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Adiponectin and Leptin in women with Polycystic ovary Syndrome

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Abstract

At a global level, the prevalence of obesity and the related diseases is constantly growing. Increased obesity rate is also present in women of reproductive age, especially in women of reproductive age with polycystic ovary syndrome (PCOS). On the other hand, there is no recent data on the prevalence of the obesity in women of reproductive age with PCOS in the R. Macedonia. The adipose tissue hormones, adiponectin and leptin, are more frequently indicated as a potential biochemical link between obesity and PCOS, and also that there is a close link between them and the insulin resistance which is often present in these women.

This review article is focused on studies which illustrate results from examinations on the role of the adipose tissue i.e. its role as an endocrine organ. The main focus is put on the adipokines leptin and adiponectin, their function and influence on the reproduction. There are several clinical, experimental and epidemiological researches that support disturbed secretion of adipokines as a main reason for obesity and insulin resistance in women with polycystic ovary syndrome. This is assumed to be influenced by complex interaction of several metabolic changes that leads to altered secretion. In this review are presented epidemiological and clinical implications of this condition.

Keywords: *Obesity; Adipose tissue; Adipokines; Leptin; Adiponectin; Insulin resistance*

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Introduction

Obesity is one of the major problems at present, primarily because of the diseases which are related to it, like cardiovascular conditions, type 2 diabetes, certain types of cancer. On a global level, there are 400 10^6 adults classified as obese and it is expected that this number will be doubled by 2015. Obesity is a multifactorial disease caused by a chronic energy imbalance.

When the input of energy surpasses its output, there is an increase in the adipose tissue. The regulation of the energy homeostasis is a complex process and it is a challenge for the scientists to explain the pathogenesis of the obesity. The existing obesity epidemic is a result of many complex factors. Although it is clear that the improper diet, the sedentary lifestyle and the lack of physical activity play a major

role in the occurrence of obesity, there are also other significant factors, like genetic predisposition and the epigenetic modifications (in uretro) [1] connected with the age of the mother, her lifestyle, the accumulation of bioactive toxins from the environment.

Obesity is best explained through the body mass index (BMI). The BMI is calculated as a body weight in kilogrammes divided by the square of the height in meters. The normal body weight is considered as BMI <25 kg/m^2, overweight BMI 25–30 kg/m^2 and obese BMI >30 kg/m^2. [2] The main characteristic of the obesity is the expansion of the adipose tissue which leads to development of insulin resistance of the peripheral tissues, such as the skeletal muscles and the liver.

White adipose tissue

Storing energy is one of the biological imperatives of life of almost all animal species. Lipids are the primary source of stored energy in mammals, and the main storage location is the white adipose tissue. When the energy needs cannot be met by the circulating and stored carbohydrates, then fatty acids of the white adipose tissue are mobilised through the process of lipolysis, a breakdown of triglycerides to glycerol and free fatty acids. [3]

The Larger part of the adipose tissue in mammals consists of the white adipose tissue; the brown adipose tissue is found only in newborns and plays a role in maintaining the body temperature. The white adipose tissue is composed of adipocytes, i.e. stroma which is composed of preadipocytes, macrophages, endothelial cells, leukocytes and fibroblasts. The white adipose tissue was seen for a long time as a passive organ for storage of energy in the form of triacylglycerides. However, the findings of the last decade indicate that it is an organ with an active function in the metabolic processes for maintaining the energy homeostasis.

The turning point for these views is the moment of discovery of the protein which is produced by the adipose tissue – leptin, by Friedman., *et al*. [4] The cells of the white adipose tissue i.e. the adipocytes, produce a large number of bioactive peptides and proteins – cytokines with endocrine, paracrine and autocrine effect: Leptin, Adiponectin, resistin, TNF-α, interleukin 6 (IL-6), plasminogen activator inhibitor 1 (PAI-1), angiotensin [5], visfatin, retinol-binding protein-4, enzymes – lipoprotein lipase [6]. Apart from the adipocytes, the other adipose tissue cells, preadipocytes, macrophages, fibroblasts, also have the ability to produce adipokines.

