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Menstrual Health and the Metabolic Syndrome in Adolescents

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Abstract

The metabolic syndrome, a constellation of interrelated risk factors for cardiovascular disease and type 2 diabetes mellitus, has become a major public health concern against the backdrop of increasing rates of obesity. Insulin resistance plays a pivotal role as the underlying pathophysiological linchpin of the various components of the syndrome. The metabolic syndrome is well recognized in adults, and there is convincing evidence that it starts in childhood, with progressive clustering of the various components over time and tracking through adulthood. Adult women and adolescents with polycystic ovary syndrome (PCOS) have higher prevalence rates of the metabolic syndrome compared with the general population. Several anthropometric (obesity, particularly abdominal obesity), metabolic (insulin resistance/hyperinsulinemia, dyslipidemia) and hormonal (low IGFBP1, IGFBP2 and low sex hormone binding globulin) features of adolescents with PCOS are also features of the metabolic syndrome. Insulin resistance, believed to be a key pathogenic factor in both PCOS and the metabolic syndrome, may be the thread that links the two conditions. Menstrual health in adolescents could be viewed as yet another component in the evaluation of the metabolic syndrome. Careful assessment of menstrual history and appropriate laboratory work-up could reveal the presence of PCOS in obese at-risk adolescent girls with a family history of the metabolic syndrome.

Keywords

adolescents; menstrual cycle; metabolic syndrome

Introduction

The metabolic syndrome is generally recognized as a cluster of closely related risk factors, linked by insulin resistance/hyperinsulinemia, which predisposes the individual to cardiovascular disease morbidity and mortality. This syndrome has become a major public health problem against the backdrop of increasing obesity rates, and is recognized by the National Cholesterol Education Program as a secondary target of cardiovascular risk-reduction therapy.¹ Traditionally the metabolic syndrome is considered an adult condition. However, over the last decade there has been a growing appreciation of its presence among children and

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Conflicts of Interest

The authors declare no conflicts of interest.

adolescents, especially obese ones.^{2,3} In the United States, one-third of adult women 18–40 years old with polycystic ovary syndrome (PCOS)—a condition characterized by menstrual irregularities (oligomenorrhea or amenorrhea) and clinical and/or biochemical hyperandrogenism in the presence or absence of polycystic ovaries (OMIM %184700)—are estimated to have the metabolic syndrome.⁴ Among adolescents with PCOS this prevalence is estimated as 37–47%.⁵ These prevalence rates both in adults and adolescents are much higher than in the general population, where the metabolic syndrome is estimated to affect 0.6–8.9% of the adolescent girls in the 12–19-year age group,^{3,6} 12–14% of women in the 20–29-year age group, and 23% of women in the 30–40-year age group.⁷

There is evidence that the menstrual and the metabolic disturbances in adult women with PCOS have a perimenarcheal onset. Adolescent girls with menstrual disturbances within the spectrum of PCOS share several anthropometric, hormonal, and metabolic features of the metabolic syndrome^{5, 8, 9} (Fig. 1). Oligomenorrhea or amenorrhea in adolescent girls can be a sign of underlying metabolic disturbances that have major implications in adult life. In this chapter we will review the metabolic syndrome and menstrual health in adolescents. We propose that menstrual health can be viewed as yet another component in the evaluation of the metabolic syndrome in female adolescents. We will start with a definition of the metabolic syndrome, then explore the proposed link between this syndrome and menstrual health, namely insulin resistance, and review research studies that assessed features of the metabolic syndrome among adolescents with menstrual disturbances.

Metabolic Syndrome in Adolescents

Definition

In his Banting Lecture in 1988, Gerald Reaven coined the term “Syndrome X” in reference to the association of insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol, and increased very-low-density lipoproteins.¹⁰ This association has since been the subject of research and controversy,^{11, 12} and various terminologies have been used for it, including the metabolic syndrome, insulin resistance syndrome, and Reaven's syndrome. Currently there are six accepted definitions of the metabolic syndrome in adults, with different cutoffs and different mandatory inclusion criteria, yielding different prevalence rates of the syndrome.¹³ Nevertheless, there is general consensus on the main components of the syndrome, which include insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, hypertension, and dyslipidemia.

