

Leptin, Ghrelin, Adiponectin, Homocysteine and Insulin Resistance Related to Polycystic Ovary Syndrome

Saghar Salehpour, M.D.^{1*}, Parisa Taherzadeh Broujeni, M.D.²,
Elham Neisani Samani, M.D.²

1. Obstetrics and Gynecology Department, Infertility and Reproductive Health Research Center (IRHRC),
Shahid Beheshti University (MC), Tehran, Iran

2. Obstetrics and Gynecology Department, Shahid Beheshti University (MC), Tehran, Iran

Abstract

The relationship between leptin, adiponectin, ghrelin, homocysteine, insulin resistance and other biochemical factors in women with polycystic ovary syndrome (PCOS) is controversial. We review how the expanded role of these factors in reproduction might impact our understanding of PCOS. For purposes of our review, we accessed the PUBMED database during the past 10 years. Our review confirms that these factors can have etiopathogenetic importance in some enigmatic reproductive disturbances such as PCOS. Moreover understanding the role of these biochemical factors might be useful for new treatments in PCOS.

Keywords: Leptin, Adiponectin, Ghrelin, Homocysteine, Polycystic Ovary Syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder of functional androgen excess, detectable either by laboratory analysis or by clinical exam, with ovulatory dysfunction and polycystic ovarian morphology also affecting a large proportion of these patients (1, 2). PCOS is now thought to be a complex genetic trait, similar to cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome, where multiple genetic variants and environmental factors interact to foster the development of the disorder (2, 3).

Life style changes, medical therapy and laparoscopic electrocautery may be recommended depending on the patient's goal (3-5).

In this review, we discuss the status of leptin, adiponectin, ghrelin, homocysteine and insulin resistance in patients with PCOS.

Leptin

Adipose tissue synthesizes and secretes numerous peptides such as leptin, and adiponectin that are involved in the regulation of energy homeostasis, reproduction, insulin action and lipid metabolism.

The relationship between these peptides and

reproductive function is complex and incompletely understood (6).

Leptin, a key hormone in energy homeostasis and neuroendocrine function, has a permissive role in the pathogenesis of reproductive dysfunction. It is the product of the ob gene secreted from adipose tissue which signals the amount of energy stores to the brain and is implicated in the regulation of food intake and energy balance (6, 7).

Leptin was discovered as a result of studies with ob/ob mice, a strain of hyperphagic obese mice, known to lose weight when their circulation is attached to normal mice (8, 9).

Subsequent studies revealed that ob/ob mice have a mutation which results in their inability to produce a protein, first called the ob protein and later leptin, that regulates food intake. In addition to being obese these mice are infertile due to gonadal hypofunction (10).

In humans the leptin gene is located on chromosome 7q 32 and consists of three exons and two introns that span 20 kilobases (kb) of DNA. The mouse and human ob genes are 84 percent homologous. Recent studies suggest that leptin may mediate some of the

Received: 29 Nov 2008, Accepted: 11 Jan 2009

* Corresponding Address: Obstetrics and Gynecology Department,
Infertility and Reproductive Health Research Center (IRHRC), Shahid Beheshti University (MC), Tehran, Iran
Email: saghar_salehpour@yahoo.com



Royan Institute
International Journal of Fertility and Sterility
Vol 2, No 3, Nov-Dec 2008, Pages: 101-104

adverse effects of obesity on ovarian function in PCOS (10, 11). Brzechffa et al have reported increased levels of leptin in PCOS (12) while others report normal leptin levels (13, 14). In these studies, significant positive correlations are found between leptin levels and body mass index. Bias in the selection of patients and matching control groups may define these differences. In addition Micic suggested in PCOS leptin secretion is less than expected because of insulin resistance and the presence of visceral fat (15).

Karlsson et al found that leptin inhibited LH-stimulated estradiol production by granulosa cell (16).

Jacobs summarized the expanded role of leptin in PCOS as follows: interaction with insulin and adipose tissue and its effects on ovarian function (17).

Adiponectin

Adiponectin, is the most abundant protein secreted by adipose tissue. Unlike other proteins, it circulates in lower concentrations in obesity and insulin-resistant states (18). Yamauchi suggested that adiponectin is a mediator of insulin sensitivity (19). In the study of Spranger et al adiponectin is not lower in women with PCOS as compared to body mass index matched ovulatory controls. Spranger et al showed that metformin therapy did not increase adiponectin concentration in women with PCOS (20). Sieminska observed lower adiponectin levels in the PCOS group than the control group. These differences are probably due to cases with a higher prevalence of insulin resistance (21).

