molecular weight, Hexamer form with medium molecular weight and Multimer form with high molecular weight. Biological effects of different forms of adiponectin are diverse (11). Three receptors of AdipoR1, AdipoR2 and T-Cadherin have been identified for adiponectin. AdipoR1 and AdipoR2 receptors are expressed in all tissues, especially in women's reproductive tissues, including ovaries, placenta, uterus and Fallopian tubes. Therefore, it is said that AdipoR1 and AdipoR2 play an important role in fertility. However, apparently T-cad receptor is essential for beneficial effects of adiponectin on heart (11,12).

Adiponectin levels decline due to obesity and increase with weight loss. The main actions of adiponectin include increased sensitivity to insulin through the stimulation of glucose recieving in the liver and muscle tissues, a decrease of gluconeogenesis in the liver cells and stimulate the beta-oxidation of fatty acids in the skeletal muscle. As a result, adiponectin will decrease the triglyceride storage and will increase the sensitivity to insulin. The Adiponectin message transmission takes place via activation of AMPK (11).

Now, the study of the relation between serum level of adiponectin and Polycystic ovary syndrome is a controversial topic. In a number of studies, adiponectin serum concentration in patients with PCOS was reported lower than the control group (13-17). While, in other studies, no difference between the concentration of adiponectin in patients with PCOS and a control group was observed (18-20). According to the study of Imadi et al in 2012 of 45 Iranian patients with PCOS, no significant differences between adiponectin serum levels in patients with PCOS and a control group was observed (21). The results of a meta-analysis that was conducted in 2009 by Toulis and colleagues showed that when patients with PCOS and control groups were matched in terms of BMI, serum level of adiponectin in patients with PCOS is lower than the control group (22). In the study of Nayak and colleagues in 2010, patients with polycystic ovary syndrome, with high levels of body mass index and insulin resistance, showed a decrease level of adiponectin in the blood (23). Some reports suggest a close relation between adiponectin with high molecular weight and insulin sensitivity (24). In 2010, O'Connor and colleagues demonstrated that reducing the serum level of adiponectin with high molecular weight in patients with PCOS is independent with obesity and insulin resistance (25).

Given that adiponectin is the most abundant adipokine in the human body, it seems to be involved in the PCOS pathophysiology. Still, the fact that whether the hypoadiponectin observed in PCOS is an inherent feature of this syndrome, occurs because of obesity or the interaction between IR and hyperandrogenic, or not, is under discussion.

Omentin

Omentin is an Adipokine with molecular weight KD 120 that has a structure with three similar sub-units. Disulfide bonds link the subunits of this molecule together and it is made of a large amount of Amntal adipose tissue and to a lesser amount of visceral adipose tissue, lung, heart, vascular cells, fatty tissue under the skin and at trace levels in muscles and kidneys (26,27). The secreted protein was discovered in 2003 by Yang and first was introduced with intelectin1 and FEST2 names. Omentin has 2 isoform called Omentin-1 and omentin-2 that their genes have been together in chromosomal region 1q22-q23. About 83% of the amino acids omentin-2 are similar to omentin -1 (28).

Omentin-1 is the original form of omentin in human plasma. Omentin-1 plasma concentrations are negatively associated with BMI, waist circumference, insulin resistance index (HOMA-IR), levels of resistin, leptin, IL-6, IL-18, TNF-α and positively with adiponectin, ghrelin, HDL and cholesterol (29).

Omentin will increase the insulin signaling interactions via phosphorylation and activation of protein kinase Akt (protein kinase B) and stimulate glucose transport into adipocytes Amntal and human muscle tissue. This Adipokine has a paracrine and endocrine role in the regulation of insulin sensitivity, but has no effect on basal levels of glucose. When weight loss occurs due to insulin sensitivity, Omentin-1 level goes up. In addition, the omentin 1 level decreases in pre-diabetes steps, T1DM and T2DM. Omentin-1 plasma concentration in lean women with PCOS with insulin resistance is natural, and in obese women with PCOS with insulin resistance is lower than the control group (30, 31). According to the study of Saadati et al in 2012, the omentin serum levels in patients with PCOS have been reported lower than the control group (32). In addition, studies have shown that the Omentin-1 has a lower expression both at the protein level and at the mRNA level in Amntal adipose tissue in lean women with PCOS than the control group (30). So apparently, a decrease in the serum level of omentin is independent of changes in body mass index in patients with polycystic ovary syndrome. Therefore, it might be used the changes in serum levels of omentin as a significant diagnostic marker along with other markers for the diagnosis and confirmation of polycystic ovary syndrome.

