Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Invited review

Insulin and the polycystic ovary syndrome

Djuro Macut [a,*], *Jelica Bjekić-Macut* [b], *Dario Rahelić* [c], *Mirjana Doknić* [a]

[a] *Clinic of Endocrinology, Diabetes and Metabolic Diseases, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[b] *Department of Endocrinology, UMC Bežanijska kosa, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[c] *Department of Endocrinology, Diabetes and Clinical Pharmacology, Clinic for Internal Medicine, School of Medicine Zagreb, Dubrava University Hospital, Zagreb, Croatia*

ARTICLE INFO

Article history:
Received 15 March 2017
Accepted 6 June 2017
Available online 12 June 2017

Keywords:
Insulin
Insulin resistance
Polycystic ovary syndrome
Androgens
Metformin

ABSTRACT

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy among women during reproductive age. PCOS is characterised by hyperandrogenaemia, hyperinsulinaemia, and deranged adipokines secretion from the adipose tissue. In addition to the reduced insulin sensitivity, PCOS women exhibit β-cell dysfunction as well. Low birth weight and foetal exposure to androgens may contribute to the development of the PCOS phenotype during life. Further metabolic complications lead to dyslipidaemia, worsening obesity and glucose tolerance, high prevalence of metabolic syndrome, and greater susceptibility to diabetes. PCOS women show age-related existence of hypertension, and subtle endothelial and vascular changes. Adverse reproductive outcomes include anovulatory infertility, and unrecognised potentiation of the hormone-dependent endometrial cancer. The main therapeutic approach is lifestyle modification. Metformin is the primary insulin-sensitising drug to be used as an adjuvant therapy to lifestyle modification in patients with insulin resistance and impaired glucose tolerance, as well as in those referred to infertility treatment. Thiazolidinediones should be reserved for women intolerant of or refractory to metformin, while glucagon-like peptide 1 analogues has a potential therapeutic use in obese PCOS women. Randomised clinical trials and repetitive studies on different PCOS phenotypes for the preventive actions and therapeutic options are still lacking, though.

Contents

* Corresponding author at: Clinic of Endocrinology, Diabetes and Metabolic Diseases, dr Subotica 13, 11000 Belgrade, Serbia.
E-mail address: djmacut@gmail.com (D. Macut).

http://dx.doi.org/10.1016/j.diabres.2017.06.011
0168-8227/

1. Introduction

Polycystic ovary syndrome (PCOS) is considered as the most common endocrinopathy in women of reproductive age. Women with PCOS are characterised by hyperandrogenaemia, hyperinsulinaemia, hypothalamic-pituitary-ovarian axis dysfunction, and deranged adipokines secretion from the adipose tissue. These specific alterations interact in different tissues, such as fat, liver, muscle and ovaries, resulting in a variety of phenotypes of the syndrome [1]. A recent survey showed that metabolic disorders, obesity, and type 2 diabetes (T2D) were recognised as the most important long-term concerns related to PCOS [2]. Moreover, longitudinal studies showed that worsening of insulin resistance (IR) over time in obese PCOS women is a risk factor for the early development of T2D [3].

2. Diagnosis and prevalence of PCOS

The diagnosis of PCOS is based on clinical grounds, while sets of criteria for defining it were put forward at two major expert conferences. The 1990 criteria, or the NIH criteria, require that both clinical hyperandrogenism and/or biochemical hyperandrogenaemia, together with chronic oligo-/anovulation be present [4]. The 2003 criteria, or the Rotterdam criteria, added the third major criterion, ultrasound presentation of polycystic ovaries, and require the presence of two of the three criteria in question: oligo-/anovulation, clinical and/or biochemical hyperandrogenism, and ultrasonographic ovarian morphology [5]. The change that the Rotterdam criteria brought about by including an ultrasound image of polycystic ovary led to the recognition of PCOS as a syndrome with a variety of complex clinical phenotypes with various outcomes. In order to reconcile the differences between these two sets of criteria, the obligatory presence of hyperandrogenism was proposed by the Androgen Excess and PCOS Society in 2009 [6].

Prevalence of PCOS varies depending on the criteria used and population analysed. It is estimated to range between 6% and 25% [4–6]. This suggests that a thorough understanding of PCOS pathophysiology and its association with reproductive and metabolic disturbances is essential for addressing women's health and for expanding knowledge on how to treat this highly multifaceted syndrome [1].

3. Pathophysiology of insulin resistance and hyperinsulinaemia in PCOS

Insulin resistance refers to an increased amount of insulin needed to perform metabolic action. Besides metabolic effects, insulin exerts both mitogenic and reproductive actions. The complexity of the clamp technique and frequently-sampled i.v. glucose tolerance test with minimal model analysis have directed clinical researchers towards the use of fasting parameters of glucose homeostasis as surrogate measures of insulin resistance. Therefore, homeostatic model assessment, fasting glucose-to-insulin ratio, and quantitative insulin sensitivity check index have been developed and broadly used in clinical research, including metabolic studies in PCOS [7].

Abdominal obesity contributes to insulin resistance in women with the syndrome [8,9], possibly through subclinical inflammation [10]. It is not clear whether metabolically active intra-abdominal adipose tissue is increased in PCOS. However, subcutaneous adipose tissue as a dysfunctional adipose tissue compartment represented by lower circulating adiponectin was found in PCOS, and was shown to be associated with IR [11]. Moreover, it is possible that lower adiponectin concentrations and accumulation of ectopic fat in the liver, skeletal muscle and perimuscular tissue may play a unique role in the pathogenesis of IR in women with PCOS [12,13].

3.1. *Prevalence of the glucose metabolism disorders in PCOS*

3.1.1. *Prevalence of insulin resistance*

Prevalence of IR in PCOS differs with respect to the method used. It ranges from 44% to 70% when measured by using