The role of adipokines

The adipokines play an important role in the maintenance of the physiological processes, like the nutrition intake, energy balance regulation, metabolism of lipids and glucose, energy regulation, insulin production, angiogenesis, blood pressure and coagulation processes [7]. The production of the adipokines is influenced by the food intake and the degree of alimentation. Some of the hormones which are products of the adipose tissue, like leptin, visfatin, resistin, apelin and adiponectin, have a major role in the regulation of the weight. The central effect of the adipokines is expressed through the regulation of the appetite and the energy output. Also, they peripherally affect the insulin sensitivity of the tissues, then the utilising of the stored lipids and the oxidative capacity [8].

There are studies that confirm that there is impaired reproductive capacity in the obese women. Brewer CJ., et al. 2010 indicate that the obesity affects ovulation, oocyte maturation, development of the endometrium, implantation, anovulation, irregular menstrual period and sterility.

There are complex hormonal mechanisms working to support the reproductive system, in order to maintain control over the menstrual period, the ovulation and the development of the endometrium. Obesity impairs this balance through several direct and indirect mechanisms. It is actually proven that the adipose tissue impairs the secretion and the bio-avidity of the sexual hormones. Indirectly, its effects are demonstrated through the insulin and the adipokines - Leptin, Adiponectin, resisting, omen tin. [9] Stagier., et al. 2002 explain the relationship of the adipokines and the adipose tissue with the modulation of the insulin sensitivity. He indicates that the production of adiponectin is regulated by intra-abdominal visceral fat tissue and it is inversely correlated with the serum insulin. [10]

One of the reproductive dysfunctions which are most often related to obesity is the polycystic ovarian syndrome. The polycystic ovarian syndrome is a heterogeneous endocrine disorder whose pathogenesis has not been fully explained yet. It is globally present in 7-10% of the women in reproductive age [11]. Obesity is a health problem with a growing prevalence and the women with PCOS are exposed to a higher risk of weight increase and obesity compared to the rest of the population [12]. In 50-70% of the women with diagnosed PCO syndrome, there is altered the level of insulin resistance and hyperinsulinemia [13], they are exposed to a higher risk of developing hyperandrogenemia, dyslipidemia, cardiovascular disorders, as well as diabetes mellitus type 2 [14]. Insulin resistance affects the development of the metabolic changes but the causes of the insulin resistance have not been explained yet [15]. The insulin resistance with hyperinsulinemia plays a major role in the initiation of the hyperandrogenism through the increase of the biosynthesis of the androgenic hormones in the ovaries. In the long run, the insulin resistance with hyperinsulinemia increases the risk of metabolic disorders such as impaired glucose tolerance and type 2 diabetes, cardiovascular disorders. [16,17]

Panidis., et al. 2003 и *Bulent., et al.* 2008 illustrate in their studies that in PCOS, the hyperinsulinemia, dyslipidemia, and/or hypertension are significantly correlated with the obesity. [18] Some of the adipokines produced by the adipose tissue also demonstrate a close correlation with the occurrence of insulin resistance in obese patients.

Spanos., et al. 2012 illustrate in his study that in the overweight patients there is an impairment of the production of the Adipokines and he relates this with the insulin resistance, with the hypoandrogenism and with the polycystic ovarian syndrome [19]. There are several research studies that examine the influence of the specific Adipocytokines in the pathogenesis of PCOS.

Leptin -General characteristic of leptin

Leptin is a cytokine which is produced by the white adipose tissue. It is a protein composed of 167 amino acids and its molecular mass is 16kDa. Leptin is a key hormone that participates in maintaining the energy homeostasis and the weight through the limitation of food intake and an increase in energy output. Leptin is coded by the ob gene and it is produced in the mature and differentiated adipocytes. Leptin binds to the long form of the leptin receptor (Ob-Rb) in the hypothalamus which provides the information about the quantity of stored energy and in this way regulates the food intake and the energy output20. Several studies indicate that this hormone is involved in several different physiological processes, such as the metabolic control, control of growth, reproduction, puberty, hematopoiesis, angiogenesis, osteogenesis, blood pressure regulation [11,2].