Ghrelin

The novel peptide ghrelin displays multiple endocrine and non-endocrine actions. In obesity, ghrelin administration induces growth hormone secretion, enhances glucose and reduces insulin levels. Glintborg et al found that ghrelin levels decreased in hirsute PCOS patients (22).

In Italy, Fusco et al studied the effects of ghrelin administration on endocrine and metabolic parameters in nine obese women with PCOS. In both obese and PCOS obese patients leptin levels are not influenced by ghrelin administration (23). Arvat et al found elevated ghrelin concentrations might diminish reproductive function by inhibiting luteinizing hormone (24). The suppressive effects of elevated ghrelin levels may interfere with ovulation in pa-

tients with PCOS. Ghrelin assays vary from study to study, some evaluating total ghrelin and others active ghrelin.

Homocysteine and Insulin resistance

Homocysteine is an intermediate product formed by the breakdown of methionine that can change with age, sex, nutrition, smoking, chronic inflammation and physical activity (25). Elevated plasma homocysteine is shown to be a risk factor for cardiovascular disease (26). Yarali et al concluded that there is a probable relation between increased serum homocysteine and insulin resistance in women with PCOS (27). On the other hand, Sills et al report no correlation between PCOS and homocysteine levels (28). Although Kilic Okman found no correlation between insulin resistance and elevated homocysteine (29) recently, Badawy et al confirmed the correlation between insulin resistance and elevated homocysteine (30).

We suggest that discrepancies in defining PCOS, the homocysteine cut-off levels and the method of selecting PCOS patients could explain these differences.

Our study confirms the strong association between leptin, adiponectin, ghrelin, homocysteine, insulin resistance and PCOS manifestations. Adiponectin expression appears to be down-regulated by increased fat mass; this is particularly evident in the case of adiponectin expression in women with PCOS.

It is probable that insulin resistance is a factor that may contribute, in part, to these findings. Our review supports the conclusion that body mass index and insulin resistance are the two main factors governing serum levels of these peptides. When matched for body mass index status, the peptides leptin and ghrelin are not different in patients with PCOS.

These biochemical factors can be involved in the pathophysiology of PCOS. Further studies with larger matched groups are warranted in order to examine the status of these peptides.

References

1. Stein IF, Leventhal NL. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol.* 1935; 29: 181.
2. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007; 370: 685.
3. Salehpour S, Aghaee A. The effect of ovarian drilling on the fertility of patients with PCOS. *Pajohande.* 1999; 4(20): 423-428.