In children and adolescents, there is no accepted unified definition of the metabolic syndrome. Yet, pediatric researchers have used modified adult definitions with inconsistent cutoff criteria.^{2, 6, 14–17} Recently, the International Diabetes Federation proposed a simple clinically applicable definition of the metabolic syndrome (Table 1) that can be used worldwide.¹⁸ Also, a recent study proposed the use of age-specific criteria for the metabolic syndrome based on growth-curve models generated from NHANES III data for each component of the metabolic syndrome.¹⁷

Irrespective of the definition or the criteria used, the metabolic syndrome is more prevalent among obese youth than normal-weight youth.^{2, 3, 15} Obesity among children and adolescents increased significantly over the last decade. NHANES data from the 2003–2004 period indicate that 17.4% of children aged 12–19 years are overweight, compared to 14.8% in the 1999–2000 period. An additional 34.3% are at risk of becoming overweight, compared to 30.0% in 1999–2000.¹⁹ A disturbing trend of increasing abdominal obesity of 65.4% in boys and 69.4% in girls was reported during the same time period.²⁰ Abdominal obesity in childhood plays a major role in the clustering of the metabolic syndrome, because of the association of visceral adipose tissue with insulin resistance.^{21, 22} Moreover, childhood obesity seems to predict the

development of the metabolic syndrome in adulthood,^{23, 24} with the indicators of the metabolic syndrome tracking from childhood into young adulthood.^{25, 26} There is evidence to suggest that obesity contributes to the pathogenesis of PCOS by aggravating the intrinsic insulin resistance in predisposed individuals.²⁷ Thus the increasing rates of obesity in youths may be “pulling the trigger” for PCOS and the metabolic syndrome in parallel.

Epidemiology

The reported prevalence of the metabolic syndrome among U.S. adolescents 12–19 years old ranges from 2–9.4%,^{3, 6, 17} depending on the criteria used. This prevalence increases to 31.2%¹⁵ and 39%⁶ among obese children, and to 50% in one study of morbidly obese adolescents.¹⁴ The overall prevalence is slightly higher among boys (3–13.2%) as compared to girls (0.6–5.3%). Mexican Americans have the highest prevalence followed by non-Hispanic whites and non-Hispanic blacks.^{6, 15} The rates are highest in the West and Midwest and lowest in the Northeast.¹⁵ This overall prevalence was derived from NHANES III data, and is expected to have increased, given the persistent increase in obesity rates among adolescents.¹⁹ On the other hand, prevalence rates of the metabolic syndrome are much higher among adolescent girls with PCOS, ranging from 37–47% compared with 5–13% of the NHANES III girls depending on the criteria used.⁵

Metabolic Syndrome and Menstrual Health: What Is the Link?

Each component of the metabolic syndrome could develop secondary to a myriad of environmental and genetic causes. The common thread that would predispose an individual to have a clustering of these components beyond chance alone is the subject of active research. Insulin resistance/hyperinsulinemia is believed to be the key pathogenetic factor.¹² Obesity, in particular visceral adiposity, plays a major role. Features similar to those of the metabolic syndrome can be seen in other conditions, such as PCOS, in which insulin resistance is a key factor.^{4, 8, 28-31}

Insulin resistance is not a disease by itself, but is a physiological alteration that may occur in nonpatho-logic states such as puberty and pregnancy, and in pathologic states such as type 2 diabetes mellitus, obesity, hypertension, stress, and acute illness. Insulin, a potent anabolic hormone, has pleiotropic effects that result in enhanced energy production and utilization. It has both metabolic and mitogenic actions. Insulin's metabolic actions are primarily exerted on the liver, adipose tissue, and skeletal muscle. It promotes glycogen synthesis, decreases hepatic glucose production, promotes glucose uptake, and increases lipogenesis and protein synthesis.^{32, 33} Insulin resistance refers to the impairment in its metabolic effects, while its mitogenic effects may not be affected. Individuals who are insulin resistant are prone to a plethora of metabolic derangements, which are summarized in Table 2.

Insulin resistance is compensated for by an increase in insulin production by the beta cell. The consequent hyperinsulinemia may manifest in increased mitogenic effects of insulin, such as seen in acanthosis nigricans. Hyperinsulinemia can affect menstrual health via its impact on ovarian and adrenal sex hormone steroidogenesis, hepatic SHBG, IGFBP1 and IGFBP2 production, and gonadotropin feedback regulation,²⁷ which are discussed further in this chapter.