Adipsin

Supplement D Factor or Adipsin is a member of the chymotrypsin for serine protease family (33,34) that was isolated for the first time in 1986 from adipocytes and mainly is secreted by adipocytes 3T3-L1 into the bloodstream (35). This Adipokine is involved in diverse biological processes such as blood clotting, supplements activation, fertility, immune system, development and repair of tissues, blood pressure, effects on body weight, nutrient absorption, fibrinolytic, cell proliferation, and form bone and apoptosis (33,36). The gene CFD (Complement Factor D) on chromosome 10 expresses the Adipsin for mice. The Adipsin gene position is different to the location of the diabetes gene (chromosome 4) and obesity gene (chromosome 6). Therefore, changes in the Adipsin concentration in these diseases are due to regularity failure rather than a direct genetic lesion (37). Adipsin plays an important role in the host defense system as a speed restriction enzyme of reactions in the alternative complement pathway. This biological pathway plays an important role in the body's natural defense against infectious agents (33,38).

Adipsin identification is not very old as an important factor in diseases such as obesity and diabetes and not yet fully known the function of this protein (39). On the other hand, the only study that has been so far conducted on the links between Adipsin and polycystic ovary syndrome is Hashemi and colleagues' study in 2012 of 45 patients with PCOS. The results of this study showed no significant correlation between serum levels of Adipsin and polycystic ovary syndrome disease. According to this study, no significant correlation was observed between serum levels of Adipsin and insulin resistance index (HOMA-IR) (40). While in the year 2007, Mlinar and his colleagues said that the Adipsin rate increases in insulin resistance (41). Meanwhile, Xia et al in a study in 2003 has reported that in men, the Adipsin level increases in central adipose tissue and decreases in subcutaneous adipose tissue. Thus, with increasing body mass index that goes up toward central adipose than subcutaneous fat, Adipsin also increases. However, in women with an increase in body mass index, Adipsin rate decreases that probably the Adipsin expression reduction in adipose tissue of women is because of limiting the development of adipose tissue in obesity (42). As in women, with increasing body mass, the serum Adipsin level decreases and on the other hand, with an increase in insulin resistance, its volume increases, so the lack of difference in this group, may be due to the confounding effect of these two factors. Maybe with an increase in the statistical population of the study, achieve greater results with certainty.

Chemerin

Chemerin is an adipokine that is synthesized in the form of prochemerin inactive precursor in the liver and visceral adipose tissue and is converted during the inflammation quickly by proteolysis defeat to the active form, and then excreted. Its immature form is the polypeptide with a molecular weight of 18 kDa that becomes a mature chemerin with a molecular weight of 16 kDa, by serine protease enzymes help with the removal of six amino acids from the mark C-terminal of the polypeptide (43,44).

Chemerin acts as an anti-inflammatory agent in controlling the immune response in the areas of inflamed and injured tissue (45). In addition, Chemerin plays a role in Adipogenesis, adipocytes metabolism and glucose metabolism. Chemerin as a new Adipokine has a high expression in white adipocytes and is linked with obesity, metabolic syndrome and type 2 diabetes. Research shows that plasma concentrations of Chemerin are linked strongly with BMI, fasting blood glucose, leptin, resistin, TNF-α, IL-6, plasma triglycerides and blood pressure. Chemerin can also adjust insulin sensitivity and insulin secretion. On the other hand, insulin induces the Chemerin release from adipocytes (46,47).

