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Genetic Polymorphisms in Polycystic Ovarian Syndrome

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ABSTRACT

Polycystic ovarian syndrome can be defined as an endocrine disorder that most affects the reproductive system of women of childbearing age; its causes are not exactly known. However, the majority of the experts agree that it is a multifactorial entity with multiple factors. Genetics is becoming increasingly important. In recent years, several genes that are involved in the pathogenic processes of this syndrome have been identified. Within these, the most important ones are the ones that encode steroidogenesis enzymes and insulin receptors, as well as other hormones that are associated with the actions of insulin and gonadotropins and their receptors. The results obtained included 1) women with PCOS had significantly lower levels of adiponectin compared to controls. Adiponectin levels were significantly lower in both lean and obese women with PCOS compared to the control group. 2) PCOS women had significantly higher levels of LH, FSH, LH/FSH ratio, and total testosterone compared to controls. 3) Both lean and obese PCOS women had significantly higher levels of LH, LH/FSH ratio, and total testosterone compared to the control group, however, FSH levels were significantly increased only in obese PCOS women compared to controls. 4) PCOS women had significantly higher levels of total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol, and lower levels of HDL-cholesterol compared to controls. 5) Both lean and obese PCOS women had significantly higher levels of total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol compared to controls. Only obese PCOS women had significantly lower levels of HDL-cholesterol compared to the controls. 6) The genotype analysis of FSHR gene polymorphism showed that the heterozygote Ala/Thr genotype was significantly more frequent in PCOS patients than in controls (64.1% versus 40%).

1. Introduction

In 1935, Stein and Leventhal called polycystic ovarian syndrome (PCOS) a clinical picture characterized by the presence of ovaries with small cysts, amenorrhea, hirsutism, and obesity, which, in honour of these authors, was called Stein-Leventhal syndrome which is now also known as functional ovarian hyperandrogenism. Since then, much research has been done on the subject, mainly with regard to its pathogenic mechanisms and diagnostic criteria (Erel et al., 2002), but it was not until 1990 that the National Institute of Health proposed a way of stating PCOS, which was ratified in 1995 in the Serono Symposium on PCOS. It was agreed to define it as a syndrome that can be identified by hyperandrogenism and chronic anovulation in women with no specific cause of adrenal or pituitary dysfunction (non-classical congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, and androgen-secreting tumors).

This syndrome represents an endocrine disorder that most affects the reproductive system during a woman's fertile period. Its origins are not exactly known; however, the majority of the experts agree that it is an entity of multifactorial origin in which genetic factors intervene and environmental factors are only partially known. Intensive research is therefore required to determine what causal elements are contributing to the appearance of this clinical picture (Jakubowki, 2005). The existence of stigmata of the syndrome in first-degree relatives of patients who have PCOS has made it possible to suspect a hereditary factor

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through mutation or overexpression of one or more genes. The first genetic study in PCOS was carried out in 1968 (Cooper et al., 1968) it included 18 patients who had Stein-Leventhal syndrome and observed a higher frequency of oligo menorrhea, hirsutism, and ovarian enlargement in the sisters of affected cases compared to the sisters of controls. Three years later, Givens and others published a first report, which described two families' women of several generations with hirsutism and enlarged ovaries.

Within the male offspring, 89% of the sons presented an LH/FSH index greater than 2. The study conducted by Ferriman and Purdie (1979) observed 381 patients with hirsutism and/or oligomenorrhea, as well as a control group that included 179 women, and found a high frequency of hirsutism and increased ovarian volume in first-degree relatives of patients, compared with the relatives of first-degree of the control group, which had normal size ovaries. The study studied 29 affected women and ten controls, using the presence of the polycystic ovaries on the ultra-sound with or without clinical manifestations or biochemical aspects of PCOS as diagnostic criteria, and it was found that 61% of first-degree relatives of affected women and 22% of first-degree male relatives had baldness prior to the age of 30.