Insulin Resistance/Hyperinsulinemia and Hyperandrogenism

The concept of a link between insulin resistance/hyperinsulinism and hyperandrogenism is not a new one. In 1921, two French scientists, Achard and Thiers, described *la diabète des femmes à barbe* or “diabetes of bearded women.” In addition, several well-recognized disorders of insulin resistance and disordered carbohydrate metabolism have associated hyperandrogenism (Table

3), with manifestations that range from gonadal enlargement, as in leprechaunism, to menstrual disturbances, as in PCOS, and true virilization, as in type A insulin-resistance syndrome.

The strongest evidence supporting a link between hyperinsulinism and hyperandrogenemia comes from studies of PCOS patients. Correction of hyperinsulinemia, either through weight loss³⁴ or administration of diazoxide, metformin, or troglitazone,³⁵⁻³⁸ in women and adolescents with PCOS leads to attenuation of the hyperandrogenemia and improvement of ovulatory function. In women with PCOS, this link between insulin and hyperandrogenemia seems to hold true even in lean subjects. In a recent study, lean PCOS women experienced a significant decrease in free testosterone levels and an increase in SHBG levels after suppression of insulin secretion by diazoxide treatment. These effects were more pronounced than after suppression of LH with long-acting GnRH agonist.³⁹ *In vitro* studies also support this concept. Insulin stimulates androgen production by cultured ovarian cells to a greater extent in women with PCOS compared with control subjects.⁴⁰ Combined stimulation with LH and insulin, at physiologic concentrations, increases androgen biosynthesis by ovarian tissues from normal and PCOS women.⁴¹

In females, 50% of the plasma testosterone is generated in equal amounts by the ovarian thecal cells and adrenal cortical cells, whereas the other half originates from conversion of androstenedione in peripheral tissues including adipose tissues.⁴² Androgen synthesis in the ovaries and adrenal glands occurs under LH and ACTH stimulation, respectively. The cytochrome P450_{C17} is a key enzyme in both adrenal and ovarian androgen production. It consists of two elements: 17 alpha-hydroxylase and 17,20-desmolase. Insulin has been shown to stimulate P450_{C17} mRNA expression and activity in the ovaries and adrenals. Insulin's stimulation of 17 alpha-hydroxylase seems to be mediated by phosphatidyl inositol 3-kinase in human ovarian theca cells.^{40, 43, 44} Serine phosphorylation inhibits the insulin receptor activity and promotes the 17,20-desmolase activity. This is believed to be the link between insulin resistance and hyperandrogenemia in women with PCOS.⁴⁵ Moreover, insulin in high concentrations suppresses hepatic sex hormone-binding globulin (SHBG) gene expression. This results in an increased proportion of bioavailable testosterone.²⁷ Likewise, insulin in high concentration suppresses hepatic production of insulin-like growth factor binding proteins 1 and 2 (IGFBP1 and IGFBP2). This leads to increased concentration of free insulin-like growth factor-1 (IGF-1). Both insulin and IGF-1 act synergistically with LH and ACTH to further stimulate androgen production. The end result is an increase in circulating bioavailable androgens, and decrease in SHBG accompanied by functional adrenal hyperandrogenism.⁴³ The increased circulating concentration of bioavailable androgens results in impaired regulation of GnRH secretion. Both premenarcheal and postmenarcheal girls with hyperandrogenism have elevated LH levels and a rapid frequency of GnRH pulse generator that persists through 24 hours.⁴⁶ Hyperinsulinemia *per se* or insulin resistance does not seem to be the cause in impaired GnRH/LH pulse secretion. Prolonged insulin infusion and reduction of insulin resistance by pioglitazone treatment did not result in a change in LH pulsatile secretion.⁴⁷

In prepubertal girls, increased levels of circulating androgens may manifest as premature adrenarche or pubarche. In pubertal adolescents it may manifest as acne, hirsutism, and irregular menses (Fig. 2). Within this group of adolescent girls, especially obese ones with irregular menses, hirsutism, and acne, with or without acanthosis nigricans, vigilance should be maintained to identify features of the metabolic syndrome. Literature from adult women with menstrual disturbances in the spectrum of PCOS supports this concept, and has led Dunaif to propose calling PCOS "Syndrome XX."⁴⁹ In the following paragraphs, we will review the research studies that investigated features of the metabolic syndrome among adolescents with menstrual pathology.

