Polycystic Ovary Syndrome

Subjects: Pathology

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The application of metabolomics in searching for the mechanisms of the polycystic ovary syndrome (PCOS) pathophysiology gives a promising insight into the research on PCOS. There is a need to investigate the metabolic pathways, which could be involved in the pathophysiology of PCOS and to find the metabolic markers of this disorder. Metabolomics is a valuable and rapidly expanding tool, enabling the discovery of novel metabolites, which may be the potential biomarkers of metabolic and endocrine disorders.

Keywords: metabolomics ; polycystic ovary syndrome (PCOS) ; metabolites ; biomarkers ; mass spectrometry

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy, which affects more than 10% of women of reproductive age [1]. It is the main cause of female infertility due to oligo- or anovulation. Despite such a high incidence, the pathogenesis of PCOS is still unexplained. Some studies suggest that it is due to the genetic factors associated with ovarian steroidogenesis [2]. According to the Androgen Excess and PCOS Society (AE&PCOS), the diagnosis of PCOS should be based on the presence of clinical and/or biochemical hyperandrogenism (HA) and the ovarian dysfunction defined as menstrual abnormalities (anovulatory oligomenorrhea (AnO)) or/and the presence of the polycystic ovary morphology (PCOM) in the transvaginal ultrasound (TV-US) [3]. These criteria yield three separate PCOS phenotypes: A, B, and C. Phenotype A includes all the three features (HA, AnO, and PCOM) whereas phenotype B and C only two (HA and AnO or HA and PCOM, respectively). However, regarding Rotterdam criteria, the fourth phenotype (D) was separated to comprise AnO and PCOM presence. The clinical symptoms of hyperandrogenism include hirsutism (present in 60% of women), androgenic alopecia, and acne, which negatively affect women's psyche, their femininity and lead to low self-esteem and depression [4]. In addition to the reproductive and endocrine dysfunction, PCOS is characterized by intrinsic insulin resistance (IR), which lead to the development of the metabolic syndrome (MetS) and its consequences such as disturbed carbohydrate metabolism and type 2 diabetes mellitus (T2DM). Most common clinical manifestation in PCOS is abdominal obesity, which is involved in the development of dyslipidemia, arterial hypertension (AH), as well as non-alcoholic fatty liver disease (NAFLD) [5][6][7][8]. These in turn lead to the development of cardiovascular disease (CVD), which still remains the main cause of death among women [9]. The clinical picture of this complex endocrinopathy was presented in Figure 1. Therefore, the treatment of PCOS focuses not only on the symptoms of hyperandrogenism and infertility, but also on improving IR and its metabolic consequences [10]. Thus, there is a need for a better understanding of the pathomechanisms of this complex disorder through the identification of potential biomarkers with the use of new, non-invasive and specific methods. In recent years, one of the developing scientific approaches is metabolomics [11].