It has been found that of 52 sisters of women with PCOS studied, 45 (87%) had ultrasound imaging of polycystic ovaries and/or elevated androgen levels, as did 67% of the mothers (Xita et al., 2003). Nonetheless, a more recent study carried out on 29 women who had PCOS and ten controls raised the possibility of an autosomal dominant inheritance pattern in this entity. All these data have to be analyzed carefully, taking under consideration the diversity of criteria used in the diagnosis, the number of cases studied, and the populations under study.

The study conducted by Stankiewicz and Norman, (2006) reported that women who have PCOS, 11 had sisters with ultrasound suggestive of polycystic disease, 13 of the sisters showed elevated testosterone levels, and 10 had hyperinsulinism. In the US, they studied 80 females with PCOS and found that 36 of the 80 sisters (45%) had signs of hyperandrogenism. A more recent study carried out on sisters of women who have PCOS exhibited evidence of insulin resistance, which is frequent in PCOS. On the other hand, some authors report higher numbers (93%) of patients with PCOS who have first-degree relatives with oligo menorrhea, hirsutism, or elevated testosterone levels (Diamanti-Kandarakis et al., 2004).

In light of this evidence, and despite the lack of uniformity in the criteria used in the investigations and variability in the studied populations, they made the scientific community think about the existence of an important genetic basis in the pathogenesis of this entity. With the development of molecular biology, has been able to identify a series of candidate genes involved in the different processes that give rise to the manifestations that characterize the syndrome (Kahsar-Miller et al., 2001).

In this study, adiponectin levels were measured in serum samples of PCOS and control groups. Women with PCOS had significantly lower levels of adiponectin compared to controls. Lower levels of adiponectin remained consistent and statistically significant after adjustment for BMI ($P < 0.001$). These results were consistent with other studies which have shown an association of low adiponectin levels in PCOS women irrespective of BMI (Desai, Roy & Mahale, 2013; Chen et al. 2004).

On the other hand, these results were in contrast with the results of the study, they found that adiponectin levels were lower in PCOS women. However, after adjusting for fat mass, these differences were no longer significant. In addition, other studies have not found an association between adiponectin and PCOS (Goodarzi et al, 2011).

2. Materials and Methods

2.1. PCOS Definition and Diagnostic Criteria

The National Institutes of Health (NIH) in 1990 had defined PCOS and covered each ovulatory dysfunction and hyperandrogenism. According to NIH, PCOS represents a syndrome concerning the defects in the primary mechanisms of mobile control, which lead to expressing hyperandrogenism and chronic anovulation (Azziz, et al., 2004). In 2003, the European Society for Human Reproduction and Embryology (ESHRE), Rotterdam conference, and American Society for the Reproductive Medicine (ASRM) had generalized PCOS definition by utilizing along with the PCO morphology and requirements for a minimum of 3 diagnostic capabilities (Diamanti-Kandarakis, et al., 2004).

In 2006, the Androgen Excess and PCOS Society (AEPS) suggested innovative criteria for diagnostics, which has resulted in making the hyperandrogenism basic as well as excluding phenotype of nonhyperandrogenic females with ovulatory dysfunction that has been blanketed by means of Rotterdam criteria (Azziz, 2006). In some of these three definitions, hyperandrogenism is defined as scientific and/or biochemical hyperandrogenism. In addition, these types of three definitions require exclusion of other disorder types which would mimic PCOS, which include hyperprolactinemia, androgen-secreting tumors, non-classical congenital adrenal hyperplasia, and Cushing's syndrome (Livadas & Diamanti-Kandarakis, 2013).

With the use of potential combos of those standards, four different PCOS phenotypes at the moment are recognized:

- Type A: hyperandrogenism, persistent anovulation, and polycystic ovaries
- Type B: chronic anovulation and hyperandrogenism
- Type C: polycystic ovaries and hyperandrogenism
- Type D: persistent anovulation and polycystic ovaries

2.2. Prevalence of PCOS

In most research, the superiority of PCOS in ladies of reproductive ages is envisioned to be 5-10%. However, the stated prevalence prices are evidently depending on the exact definition used and on the ethnicity of the population under study (Azziz et al. 2006) Based on the National Institute of Health Standards, 6-8% of women within the trendy population have PCOS (Azziz, et al., 2004). A recent Australian observe, along with often Caucasians, located that superiority of PCOS underneath Rotterdam and AES criteria turned into two times that produced by using the NIH requirements because of the inclusion of PCOS morphology (Azziz, et al., 2006).