Common Metabolic Features between PCOS and the Metabolic Syndrome

Insulin Resistance

Insulin resistance is a well-recognized feature among adult women with PCOS. It is especially prevalent among obese ones, but can also be seen in lean PCOS women.²⁸⁻³¹ Studies in adolescent girls with PCOS reveal that insulin resistance is present early in the course of the syndrome.^{5, 8, 9} Obese adolescent girls with PCOS compared with equally obese non-hyperandrogenic girls matched for age, body composition, and Tanner stage, had 50% lower *in vivo* peripheral insulin sensitivity, measured by the hyperinsulinemic euglycemic clamp, with evidence of hepatic insulin resistance. This decrease in insulin sensitivity was compensated by increased insulin production. The PCOS group had a two-fold higher fasting insulin level and a 70% higher first-phase and a 44% higher second-phase insulin secretion during hyperglycemic clamp⁸ (Fig. 3). Hepatic insulin resistance was documented in obese hyperandrogenic adolescents in another study, but there was no assessment of peripheral insulin sensitivity.⁵⁰ Studies using surrogate indices of insulin resistance also point towards a higher prevalence of insulin resistance among PCOS adolescents compared with age- and body mass index-matched adolescent girls without PCOS.^{5, 9}

Impaired Glucose Tolerance

In the presence of severe insulin resistance, abnormalities in glucose metabolism are high among adolescents with PCOS. Impaired glucose tolerance was detected in ~30% of adolescent girls with PCOS, including lean subjects.⁹ Obese PCOS girls with impaired glucose tolerance had deficient first-phase insulin secretion compared with matched obese PCOS girls with normal glucose tolerance. They also had 50% lower glucose disposition index, which is an index of insulin secretion relative to insulin resistance, and indicates beta cell dysfunction.⁵¹ This is consistent with data from adult women with PCOS who were shown to have profound insulin resistance with beta cell dysfunction and increased risk of impaired glucose tolerance and type 2 diabetes mellitus.^{28-30, 45}

Type 2 Diabetes Mellitus

One of the well-recognized features of type 2 diabetes mellitus in children is its presence in increased proportions among females, especially those with obesity, hyperandrogenism, irregular menses and acanthosis nigricans.⁵² Impaired insulin sensitivity and secretion, beta cell dysfunction, and impaired glucose tolerance are precursors to type 2 diabetes mellitus. The high prevalence of these risk factors among adolescent girls with PCOS^{5, 8, 9, 51} puts them at increased risk of developing type 2 diabetes mellitus. Indeed screening of PCOS adolescents with oral glucose tolerance testing (OGTT) revealed a prevalence rate of ~3.7% of type 2 diabetes by 2-hour glucose value.⁹ This high prevalence of prediabetes and type 2 diabetes mellitus in adolescents with PCOS is consistent with data in adult women showing overall abnormalities in glucose metabolism of ~30–40% and type 2 in ~4.5%.^{28, 29}

Obesity

Obesity is highly prevalent among women and adolescent girls with PCOS, with a predilection towards abdominal obesity and increased visceral fat. In one study of 49 white non-Hispanic girls with PCOS aged 14–19 years, 55% were obese, with BMI above the 95th percentile, and 38% were severely obese, with a BMI above the 97th percentile.⁵ In another study of 27 girls with multiethnic background, the mean BMI was $38.8 \text{ kg/m}^2 \pm 8.8 \text{ SD}$, and the mean waist-to-hip ratio was 0.86.⁹ Glueck *et al.* reported a 73% prevalence of overweight (BMI > 95th percentile) girls among a referral population of PCOS adolescents.⁵³ In the three studies, there was a predisposition towards central obesity as measured by waist circumference or waist-to-hip ratio. Larger waist circumference among PCOS adolescents persisted after matching for

BMI.⁵³ Such data are in agreement with studies of adult PCOS women, in whom the reported prevalence of obesity ranges between 42% in a nonselected Southeastern population⁵⁴ to 70% in a referral population.²⁹ Those rates are significantly higher compared to the 16.4% prevalence of obesity among adolescents in the general U.S. population, and the 33.2% prevalence of obesity in women in the general U.S. population.¹⁹