In 2009, Tan and colleagues reported that in patients with PCOS, a significant increase in serum levels of Chemerin is observed. In addition, they commented that the expression of protein and Chemerin mRNA in Amntal adipose tissue and subcutaneous increases (48). Studies show that serum levels of Chemerin in patients with obesity and type II diabetes increases (46). Another study is reported the Chemerin level of the blood and adipose tissue in obese women with polycystic ovary syndrome was higher than the control group (49). The study of Haghighi and colleagues in 2012 is also reported the serum level of Chemerin in PCOS higher than the control group, in line with other studies. This study showed that an increase at serum levels of Chemerin in patients with polycystic ovary syndrome is independent of BMI (49). So perhaps we can use the changes in chemerin serum level as one of the diagnostic criteria in polycystic ovary syndrome.

TNF-α

Alpha Tumor necrosis factor (TNF-α) is an Adipocytokine that is involved in inflammatory system and acute phase response. Basically, TNF-α is secreted by macrophages, but it is secretable by a wide range of other cells, including adipocytes (50,51). The combination of TNF-α is a glycoprotein that initially is synthesized in the form of 26-kDa protein lacking the classical signal peptide. This form of 26 kDa is called pro-TNF-α and is expressed in the plasma membrane. Then its extracellular domain is broken by matrix metalloproteinases and the mature 17 kDa protein will be released that is secreted and soluble form of the TNF-α. Both forms 26 and 17 kDa in Preset mode have biological activities (52).

Two types of TNF-α receptors are, respectively, type I ((p60, p55, CD120a, TNFR1 and type II (p75, p80, CD120b, TNFR2) and both are width membrane glycoproteins with the cysteine-rich repeats in the extracellular N- terminal domain. Extracellular domain has both structural and performance similarity. Their intracellular domains are distinct and activate different signaling pathways by calling the cytosolic proteins (53).

TNF-α Adipokine inhibits the insulin signal transmission and affect glucose metabolism. A disorder in TNF-α metabolism is involved in metabolic diseases such as obesity, insulin resistance and type 2 diabetes (50).

Reports indicate that serum levels of TNF-α in-patient with PCOS is higher than the control group (54-58). However, a number of studies are known an increase level of TNF-α in a close relation to obesity (54,55). Other studies have reported higher levels of TNF-α in women with PCOS independent of obesity (56-58). According to the study of González and colleagues, an increase in the secretion of TNF-α in-patient with PCOS, especially in obese patients, is linked to IR and hyperandrogenism. Thus, changes in levels of TNF-α in-patient with polycystic ovary syndrome may be linked to insulin resistance in these patients because IR a common complication in patients with PCOS (58). The fact that an increase at the serum concentrations of TNF-α was observed in PCOS is an inherent feature of this syndrome or or it occurs due to obesity or insulin resistance, can be investigated.

Conclusion:

Adipose tissue is associated with hormones secreted from it, including Adipokine with the brain, ovaries and uterus. About half of patients with PCOS are obese that it seems the obesity is associated with insulin resistance and hyperandrogenism. On the other hand, the obesity is an independent and critical risk factor for the development of PCOS. Abnormal levels of Adipokines in PCOS patients, regardless of the presence or absence of obesity, may also reflect the fact that PCOS affects mutual on the secretion of Adipokines. Now, due to some antithetic data, the relation between Adipokines such as adiponectin, omentin, Adipsin, Chemerin and Alpha tumor necrosis factor with PCOS is a controversial topic. However, the same data shows the cluttered serum levels of Adipokines in patients with PCOS. So one might conclude that Adipokines are involved in the pathology of PCOS.

Table 1. Adipokines serum levels in patients with PCOS compared to control group

Adipokine	Serum levels in patients with PCOS compared to controls
Adipokine	Some sources have reported the same level and some reductions
Omentin	Decrease
Adipsin	Same
Chemerin	Increase
TNF-α	Increase

Table 1 shows Adipokines serum levels in PCOS patients compared with the control group briefly.

It should be noted that studies conducted on patients with PCOS, just check the levels of Adipokines in the bloodstream so far. A limitation of these studies is because the paracrine and autocrine mechanisms of Adipokines are ignored on the tissues in PCOS and only the endocrine effects of these cytokines is checked. While the Adipokines serum levels may not be a good reflection of events occurring at the tissue level. It is obvious that the current information about Adipokines role in PCOS is not complete. So further studies and molecular studies are essential to better understanding the link between PCOS and Adipokines.

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