4. Salehpour S, Saadat N, Ashrafi M, Emami H. The effect of metformin therapy on menstrual function in polycystic ovary syndrome. *Med J Iran Hosp.* 2002; 15(1): 20-22.
5. Salehpour S, Kalantari M, Shayanfar SH, Valaee N. Coincidence of criterions Transvaginal sonography of suspicious Polycystic ovary syndrome in Iranian groups. *Pajohande.* 2003; 8(1): 49-52.
6. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Identification and expression cloning of a leptin receptor, OB-R. *Cell.* 1995; 83(7): 1263-1271.
7. Coleman DL. Effects of parabiosis of obese with diabetes and normal mice. *Diabetologia.* 1973; 9: 294.
8. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994; 372(6505): 425-432.
9. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science.* 1995; 269: 540.
10. LaZovic G, Radivojevic U, Milicevic S, Spremovic S. Influence of adiposity on leptin, LH and androgen levels in lean, overweight and obese PCOS patients. *Int J Fertil Womens Med.* 2007; 52(2-3): 82-88.
11. Atamer A, Demir B, Bayhan G, Atamer Y, Ilhan N, Akkuş Z. Serum levels of leptin and homocysteine in women with polycystic ovary syndrome and its relationship to endocrine, clinical and metabolic parameters. *J Int Med Res.* 2008; 36(1): 96-105.
12. Brzechffa PR, Jakimiuk AJ, Agarwal SK, Weitsman SR, Buyalos RP, Magoffin DA. Serum immunoreactive leptin concentrations in women with polycystic ovarian syndrome. *J Clin Endocrinol Metab.* 1996; 81: 4165-4169.
13. Chapman IM, Witter GA and Norman RJ. Circulating leptin concentrations in polycystic ovary syndrome: relation to anthropometric and metabolic parameters. *Clin Endocrinol.* 1997; 46: 175-181.
14. Laughlin GA, Morales AJ, Yen SS. Serum leptin levels in women with polycystic ovary syndrome: the role of insulin resistance/hyperinsulinemia. *J Clin Endocrinol Metab.* 1997; 82: 1692-1696.
15. Micic D, Macut D, Popovic V. Leptin levels and insulin sensitivity in obese and non-obese patients with polycystic ovary syndrome. *Gynecol Endocrinol.* 1997; 11: 315-320.
16. Karlsson C, Lmdell K, Svensson E, Bergh C, Lind P, Billig H, et al. Expression of functional leptin receptors in the human ovary. *J Clin Endocrinol Metab.* 1997; 82: 4144-4148.
17. Jacobs HS, Conway GS. Leptin, polycystic ovaries and polycystic ovary syndrome. *Hum Reproduction Update.* 1999; 5(2): 166-171.
18. Carmina E, Chu MC, Moran C, Tortoriello D, Vardhana P, Tena G, et al. Subcutaneous and omental fat expression of adiponectin and leptin in women with polycystic ovary syndrome. *Fertil Steril.* 2008; 89(3): 642-648.
19. Yamauchi T, Kamon J, Minokoshi Y, Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med.* 2002; 8: 1288-1295.
20. Spranger J, Mohlig M, Wegewitz U, Ristow M, Pfeiffer AF, Schill T, et al. Adiponectin is independently associated with insulin sensitivity in women with polycystic ovary syndrome. *Clin Endocrinol.* 2004; 61: 738-746.
21. Sieminska L, Marek B, Kos-Kudla B, Niedziolka D, Kajdaniuk D, Nowak M, et al. Serum adiponectin in women with polycystic ovarian syndrome and its relation to clinical, metabolic and endocrine parameters. *J Endocrinol Invest.* 2004; 27(6): 528-534.
22. Glinborg D, Andersen M, Hagen C, Frystyk J, Hulstrøm V, Flyvbjerg A, et al. Evaluation of metabolic risk markers in polycystic ovary syndrome (PCOS). Adiponectin, ghrelin, leptin and body composition in hirsute PCOS patients and controls. *Eur J Endocrinol.* 2006; 155(2): 337-345.
23. Fusco A, Bianchi A, Mancini A, Milardi D, Giampietro A, Cimino V, et al. Effects of ghrelin administration on endocrine and metabolic parameters in obese women with polycystic ovary syndrome. *J Endocrinol Invest.* 2007; 30(11): 948-956.
24. Arvat E, Maccario M, Divito L, Broglio F, Benso A, Gottero C, et al. Endocrine activities of ghrelin, a natural growth hormone secretagogue (GHS), in humans: comparison and interactions with hexarelin, a nonnatural peptidyl GHS and GH-releasing hormone. *J Clin Endocrinol Metab.* 2001; 86: 1169-1174.
25. Schneede J, Refsum H, Ueland PM. Biological and environmental determinants of plasma homocysteine. *Semin Thromb Hemost.* 2000; 26: 263-279.
26. Knekt P, Alfthan G, Aromaa A, Heliövaara M, Marniemi J, Rissanen H, et al. Homocysteine and major coronary events. *J Intern Med.* 2001; 249: 461-465.
27. Yarali H, Yildiz A, Aybar F, Kabakçi G, Bükülmez O, Akgül E, et al. Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with PCOS. *Fertil Steril.* 2001; 76: 511-516.
28. Sills ES, Genton MG, Perloe M, Schattman GL. Plasma homocysteine, fasting insulin and androgen patterns among women with PCOS and infertility. *J Obstet Gynecol Res.* 2001; 27: 163-168.
29. Kilik-Okman T, Guldiken S, Kucuk M. Relationship between homocysteine and insulin resistance in women with PCOS. *Endocr J.* 2004; 51(5): 505-508.

30. Badaway A, State O, El Gawad SSh, El Aziz OA. Plasma homocysteine and PCOS: the missed

link. *Eu J Obstet Gynecol Rep Biol.* 2006; 5: 112-116.

Archive of SID