The role of leptin in body weight regulation

The mutation of the ob/ob gene of obesity in mice with a deficit of leptin causes hyperphagia, an increase of weight and development of insulin resistance, diabetes type 2 and other endocrinological dysfunctions. When recombinant leptin is administered intravenously, it binds to the leptin receptors in the hypothalamus and it produces a signal for an increase of the energy output and reduction of the food intake. Leptin affects the regulation of the metabolism of glucose and insulin and then it causes a decrease of the appetite in these animals, increase of the basal metabolism and significant decrease of weight. [22]

The quantity of leptin in the blood is closely related to the degree of presence the adipose tissue. After the adjustment of the BMI, women have higher values of leptin and it is related to the higher percent of peripheral adipose tissue or it is due to the stimulation of leptin caused by estrogen, progesterone or by the androgen hormones. High concentrations of leptin are found in obese patients, compared to the thin ones, and this is probably because of the higher number of adipose cells, which is contrary to the experimental models.

Although there is a higher concentration of leptin, which should be producing a signal for reduction of food intake and a decrease of the body weight, in obese patients probably there is a leptin resistance and they are insensitive to the production of the endogenous Leptin. [23] The administration of recombinant leptin in different doses produces a significant decrease of the body weight in obese patients, but only if the doses are up to 40 times higher than the placebo or the basic leptin values, which indicates that most probably there is a leptin resistance; high doses of leptin are necessary to overcome it. In terms of pathophysiology, there is a saturation of the leptin transporters at CNS level and this inhibits its transport. [24]

The prospective study WOSCOPS-West of Scotland Coronary Prevention Study proves for the first time that leptin is an independent risk factor for cardiovascular diseases (CVD). Leptin in this study is significantly higher in 377 examinees who are registered with a cardiovascular event during a period of 5 years, compared to the 783 patients who are not registered with diseases of the cardiovascular system. [25]

The study of Carmina E., *et al.* 2005 and Chakrabarti J. 2013, demonstrates that in PCOS patients there is a positive correlation between leptin and the body weight, expressed through BMI, with the insulin sensitivity, and that the correlation between leptin and the insulin resistance directly depends on the changes of the body weight. [26,27]

The conclusion is that leptin is the main adipostatic hormone that signals for a limited food intake and increased energy output. Apart from these activities, leptin improves the peripheral insulin sensitivity (of the liver and of the skeletal muscles) and modifies the function of the β–cells of the pancreas. Most often and when there is inactivity of the leptin receptors, and it circulates in high concentrations, in most cases of obesity, leptin does not cause a decrease in weight because of the leptin resistance. In theory, the resistance can occur in several spots of the signal trajectory of leptin, but this has not been fully explained yet.

***Adiponectin* -General characteristics of adiponectin**

Adiponectin is a protein composed of 244 amino acids, with a molecular mass of 30 kDa. The Adiponectin gene is positioned on the chromosome 3q27. It was discovered in 1995 by several independent groups, which is the reason why it has different names: ACRP30 (adipocyte complement-related protein of 30kD), AdipoQ, GBP28 (gelatin-binding protein of 28 kD), apM1 (adipose most abundant gene transcript 1); [28].

Adiponectin is synthesised and secreted only by the adipose tissue. Its concentration in the blood ranges from 5 to 30 mg/ml and about 0.01% of the total plasma proteins belong to it. Adiponectin is a hydrophilic protein composed of the carboxy-terminal globular domain, variable region and collagen domain and amino-terminal domain.

In the circulation system, this cytokine is found in the multimeric forms: trimer, hexamer, oligomer and full-length adiponectin in (fAd). fAd can liberate a fragment which contains a C-terminal globular domain that has an important role in the metabolism of the adipose tissue. Adiponectin demonstrates a structural homology with the complement factor C1q and collagen VII and X [29]. Two receptors through which it expresses its effects have been cloned: AdipoR1 mostly present in the skeletal muscles and AdipoR2 present in the liver.