Hypertension

Adolescent girls with PCOS compared with age-matched controls from the NHANES III had higher prevalence of hypertension ($27 \pm 6\%$ vs. $1 \pm 1\%$; $P < 0.0001$).⁵ The nocturnal dip in $\pm$ systolic BP $\pm$ that is normally seen in adolescents was not present in obese PCOS girls with impaired glucose tolerance (IGT), compared to age-matched obese PCOS girls with normal glucose tolerance.⁵¹ Larger studies are needed in adolescents with PCOS to determine whether the higher prevalence of hypertension is reproducible, and to assess whether it is independent of the higher rates of obesity among this group. Studies from adult women with PCOS are conflicting, with some reporting higher prevalence of hypertension and some reporting no difference.⁵⁵ Women with PCOS were also reported to have reduced vascular compliance,⁵⁶ and to have vascular endothelial dysfunction.⁵⁷ A clear clustering of risk factors for cardiovascular disease is seen among women with PCOS. Whether this clustering leads to increased cardiovascular events/death remains controversial, and requires more research.^{55, 58}

Several potential mechanisms are proposed for the hypertension among females with menstrual disturbances in the spectrum of PCOS. Obesity and insulin resistance, both highly prevalent in this population, are associated with hypertension, and endothelial dysfunction. In addition, androgens may independently play a role in blood pressure regulation. Differences in blood pressure between genders are well established.⁵⁹ Males have higher blood pressure than age-adjusted premenopausal females, beginning as early as puberty and persisting until around 59 years of age.⁶⁰ Serum androgen concentration was reported to be an important predictor of blood pressure in young healthy women without PCOS.⁶¹ In women with PCOS, hyperandrogenism is correlated with systolic and diastolic blood pressure at a young age, independent of insulin resistance, obesity, dyslipidemia, and age.⁶² Androgen stimulation of the renin-angiotensin system and endothelin production have been proposed as potential mechanisms for the associated increase in blood pressure.⁶³

Dyslipidemia

While disturbances in lipid metabolism have been extensively studied in women with PCOS, studies in young adolescents are relatively limited. Adolescent girls with PCOS were reported to have higher triglycerides (TGs), higher LDL and lower HDL levels compared with controls. This difference did not persist, however, after adjusting for BMI and age.⁵³ In another study, no significant differences were found in the prevalence of elevated LDL-C or non HDL-C between girls with PCOS and NHANES III girls.⁵

In women with the polycystic ovary syndrome, a characteristic profile of high triglycerides and low HDL was reported in most studies. Insulin resistance and hyperinsulinemia were associated with this lipid profile.^{55, 64, 65} In one study of white non-Hispanic women with PCOS, elevated LDL-C levels were the predominant lipid abnormality independent of obesity.⁶⁶ Most reported lipid values were not extremely elevated. Androgens have been suggested to affect lipid and lipoprotein levels in women with PCOS.⁶⁷ Low SHBG has also been shown to have an independent predictive value for CVD risk profile.^{68, 69}

Metabolic Syndrome in Adolescents with PCOS

Studies in adult women with PCOS suggest that the prevalence of the metabolic syndrome is twice that in the general population, and it starts at an early age, irrespective of race and ethnicity.^{4, 31, 70} This higher prevalence persisted even after adjusting for obesity among the affected women.³¹ Limited studies have assessed the prevalence of the metabolic syndrome among adolescents with PCOS. Coviello *et al.* reported a prevalence of 37% in a group of white non-Hispanic adolescent girls with PCOS using Cook's criteria, and 47% using the de Ferranti criteria.⁵ The prevalence of the metabolic syndrome among adolescent girls of similar age and ethnic background from NHANES III is 5% and 13% using Cook's criteria and the de Ferranti criteria, respectively. Of interest, in the same study, those girls with bioavailable testosterone in the highest two quartiles were approximately 14 times more likely to have the metabolic syndrome than girls with free testosterone in the lowest 2 quartiles after adjusting for insulin resistance and obesity. SHBG was lower in the girls with the metabolic syndrome compared with those without.⁵ The prevalence of the metabolic syndrome among PCOS adolescents was three-fold greater than expected for obesity status in another study.⁷¹

