Published in final edited form as:
Fertil Steril. 2010 July ; 94(2): 690–693. doi:10.1016/j.fertnstert.2009.03.058.

Ovarian and adipose tissue dysfunction in polycystic ovary syndrome: report of the 4th special scientific meeting of the Androgen Excess and PCOS Society

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Abstract

Significant advances have been made in our understanding of ovarian dysfunction in polycystic ovary syndrome (PCOS), and alterations in adipose tissue function are likely to play an important role in its pathophysiology. This review highlights the principal novel concepts presented at the 4th special scientific meeting of the Androgen Excess and PCOS Society, "Ovarian and Adipose Tissue Dysfunction: Potential Roles in Polycystic Ovary Syndrome," which occurred on June 6, 2008 in San Francisco, California.

The 4th special scientific meeting of the Androgen Excess and PCOS Society was held in San Francisco, California on June 6, 2008. Focusing on "Ovarian and Adipose Tissue Dysfunction: Potential Roles in Polycystic Ovary Syndrome," the meeting attracted 81 participants from over 15 countries. This full-day event included four sessions; the first session described new developments in our understanding of the mechanisms underlying the ovarian pathophysiology in polycystic ovary syndrome (PCOS), and the others explored the emerging role of adipose tissue dysfunction in PCOS. Each session had two lectures by plenary speakers, and the last session also included five oral presentations with late developing findings. We provide a brief summary of the findings described in this meeting.

OVARIAN PATHOPHYSIOLOGY IN PCOS

State of Current Knowledge

Androgen excess, chronic oligo-anovulation, and enlarged polycystic ovaries are the features that are used to define PCOS and all suggest ovarian dysfunction in the syndrome. Ovarian pathophysiology in PCOS involves alterations in both theca and granulosa cell function as well as folliculogenesis. In women with PCOS, ovaries contain more antral follicles than normal, thus forming the polycystic morphology. These ovaries have excessive numbers of theca cells. Generalized dysregulation of androgen secretion due to increased activity of 17α-hydroxylase and 17,20 lyase in theca cells results in androgen excess in most women with PCOS. The follicles of the anovulatory cycles show increased responsiveness

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B.O.Y. has nothing to disclose. R.A. is a consultant for Merck & Co. and Procter & Gamble.

to gonadotropins and arrested growth at the antral stage. Various intrinsic and extrinsic factors appear to be involved in the modulation of ovarian function in PCOS, including but not limited to follicle-stimulating hormone (FSH), luteinizing hormone (LH), insulin, antimullerian hormone, and adipokines (1, 2).

Discussion

By using their previously established theca cell culture model (3), Dr. Jan McAllister and colleagues (Hershey, Pennsylvania) showed the inherent defective mitogen activated protein kinase (MAPK) signaling in ovarian theca cells of PCOS women, which might contribute to excess CYP17 gene expression and androgen biosynthesis. A comparison of metformin effects on androgen biosynthesis in normal and PCOS theca cells demonstrated that the cells from PCOS women were more sensitive. Further analysis of the metformin activated LKB1/AMP-activated kinase (AMPK) demonstrated that LKB1 phosphorylation and AMPK activation were decreased in PCOS versus normal theca cells. Metformin treatment of PCOS theca cells, or alternatively infection with LKB1 or AMPK adenovirus, reverted the cells to a normal phenotype, with reduced CYP17 gene expression and androgen biosynthesis. When comparing cell proliferation in these theca cells, flow cytometry analysis (FACS) uncovered differences in cell cycle progression in PCOS theca cells compared with controls. Metformin treatment of PCOS cells changed their cell cycle progression to a normal phenotype, but this drug had no effect on cell cycle progression in normal theca cells.

Dr. Denis Magoffin (Los Angeles, California) outlined the potential mechanisms of ovarian hyperandrogenism, addressing follicle abnormalities in PCOS that cause disproportionate accumulation of small antral follicles with excessive differentiation of theca cells. He emphasized that the reproductive dysfunction is secondary to the endocrine abnormalities common to PCOS, including hyperinsulinemia and adipose tissue secretions, rather than to critical intrinsic ovarian abnormalities (4). There has been evidence to support a potential role for select adipokines, including resistin, visfatin, and adiponectin, in ovarian hyperandrogenism. Dr. Magoffin also provided preliminary data that PCOS adipocytes demonstrate decreased glucose transport with increased tyrosine phosphorylation of glycogen synthase kinase-3 (GSK3), which suggests enhanced GSK3 action (5). This abnormality could potentially enhance androgen biosynthesis through direct stimulation of P450c17 activity.

ADIPOSITY AND PCOS

State of Current Knowledge

Adipose tissue is the most abundant endocrine organ in the body. Adiposity is closely linked to insulin resistance, diabetes, and cardiovascular disease through different mechanisms including [1] production and secretion of several hormones, cytokines, and other molecules; [2] defects in insulin signaling; [3] low-grade chronic inflammation; and [4] dysfunctional steroidogenesis (6). In PCOS, body fat amount and distribution are usually altered. Abdominal adiposity or obesity are present in most women with PCOS, adversely influencing both the metabolic and reproductive phenotype of the syndrome (7).