AdipoR1 in the muscles is stimulated by the globular domain of Adiponectin, and the receptors located in the liver are stimulated only by the full-length Adiponectin. As a result of their stimulation, the AMP-activated protein kinase is increased and it increases the activity of the nuclear receptor PPAR- α. The activation of the AMRK influenced by adiponectin results in increases of the glucose utilisation, increased oxidation of the fatty acids, increased phosphorylation and inhibition of acetyl-CoA carboxylase in the muscles.

In the liver, there will be a reduced activity of the gluconeogenesis enzymes. The secretion of adiponectin is stimulated through the exposition of the adipocytes to PPAR-γ agonists and the effect of insulin sensitivity of these ligands is due to this. Also, the receptor T-cadherin for hexametric and high-molecular-weight (HMW) forms of adiponectin were identified. It is probably a co-receptor through which adiponectin transports its metabolic signals. [30]

Adiponectin and its association with obesity

There are several known significant physiological functions of Adiponectin in the organism:

1. It increases the insulin activity in the liver and simultaneously prevents the buildup of the fatty acids in the liver, 2. It affects the increased glucose utilisation in the liver and in the skeletal muscles, 3. It increases the oxidation of the fatty acids. [31]

The synthesis and the secretion of adiponectin are most probably regulated through several mechanisms. In the cases of normal body weight, the adipocytes produce insulin-sensitizing hormones: leptin, adiponectin and other peptides. When there is an expansion of the adipose tissue and its hypertrophy, there is an alternation in its secretion function and there is a reduced production of the insulin-sensitizing hormones and increased production of the insulin-resistant hormones, which leads to obesity with insulin resistance.

Insulin and the IGF-1 factor affect the increased secretion of adiponectin in the adipocytes. Adiponectin reduces the synthesis and the production of glucose in the liver and it causes a decrease of the glucose and of the free fatty acids in the blood. At the same time, adiponectin increases the sensitivity of the hepatocytes to the effects of insulin and it causes a decrease of the concentration of the circulating lipids through its effect on the skeletal muscles. The main characteristic of adiponectin is that its concentration correlates inversely with the degree of obesity [32], contrary to the other hormones whose values have a positive correlation with the degree of obesity and with the insulin resistance.

The decrease of the concentration of the adiponectin is associated with dyslipidemia and atherosclerosis. The most potent form with the largest part in the metabolic processes in the adiponectin high molecular weight complex (HMW) [33]. There is a high correlation between the decrease of the concentration of the total adiponectin and type 2 diabetes, and what is significant here is that there is a decrease only in HMW while the concentration of the other multimeric forms remains unchanged.

There is a negative correlation between adiponectin and the abdominal obesity6 and a positive correlation with the subcutaneous adipose tissue. Same like leptin, its concentration is higher in women compared to men. Adiponectin-deficient mice are prone to developing insulin resistance, glucose intolerance, hyperlipidemia and increased sensitivity of the vascular wall and atherosclerosis. [34]

Adiponectin demonstrates vascular-protective effects. In particular, in patients who have already been registered with a cardiovascular disease, the low concentration of adiponectin is associated with a lower cardiovascular risk compared to the patients with high values of adiponectin. [5] In this respect, Pangaribuan B., *et al*. 2011 and Panidis D., *et al*. 2003 in their studies demonstrate that there is a difference in the concentrations of Adiponectin and resisting in obese and thin women with PCOS and that there is a correlation with the insulin resistance in the women with PCOS [36,16]

The latest studies elaborate that the reduced level of Adiponectin in women with PCOS correlates with the obesity degree (Panidis., *et al*. 2003; Orio., *et al*.). On the contrary, Springier J., 2004 illustrates that the PCOS is not associated with the reduced level of adiponectin, but that adiponectin has an independent association with obesity and insulin resistance both in healthy control groups and in women with PCOS. The exact mechanism through which adiponectin improves insulin sensitivity should be further examined.