Depending on the standards used, the superiority of traditional clinical manifestations of PCOS varies with about 66-seventy-five% with impaired menstruation, 60-sixty-nine% with hirsutism/acne, forty-eight-eighty% with improved androgen degrees, and within the patients, they have got identified. AES standards ~ seventy-five% have a PCO morphology (Azziz, et al., 2006). Recently, a potential evaluation was finished on a group of three, 900 Egyptian sufferers searching for fertility recommendations at a specialized fertility health facility. The prevalence of confirmed PCOS instances amongst this institution was predicted to be 10.48% (Baba et al, 2009).

2.3. Pathogenesis of PCOS

PCOS is an endocrine disorder, and its ailment physiology remains unclear. Genetic and environmental elements integrate with obesity, ovarian disorder, and hormonal drivers to make a contribution to the etiology of PCOS. Primary hormonal imbalance may involve an aggregate of androgenic hyperinsulinemia and/or hyperinsulinemia secondary to insulin resistance (IR) (Carey et al. 1994).

2.4. Hypothalamic-pituitary Abnormalities

In PCOS, ordinary pulsating luteinizing hormone (LH) secretion is elevated by increasing the amplitude and frequency of the impulses, whilst FSH secretion stays unchanged or suppressed. Consequently, the values of LH could upward thrust, and LH: FSH ratio may additionally boom to over 2.50, even in ovulatory cycles. Nonetheless, those values could be regular in up to 10% to 20% of the females who have PCOS (Desai et al, 2013, Chen et al., 2004).

The enhanced GnRH impulse launch reasons a boom inside the frequency of the LH pulse in PCOS because of the decreased negative reactions of the steroid hormone to the secretion of LH because of the multiplied androgenic (Goodarzi et al, 2011).

Additional potential reasons may additionally include the overproduction of the LH into estrogen, resulting in permanent overproduction of estrogen, leading to improved secretion of LH. In addition, an insulin-mediated boom in the amplitude of the LH pulse within the blood may also result in immoderate LH secretion (Allahbadia & Merchant, 2011).

High endogenous LH stages may have harmful results on egg maturation, fertilization, pregnancy, and miscarriage rates. A boom in the GnRH pulse frequency leads to a lower in FSH manufacturing.

2.5. Obesity and Adipose Tissue Dysfunction

In sufferers with PCOS, the occurrence of weight problems tiers someplace among 50- 75%, that's better than in the widespread populace (Azziz et al., 2004) Obesity isn't the simplest extra, not unusual among girls with PCOS; obesity may exacerbate many PCOS manifestations, together with insulin resistance and androgen degrees. With excessive weight advantage, previously asymptomatic women may additionally begin to expose signs and symptoms of PCOS (Carreau & Baillargeon, 2015). Women who have PCOS are usually overweight, or they have extra belly weight than regular women. Even in lean girls who matched BMI, women had a higher prevalence of body fats and greater accumulation of intra-abdominal, peritoneal, and visceral fats as compared to matched controls.

Compared to non-overweight girls with PCOS, obese girls with PCOS experience abnormal menstruation and non-functional uterine bleeding, in addition to an elevated occurrence of infertility, which has additionally been related to the distribution of belly fats. Obese girls with PCOS actually have a greater danger of getting diabetes or glucose intolerance compared to the lean girls with PCOS (Baptiste et al. 2010).

The present-day view of adipose tissue is an energetic secretory organ, sending signals that modulate urge for food, insulin sensitivity, energy expenditure, infection, and immunity, and these moves are completed by using adipocytes (de Luis. et al, 2012).

Specifically, the disorder of paracrine regulation of adipokine (e.g., adiponectin) by way of cytokines secreted from macrophages in PCOS helps the development of insulin resistance (Chazenbalk et al., 2010). Improving know-how of underlying mechanisms which govern the adipose imbalance and insulin resistance in the PCOS might also sooner or later define new treatment objectives for PCOS and different related problems (Goodarzi et al, 2011). Therefore, due to the fact weight problems is an important environmental aspect exacerbating medical symptoms and metabolic dangers of the syndrome. It's miles vital in PCOS control, to begin with, a way of life adjustments and focus on weight reduction in all obese and overweight women with PCOS (Baptiste et al. 2010), and the poor outcomes of obesity in ladies in PCOS.