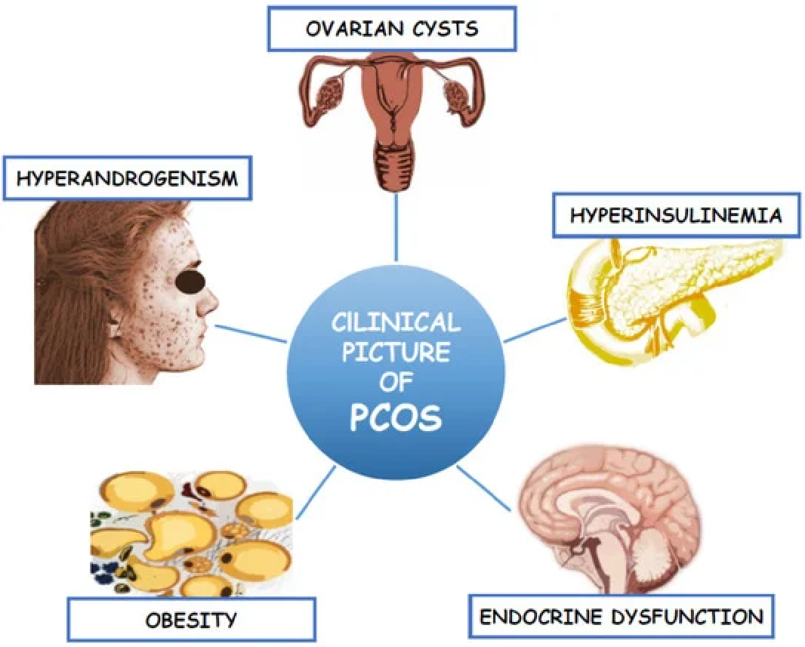

Figure 1. Clinical picture of Polycystic Ovary Syndrome.

2. Metabolomic Approach in Studying the Pathogenesis of Polycystic Ovary Syndrome

Among "omics" techniques, metabolomics plays an important role in studying the potential mechanisms responsible for the development of PCOS. Metabolomics allows to identify and quantify small molecules, which occur in all living organisms [12]. The set of all human metabolites that have been identified so far is stored in the Human Metabolome Database (HMDB). Each year, the number of identified metabolites grows. Few years ago, about 41,000 metabolites were found, but now this database contains over 114,190 compounds. Among them, the following groups can be found: amino acids, lipids, peptides, vitamins, organic acids and both endo- and exogenous carbohydrates. Therefore, metabolomics serves as a valuable source of information. The metabolome indicates not only a genetically determined phenotype, but also points to the differences determined by other factors, such as age, diet, or physical activity. The application of metabolomics enables monitoring of the state of an organism and provides information on the compounds formed as a result of many biochemical processes. Any disturbances occurring in a living organism cause changes to the qualitative and quantitative profile of the metabolites. The metabolome describes both the physiological and pathological state of the organism. For this reason, it is known to be an attractive approach, compared to genomics and proteomics, which only suggest the presence of metabolic derangements that occur in the organism [13][14][15][16]. Due to this fact, the use of metabolomics in studying the pathophysiology of PCOS allows to monitor even the smallest biochemical changes in this endocrinopathy and therefore, may help in its diagnosis [17].

Among the many analytical techniques, chromatography coupled with mass spectrometry (MS) seems to be the "gold technique". While chromatography allows for the separation of metabolites present in complex, biological samples, mass spectrometry provides specific information about the chemical structure of the compounds, such as characteristic fragmentation ions, accurate mass, and isotope distribution pattern utilized for the identification of metabolites. MS characterizes very high selectivity and sensitivity that allows to detect and measure trace amounts of metabolites [18]. The combination of MS with gas chromatography (GC-MS) and liquid chromatography (LC-MS) enables to analyse complex biological samples broadly used in metabolomics. GC-MS is suitable for volatile and non-volatile compounds, which require a derivatization step, but first of all thermally stable analytes. The LC-MS technique is widely used for targeted and non-targeted metabolomic analysis and allows to qualify and identify more polar compounds [19]. Nuclear magnetic resonance (NMR), despite its lower sensitivity than MS, allows to analyse metabolites that are difficult to ionize or require derivative reaction for MS and identify compounds with the same masses [20]. A combination of these complementary techniques enables to analyse a broader array of metabolites and offers more certain results than their separate use.

3. Matrices for Metabolomic Studies

The application of metabolomics allows the use of several matrices such as tissue and body fluids (i.e., plasma, serum, saliva, follicular fluid, semen). The choice of the matrices is associated with the aim of the conducted study as well as the characteristics of the studied disorder. Ovarian tissue can also be used; however, sampling is invasive and problematic. It is usually obtained during laparoscopic wedge resection surgery. For this reason, the use of ovarian tissue in studying the pathophysiology of PCOS is not very common. The matrices widely used in metabolomic studies associated with PCOS are plasma and urine. Serum and urine samples are more common, because they are easily collectible and simple to prepare. On comparing the significantly altered metabolites, it can be observed that the results obtained for both matrices do not completely overlap. The new alternative matrix is follicular fluid, which is innovative in case of PCOS research, especially in terms of oocytes maturation and their quality [21][22][23].

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