We would summarise that adiponectin is a hormone exclusively produced by the adipose tissue and it improves the insulin sensitivity in the liver, it increases the oxidation of the fatty acids, it reduces the decomposition of glycogen that is stored in it. [37] Related to the muscles, it stimulates the glucose utilisation and the oxidation of the fatty acids. In respect of the vascular wall, it inhibits the adhesion of the monocytes and it inhibits the transformation of the macrophages into foam cells. Furthermore, it increases the production of nitrogen oxide in the endothelial cells and stimulates angiogenesis. The whole process is enabled through phosphorylation of the insulin receptors, activation of the AMP-activated protein kinase. [38,39]

Further research is required to determine if a therapy can affect the increase of its concentrations in order to reduce the adipose tissue and the risk of the associated diseases.

Conclusion

It is more than evident that the adipose tissue has an important role as an organ that has the ability to produce a large number of hormones that are very important in the modulation of the of the metabolic processes in the organism. Leptin, adiponectin, resistin and the other adipokines that are produced by the adipocytes, circulate and affect the physiology of the other tissues. These hormones

affect the energy metabolism, the glucose and the lipid metabolism, the vascular homoeostasis, the immune response and the reproductive function.

Their role is significant when it comes to expansion of the adipose tissue and obesity. The increases in the adipose tissue and the alteration of its secretion have various effects on the endocrine and metabolic processes. Further research is of immense significance for the insight into their role and into the complicated molecular relationships between them. Detailed findings of their roles will undoubtedly introduce a new era of developing efficient therapeutic possibilities for treating obesity and the related conditions.

References

1. Emily Oken and Matthew W Gillman. "Fetal Origins of Obesity". *Obesity Research* 11.4 (2003): 496-506.
2. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization, (2000).
3. Timothy J Bartness and Maryam Bamshad. "Innervation of mammalian white adipose tissue: implications for the regulation of total body fat". *American Journal of Physiology* 27.5 (1998): 1399-1411.
4. Zhang Y., *et al*. "Positional cloning of the mouse obese gene and its human homologue". *Nature* 372 (1994): 425-432.
5. J Zmire. Debeljina i metabolicka inzulinska rezistencija MEDICUS 13.2 (2004): 27-35.
6. Tzontcheva A. The Secret life of Fat JMB 27.4 (2008).
7. Guerre-Millo M. "Adipose tissue and Adipokines: for better or worse". *Diabetes & Metabolism* 30.1 (2004): 13-19.
8. Viviane de Oliveira Leal and Mafra D. "Adipokines in obesity". *Clinica Chimica Acta* 419.18 (2013): 87-94.
9. Brewer CJ and Balen AH. "The adverse effects of obesity on conception and implantation". *Reproduction* 140.3 (2010): 347-364.
10. Staiger H., *et al*. "Relationship of Serum Adiponectin and Leptin Concentrations with Body Fat Distribution in Humans". *Obesity Research* 11.3 (2003): 368-376.
11. The Prevalence and Features of the Polycystic Ovary Syndrome in an Unselected Population JCEM 89 (2004): 2745-2749.
12. Xinwang Chen., *et al*. "Adipokines in reproductive function: a link between obesity and polycystic ovary syndrome". *Journal of Molecular Endocrinology* 1 (2013): 21-37.
13. Ovalle F and Ricardo Azziz. "Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus". *Fertility and Sterility* 77.6 (2002): 1095-1105.
14. Bulent O Yildiz., et al. "Impact of obesity on the risk for Polycystic Ovary Syndrome". Journal of Clinical Endocrinology and Metabolism 93.1 (2008): 162-168.
15. H Teedeand., *et al*. "Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan". *BMC Medicine* (2010).
16. Wild A.R., *et al*. "Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: A consensus statement by the androgen excess and polycystic ovary syndrome (AE-PCOS) society". *The Journal of Clinical Endocrinology & Metabolism* 95.5 (2010): 2038-2049.
17. Toulis AK., *et al*. "Meta-analysis of cardiovascular disease risk markers in woman with polycystic ovary syndrome". *Hum Reproduction Update* 17.6 (2011): 741-760.
18. Panidis, D., *et al*. "Serum Adiponectin levels in women with polycystic ovary syndrome". *Human Reproduction* 18.9 (2003): 1790-1796.
19. Spanos N., *et al*. "Adipokines, insulin resistance and hyperandrogenemia in obese patients with polycystic ovary syndrome: cross-sectional correlations and the effects of weight loss". *Obesity Facts* 5.4 (2012): 495-504.
20. Jean-Philippe Bastard., *et al*. "Recent advances in the relationship between obesity, inflammation, and insulin resistance". *European Cytokine Network* 17.1 (2006): 4-12.
21. Furtuno A., *et al*. "Adipose tissue as an endocrine organ: role of Leptin and Adiponectin in the pathogenesis of cardiovascular diseases". *Journal of Physiology and Biochemistry* 59.1 (2003): 51-60.
22. Gnacinska M., *et al*. "Role of Adipokines in complications related to obesity: a review". *Advances in Medical Sciences* 54.2 (2009): 150-157.