Adipose tissue dysfunction in PCOS has not yet been extensively studied. Androgens appear to have significant impact on adipocyte function and the distribution of body fat in women (8). It is interesting that prenatal exposure to androgens in primates results in increased adiposity as well as a PCOS-like phenotype in adulthood (9). There is an abnormality in insulin-stimulated glucose transport in many women with PCOS. It was recently reported that cultured skeletal muscle cells show impaired insulin responsiveness whereas isolated adipocytes show impaired insulin sensitivity but normal responsiveness in PCOS, suggesting that skeletal muscle and adipose tissue contribute differently to insulin resistance in the

syndrome (10). Finally, different compartments of fat might exhibit phenotypically important differences in contributing to adipose tissue dysfunction in PCOS. For example, catecholamine-induced lipolysis is increased in visceral fat and decreased in the subcutaneous fat of women with PCOS (11).

Discussion

The role of autonomic dysregulation in PCOS and its effect on adipose tissue and ovarian function were discussed by Dr. Elisabet Stener-Victorin (Goteborg, Sweden), whose group has demonstrated increased sympathetic nerve activity in women with PCOS, closely related to the increased testosterone levels (12). These investigators have also developed a rat PCOS model, induced by the continuous prepubertal administration of dihydrotestosterone (DHT), that exhibits irregular cycles, polycystic ovaries, insulin resistance, increased body weight as well as body fat, and enlarged mesenteric adipocytes. Gene expression analyses have demonstrated increased messenger RNA (mRNA) expression of beta 3 adrenergic receptor (ADR-β_3), ovarian nerve growth factor (NGF), leptin and interleukin 6 (IL-6) and decreased expression of uncoupling protein 2 (UCP2) in the mesenteric adipose tissue of the PCOS rats. When Stener-Victorin and colleagues examined the effects of electroacupuncture and exercise on these alterations in adipose tissue gene expression, they observed that electroacupuncture was able to normalize the expression of ADR-β_3, NGF, leptin, and UCP2, whereas exercise normalized adipose tissue NGF, leptin, and IL-6 expression (13).

Studies on the prenatally androgenized female rhesus monkey model for PCOS have demonstrated that when these monkeys become adults, they exhibit at least two out of three PCOS diagnostic criteria: [1] intermittent or absent menstrual cycles, [2] hyperandrogenism, and [3] polycystic ovaries (14). Dr. David Abbott (Madison, Wisconsin) presented new data on this nonhuman primate model of PCOS that suggests that exposure to high androgens during gestation induces PCOS-like metabolic traits in the adult prenatally androgenized female monkey (15). Early exposure to androgens during gestation resulted in the development of increased abdominal fat, particularly visceral fat, in adulthood, whereas late exposure led to an overall increase in both total body and abdominal fat. Early, but not late, prenatal androgen exposure induced increased plasma free fatty acid levels, insulin resistance, and deficient pancreatic beta-cell insulin responses to glucose. These animals also demonstrated positive correlations between visceral fat and body mass index as well as between basal serum insulin levels and total body or abdominal fat. Therefore, timing of gestational androgen exposure appears partially responsible for heterogeneity in the adult metabolic phenotype in this nonhuman primate model for PCOS.

The impact of therapeutic interventions on insulin action in PCOS was discussed by Dr. Theodore P. Ciaraldi (San Diego, California), who noted that metabolic perturbations in PCOS occur at the level of the pancreatic β-cell, in the insulin action of peripheral tissues—including adipose tissue and skeletal muscle—and in the secretory function of adipose tissue (16). Laparoscopic ovarian electrocautery has been reported to improve insulin action and lower fasting circulating insulin levels. Metformin is frequently used as a treatment for PCOS, with mixed effects on whole body insulin action and insulin levels (either no change or an improvement). Alternatively, the insulin-sensitizing thiazolidinediones (TZDs) have consistently been shown to improve whole body insulin action, augmenting both nonoxidative and oxidative glucose disposal. Thiazolidinedione treatment increases the circulating levels of the insulin-sensitizing adipokine adiponectin, whereas levels of resistin, an inducer of insulin resistance, is reduced with metformin treatment. There is limited information available concerning treatment effects on specific aspects of the insulin-signaling cascade. Nevertheless, improved insulin action after laparoscopic ovarian electrocautery was accompanied by increased expression of several proteins of the insulin-signaling cascade and decreased inhibitory serine phosphorylation of insulin-receptor

substrate-1 (IRS-1) in adipose tissue. Thiazolidinediones, however, had no effect on the same signaling proteins in skeletal muscle. Improved insulin action and glucose metabolism in PCOS women after treatment, therefore, appear to result from altered secretory function in adipose tissues and modified insulin signaling in peripheral tissues, with possible tissue specificity to this response.