Conclusion and Future Directions

Oligomenorrhea or amenorrhea could be proposed as potential components of the metabolic syndrome in women. The increasing rates of obesity, particularly abdominal obesity, with the consequent insulin resistance/hyperinsulinemia may trigger and permit the clinical expression of PCOS in genetically predisposed individuals through enhanced hyperinsulinemia-mediated metabolic pathways conducive to hyperandrogenemia. Within this schema, insulin resistance is the linchpin between PCOS and the metabolic syndrome. Careful vigilance should be maintained in the evaluation of the obese adolescent girl. A detailed history should be obtained about the age of menarche, history of premature adrenarche, as a harbinger for PCOS, and the number and frequency of the menstrual cycles with thorough evaluation for signs of hyperandrogenism. This should be interpreted within the context of the family history not only with respect to the presence or absence of PCOS, but also with respect to the existence of the metabolic syndrome among family members.⁷¹ Physical examination should include a careful evaluation of blood pressure, waist circumference (as another "vital sign"), and skin changes, including the presence of skin tags and acanthosis nigricans. Laboratory evaluation should include, besides a free testosterone panel, an assessment of the metabolic syndrome components including fasting lipid profile and glucose, with or without an OGTT. Until more research data are available, one has to rely on clinical acumen regarding whether or not to evaluate for depression, sleep-disordered breathing, and uric acid level among other clinical possibilities. Lastly, more insight into the pathophysiology of the metabolic syndrome, its relation to menstrual health, and long-term implications can only be gained from studies that carefully phenotype the physical, hormonal, and the metabolic profile of obese adolescent girls with versus without menstrual disturbances and in comparison to healthy normal-weight adolescent girls. Prospective longitudinal studies that track female development from premenarche to menarche and into adulthood may shed light on the natural history of the linkage between PCOS and the metabolic syndrome. Much remains to be learned about PCOS in youth and the metabolic syndrome within the panorama of the obesity epidemic.

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FIGURE 1.
Common features of PCOS and the metabolic syndrome.

FIGURE 2.

The role of insulin resistance/hyperinsulinemia in hyperandrogenism. (Adapted with permission from Artz *et al.*⁴⁸)

FIGURE 3.

Insulin sensitivity (*upper panel*) and insulin secretion (*lower panel*) in PCOS versus control obese adolescent girls. (Adapted with permission from Lewy *et al.*⁸)

TABLE 1
IDF criteria for metabolic syndrome in children and adolescents¹⁸

For age 6 to <10 years
Obesity $\geq$ 90th percentile (waist circumference). Metabolic syndrome can not be diagnosed, but further measurements should be made if there is family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension, or obesity.
Age 10 to <16 years
Obesity $\geq$ 90th percentile (waist circumference)
TG $\geq$ 1.7 mmol/L (150 mg/dL)
HDL $<$ 1.03 mmol/L (40 mg/dL)
BP $\geq$ 130 mmHg systolic or $\geq$ 85 mmHg diastolic
Glucose $\geq$ 5.6 mmol/L (OGTT recommended), or known T2DM
Age $\geq$ 16 years
Use existing IDF criteria.

TABLE 2
Abnormalities associated with insulin resistance^{a33}

Glucose metabolism
Impaired fasting glucose.
Impaired glucose tolerance
Lipid metabolism
Increased triglycerides
Decreased HDL
Increased postprandial accumulation of triglyceride-rich lipoproteins
Decreased LDL particle diameter
Hemodynamic changes
Increased sympathetic nervous system activity
Increased renal sodium retention
Uric acid metabolism
Increased plasma uric acid concentration
Decreased renal uric acid clearance
Procoagulant factors
Increased plasminogen activator inhibitor-1
Increased fibrinogen
Markers of inflammation
Increased C-reactive protein, White cell count, IL-6
Endothelial dysfunction
Increased mononuclear cell adhesion
Increased plasma concentration of cellular adhesion molecules
Increased plasma concentration of asymmetric dimethylarginine
Decreased endothelial dependent vasodilation
Sleep-disordered breathing
Increased testosterone

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TABLE 3
Syndromes of hyperandrogenism and hyperinsulinemia

Leprechaunism
Rabson–Mendenhall syndrome
Lipoatrophy
Type A syndrome
Type B syndrome
PCOS