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Korhonen, Seija. Searching for the Phenotype of Female Metabolic Syndrome in Relation to Polycystic Ovary Syndrome and for the Genetic Background of Polycystic Ovary Syndrome.

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ABSTRACT

Metabolic syndrome (MBS), i.e. the clustering of many type 2 diabetes and cardiovascular risk factors, is today in the scientific limelight because of the global epidemic of obesity and its accompanying burdens. However, little is known about the gynecological and endocrinological profile of women with MBS and of the role of polycystic ovary syndrome (PCOS) in MBS. PCOS is a heterogeneous clinical entity, characterized by signs and symptoms of hyperandrogenism and anovulatory disorders often associated with infertility, obesity and insulin resistance. The underlying pathogenesis has remained unknown.

The a priori hypothesis was that PCOS would be concentrated in women with MBS because of the overlapping of several long-term health disease risk factors. The first aim was to clarify this connection at the population level. The second goal of this study was to evaluate the genetic heterogeneity of PCOS with genetic association studies, namely the peroxisome proliferator-activated receptor-γ (PPARγ) in which polymorphism is associated with type 2 diabetes; microsomal epoxide hydrolase (EPHX) which has a role in female reproduction abnormalities; apolipoprotein E (apoE) as a genetic marker for dyslipidemia and atherosclerosis and tumor necrosis factor-α (TNF-α) which has a role in insulin resistance and obesity.

Altogether 543 Caucasian women living in a defined area and aged 34 to 54 years were screened in two different ways. At the beginning of the study MBS was defined by a self-constructed model from family history of type 2 diabetes, BMI, WHR, hypertension, hypertriglyceridemia, low HDL-cholesterol, abnormal glucose metabolism, and hyperinsulinemia. Three criteria were necessary for MBS diagnosis. Later MBS was defined according to the criteria proposed by the National Cholesterol Education Program (NCEP). The control group consisted of 62 overweight women without central obesity or MBS and 53 healthy lean women. In the candidate gene association studies, the study population consisted of 58-112 PCOS women and 91 healthy controls.

The prevalence of MBS appeared to be 19 %, increasing with age. PCOS defined as anovulatory periods, signs of hyperandrogenism and typical ovaries in ultrasound were found at a similar frequency (13 %-15 %) in women with MBS, simplex obesity and the lean controls. There were no differences between the groups regarding parity, infertility problems or obstetric outcome. However, with aging, oligomenorrhea appeared to be more common in the MBS women. The clinical features of hyperandrogenism and also the cutaneous markers of insulin resistance, such as androgenic alopecia and acanthosis nigrigans were detected only in the MBS group. A markedly

lower insulin sensitivity index, lower SHBG level and higher free androgen index (FAI) were detected in MBS women. Abdominal obesity and increased diastolic blood pressure were significantly associated with high FAI.

Our genetic studies support a role for PPARγ gene polymorphism in the pathogenesis of PCOS, with the presence of the Ala isoform being protective against the development of PCOS. This confirms findings that the action and signaling of insulin are important factors in the pathogenesis of PCOS. In addition, our study provides evidence to support the heterogeneity of the pathogenesis of PCOS, since the use of two intragenic single nucleotide polymorphisms in the gene encoding EPHX jointly in haplotype association analysis demonstrated that genetically determined low-activity haplotype C-G (His113-Arg139) was significantly associated with PCOS. This multipoint association may be of biological significance, since these genetic variations reduce enzyme activity, which in turn may have an impact on the reproductive system and contribute to miscarriage. On the other hand, it appeared that apoE does not play a major role in the development of dyslipidemia in the group with PCOS. In addition, polymorphism of the TNF-α gene (C850T) is unlikely to contribute to PCOS risk.

Finally, surprisingly few MBS women presented with symptoms classically associated with PCOS, which were as often detected among women without MBS. Although MBS and PCOS are clearly closely interwoven pathophysiologically, and their genetic background shares similarities with regard to insulin action and signaling, PCOS only accounts for a subgroup of a much wider problem, the metabolic syndrome.

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