Many aspects of adipose cell function are known to be regulated by sex hormones; for example, androgens inhibit adipose cell differentiation and modulate lipogenesis and lipolysis. Dr. Anne Corbould and colleagues (Melbourne, Australia) reported that testosterone treatment of cultured human adipose cells caused impaired insulin-stimulated glucose uptake, an effect selective for insulin signaling of glucose transport but not mitogenesis (17). Consequently, hyperandrogenism might perpetuate defective insulin signaling in women with PCOS in whom hyperinsulinemia increases androgen production, which in turn promotes insulin resistance in peripheral tissues. Evaluating the effects of spironolactone, an androgen receptor antagonist, in cultured human subcutaneous adipocytes of normal women and women with PCOS, these investigators observed that spironolactone exposure increased basal glucose uptake via a mechanism independent of the androgen receptor and reduced production of IL-6 (18).

Extensively applied in biomedical studies of diabetes and obesity, genomics, and proteomics promise much potential in future investigations of PCOS. Available human and animal data encouraged Dr. Héctor F. Escobar-Morreale and colleagues (Madrid Spain) to hypothesize that women with PCOS experience a vicious cycle whereby hyperandrogenism favors abdominal adiposity, which further stimulates androgen secretion by the ovaries and adrenals. After studying the omental fat of morbidly obese women with and without PCOS, these investigators reported that the transcriptome and proteome of omental fat were altered in PCOS (19, 20). It is important that these abnormalities were not limited to insulin signaling but rather spanned several biological pathways related to oxidative stress, inflammation, immune function, and lipid metabolism as well as other genes related to PCOS or the metabolic syndrome.

Dysregulation of adipocyte function in PCOS women and the endocrine role of adipose tissue in the disorder were reviewed by Dr. Enrico Carmina (Palermo, Italy). Evidence of possible dysregulation in the secretion of several adipocytokines, including leptin, adiponectin, tumor necrosis factor alpha (TNF-α), IL-6, monocyte chemoattractant protein-1 (MCP-1), visfatin, and retinol-binding protein 4 (RBP4), were reviewed. Data suggested, however, that the main factor perturbing adipocyte function in PCOS was the degree of abdominal obesity (21). Importantly, ovulatory women with PCOS generally exhibit smaller quantities of abdominal fat than anovulatory PCOS, and because of it have less evidence of adipocyte dysfunction (22).

Finally, five short oral presentations reviewed some of the latest developments in the field.

Teede and colleagues (Melbourne, Australia) assessed quantitative gene expression by real-time polymerase chain reaction and muscle enzyme activity measurements from vastus lateralis muscle biopsies in normoglycemic obese women with and without PCOS (mean body mass index: 38 ± 2 vs. 37 ± 2 kg/m^2). They reported that mitochondrial biogenesis and metabolism were similar between the PCOS and control groups, suggesting that mitochondrial dysfunction does not contribute to inherent intrinsic insulin resistance observed at least in morbidly obese women with PCOS.

Dr. Daniela Jakubowicz (Caracas, Venezuela) reported on the results of a 32-week hypocaloric diet study in 94 obese women with PCOS. The study results suggested that

increased carbohydrate and protein intake at breakfast during caloric restriction in PCOS women was effective in enhancing weight loss by reducing hunger and sugar craving.

Preliminary data were presented on the gene expression of subcutaneous adipose tissue obtained from nonobese women with and without PCOS (Dr. Gregorio Chazenbalk, Los Angeles, California) that suggested significant alterations in the expression of those genes specifically involved in inflammation, including suppressor of cytokine signaling 3 (SOCS3), IL-6, and MCP-1.

The role of adipose tissue in the pathophysiology of PCOS was highlighted by another study (Dr. Bee K. Tan, Warwick, United Kingdom), which reported significantly higher levels of circulating vaspin, a novel adipokine, in women with PCOS. Importantly, metformin treatment for 6 months reduced serum vaspin levels in these patients (23).

The last presentation provided evidence that atrial natriuretic peptide and catecholamine-induced lipolysis is impaired in PCOS women (Dr. Leanne M. Redman, Baton Rouge, Louisiana). Both lipolytic impairments could be partly recovered by aerobic training, independent of changes in body weight and circulating sex-hormone levels.

CONCLUSION

The latest research data presented in this meeting suggest that major advances can be anticipated in the areas of ovarian and, in particular, adipose tissue dysfunction in PCOS. The meeting, however, also highlighted the complexities of the molecular and cellular processes involved, and the hurdles that this research is encountering. Further research exploring the regulation of adipose tissue function in PCOS is likely to generate valuable information that will ultimately further our understanding of the syndrome.

Acknowledgments

Supported in part by NIH grants R01-HD29364 and K24-HD01346-01, and the Helping Hand of Los Angeles, Inc.

The authors thank all of the meeting presenters, and the review and critique of the Androgen Excess and PCOS Society of Officers and Directors, including Drs. Daniel Dumesic, President; Roger Lobo, Vice President; Robert Norman, Past-President; Selma Witchel, Secretary-Treasurer; David Abbott, Director; Walter Futterweit, Director; Janet McAllister, Director; Francesco Orio, Director; Helena Teede, Director; and Enrico Carmina, Executive Director.

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