3. Results and Discussion

As a result of the complexity of PCOS, the lack of knowledge that still exists about its etiology and the great frequency of its presentation. PCOS is a multi-factorial disease, where various environmental and genetic factors participate, abnormalities in ovarian steroidogenesis and follicular development have been associated in its appearance, as well as gonadotropin-releasing hormone impulses, to an excess of luteinizing hormone and insufficient secretion of FSH that helps ovarian androgen excess production and ovulatory dysfunctions, this androgen overproduction is also favored by hyperinsulinemia due to insulin resistance. Table 1. shows the diagnostic criteria for PCOS.

Table 1
Diagnostic criteria for the Polycystic Ovarian Syndrome (PCOS)

	1990 NIH critera	Revised rotterdam 2003	Androgen Excess PCOS critera
Hyperandrogenism	A. Clinical and biochemical signs of hyperandrogenism.	A. Clinical and biochemical signs of hyperandrogenism.	A. Clinical and biochemical signs of hyperandrogenism.
Ovulation	B. Chronic anovulation	B. Oligomenorrhea anovulation	B. Oligomenorrhea anovulation
Ovarian Morphology		C. Polycystic ovarian morphology	C. Polycystic ovarian morphology
Is exclusion of other endocrinopathies needed for diagnosis?	Yes	Yes	Yes
Number of critera needed	Both A and B with endocrinopathies	2 of 3 critera A-B-C with endocrinopathies	Critera A plus either B or C with endocrinophaties.

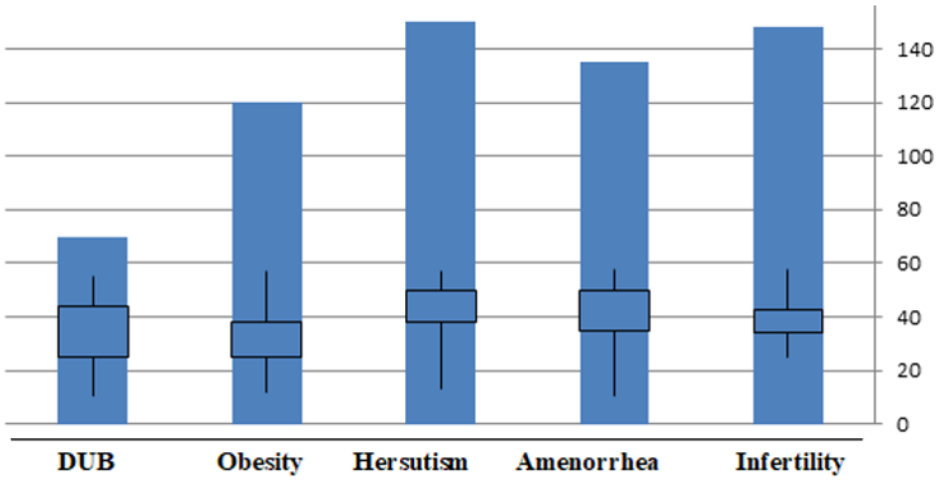

Fig. 5. The clinical symptoms for PCOS

4. Conclusion

The molecular genetics of PCOS, in addition to its clinical aspects, show that it is a complex disease. PCOS constitutes one of the main endocrine disorders present in reproductive age women, with prevalence that ranges between 8.7 and 17.8%. The phenotype of this disease is very diverse; however, all women who have PCOS present ovaries with polycystic morphology, hyperandrogenism, anovulation, and gonadotropic abnormalities, becoming the most common cause of anovulatory infertility. In PCOS, it is common to find metabolic and hormonal abnormalities related to obesity, type II diabetes mellitus, and dyslipidemia, leading to the appearance of metabolic syndrome, generating a greater risk of developing the cardio-vascular disease.

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Competing Interests

The authors have declared that no competing interests exist.

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