23. Galic S., *et al*. "Adipose tissue as an endocrine organ". *Molecular and Cellular Endocrinology* 316 (2010): 129-139.
24. Soodini GR. "Adiponectin and Leptin in relation to insulin sensitivity". *Metabolic Syndrome and Related Disorders* 2.2 (2004): 114-123.
25. Wallace AM., *et al*. "Plasma Leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS)". *Circulation* 104.25 (2001): 3052-3056.
26. Carmina EN., *et al*. "Evidence for altered adipocyte function in polycystic ovary syndrome". *European Journal of Endocrinology* 152.3 (2005): 389-394.
27. Chakrabarti J. "Serum Leptin level in women with polycystic ovary syndrome: correlation with adiposity, insulin, and circulating testosterone". *Annals of Medical and Health Science Research* 3.2 (2013): 191-196.
28. Fonseca-Alaniz., *et al*. "Adipose tissue as an endocrine organ: From theory to practice". *Jornal de Pediatria* 83.5 (2007): 192-203.
29. Nedvidkova J., *et al*. "Adiponectin, an adipocyte-derived protein". *Physiological Research* 54.2 (2005): 133-140.
30. Meier., *et al*. "Endocrine regulation of energy metabolism: review of path biochemical and clinical chemical aspects of leptin, ghrelin, Adiponectin, and resistin". *Clinical Chemistry* 50.9 (2004): 1511-1525.
31. P. Singla., *et al*. "Metabolic effects of obesity: A review". *World Journal of Diabetes* 1.3 (2010): 76-88.
32. Arita Y., *et al*. "Paradoxical decrease of an adipose-specific protein, Adiponectin, in obesity". *Biochemical and Biophysical Research Communications* 257.1 (1999): 79-83.
33. Schraw T., *et al*. "Plasma Adiponectin complexes have distinct biochemical characteristics". *Endocrinology* 149.5 (2008): 2270-2282.
34. Maeda N., *et al*. "Diet-induced insulin resistance in mice lacking Adiponectin/ACRP30". *Nature Medicine* 8.7 (2002): 731-737.
35. Hajer., *et al*. "Low plasma levels of Adiponectin are associated with low risk for future cardiovascular events in patients with clinical evident vascular disease". *American Heart Journal* 154.4 (2007).
36. Pangaribuan B., *et al*. "Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome". *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2.6 (2011): 235-45l.
37. Chandran M., *et al*. "Adiponectin: More than Just Another Fat Cell Hormone?" *Diabetes Care* 26.8 (2003): 2442-2450.
38. Yamauchi T., *et al*. "Cloning of adiponectin receptors that mediate antidiabetic metabolic effects". *Nature* 423.6941 (2003): 762–769.
39. Diez JJ and Iglesia P. "The role of novel Adipocytes- derived- hormone adiponectin in human diseases". *Eur JEndocrinology* 148 (2003): 293-300. doi:10.1530/eje.0.1480293