

Review

Prevalence, pathogenesis and management of prediabetes and type 2 diabetes mellitus in patients with polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. PCOS is not only the leading cause of anovulatory infertility but is also associated with an array of metabolic disorders, among which impaired glucose metabolism has been a topic of intense research. The aim of the present narrative review is to summarize the findings of the studies that have evaluated the prevalence and incidence of prediabetes and type 2 diabetes mellitus (T2DM) in patients with PCOS, to analyze the factors underpinning the association between T2DM and PCOS and to discuss the current strategies for screening and management of impaired glucose metabolism in this population. Both prediabetes and T2DM are highly prevalent in patients with PCOS. Accordingly, regular screening is recommended in this population for the early identification of impaired glucose metabolism, particularly in overweight or obese patients and in those with a family history of T2DM. Prevention of T2DM in patients with prediabetes is primarily based on lifestyle changes, while metformin might be considered in selected cases. The treatment of T2DM is similar in patients with and without PCOS but appropriate contraceptive measures should be implemented in patients receiving treatments other than insulin, metformin or glyburide.

Key words: Impaired glucose tolerance, Insulin resistance, Obesity, Polycystic ovary syndrome, Type 2 diabetes mellitus

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age.^{1,2} PCOS is mainly characterized by oligo- or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries and is the leading cause of anovulatory infertility.^{3,4} However, PCOS is also

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associated with an array of metabolic disorders, among which impaired glucose metabolism has been a topic of intense research. Indeed, several cross-sectional and some prospective studies reported increased prevalence and incidence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) in these patients.⁵

The aim of the present narrative review is to summarize the findings of the studies that evaluated the prevalence and incidence of prediabetes and T2DM in patients with PCOS, to discuss the factors underpinning the association between T2DM and PCOS and to present the current recommendations for screening for and management of impaired glucose metabolism in this population. A narrative review was chosen instead of a systematic review or a meta-analysis because the heterogeneity of the studies included in the review is too large, rendering the systematic review and the meta-analysis impossible to perform.

METHODS

We searched the PubMed for relevant articles using the following keywords: polycystic ovary syndrome, impaired fasting glucose, impaired glucose tolerance, type 2 diabetes mellitus, prediabetes, insulin resistance, diet, exercise, pharmacotherapy. References of retrieved articles were also evaluated for the identification of additional pertinent papers.

PREVALENCE OF PREDIABETES AND T2DM IN PATIENTS WITH PCOS

In an early case-control study in 254 patients with PCOS and 80 age- and weight-matched controls, the prevalence of IGT was 2.7 times higher in the former (31.1 vs. 14.0%, respectively).⁶ Moreover, 7.5% of patients with PCOS had T2DM compared with none in the women in the control group.⁶ In a more recent large study in 11,035 patients with PCOS, the prevalence of T2DM was 2.45 times higher than in age-matched controls.⁷ In a meta-analysis of 13 studies that compared the prevalence of IGT between patients with PCOS and controls, IGT was 2.48 times more frequent in the former.⁵ Likewise, the prevalence of T2DM was 4.5 times higher in patients with PCOS

than in controls in a meta-analysis of 15 studies⁵ and, importantly, these differences were similar in studies that included body mass index (BMI)-matched populations.⁵ Of note, it has been estimated that 15.0-35.6% of all incident cases of T2DM in white women are attributable to PCOS.⁸ Metabolic syndrome, which is associated with increased risk for T2DM,⁹ is also more frequent in patients with PCOS,^{10,11} while, in contrast, the prevalence of impaired fasting glucose or of HbA_{1c} levels in the prediabetic range (i.e. between 5.7 and 6.4%) appears to be low in patients with PCOS.^{12,13}

INCIDENCE OF PREDIABETES AND T2DM IN PATIENTS WITH PCOS

There are very limited data on the incidence of prediabetes and T2DM in patients with PCOS. In an early uncontrolled study in 67 patients with PCOS, 9% and 8% of patients with normal glucose tolerance developed IGT and T2DM, respectively, during a follow-up period of 6.2 years.¹⁴ Moreover, 54% of patients who had IGT at baseline developed T2DM.¹⁴ In a more recent study in 95 patients with PCOS and age- and BMI-matched controls, the incidence of T2DM during an 8-year follow-up period was 2.3 times higher in the former (13.4% and 5.8%, respectively).¹⁵ Moreover, obese patients with PCOS had a fivefold greater risk of developing T2DM than controls.¹⁵ In another study, the incidence of IGT was 2.4 higher in patients with PCOS than in controls, albeit this difference did not reach significance due to the small sample size ($n = 35$ and 23 , respectively).¹⁶ In a more recent uncontrolled study in 255 patients with PCOS followed up for 16.9 years, the incidence of T2DM was 1.05 per 100 person-years and the age-standardized prevalence of T2DM at the end of follow-up was significantly higher than that of the general female population of a similar age (39.3 and 5.8%, respectively).¹⁷ In another recent retrospective analysis of a large longitudinal database, patients with PCOS ($n = 21,740$) had a 3 times higher risk of developing T2DM during a follow-up of 4.7 years.¹⁸ Interestingly, the incidence of T2DM was also 1.7 times higher in patients with PCOS than in BMI-matched controls.¹⁸

PATHOGENESIS OF PREDIABETES AND T2DM IN PCOS

Insulin resistance (IR) is intimately involved in the increased risk for prediabetes and T2DM in PCOS,¹⁴ with IR being present in approximately 60-80% of patients with PCOS and in 95% of obese patients with this syndrome.^{19,20} In addition, IR worsens with age in patients with PCOS.^{21,22} The pathogenesis of IR in patients with PCOS is multifactorial.²³ Insulin-stimulated glucose uptake is mediated by the activation of phosphatidylinositol-3 kinase, while insulin-induced cell growth and differentiation is mediated through the mitogen-activated protein kinase (MAPK) <http://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/mapk-erk-pathway/> extracellular signal-regulated kinase (ERK) that stimulates a cascade of enzymes, including serine/threonine, Raf, MAPK and MAPK-ERK1/2.²⁴ A pivotal study in obese and non-obese patients with PCOS showed that IR in this syndrome is independent of obesity and is due to impaired insulin action.²³ More recent studies also support the presence of an intrinsic IR in patients with PCOS.^{25,26} Higher basal insulin secretory rates and attenuated secretory responses to meals have also been reported in patients with PCOS, which factors contribute to hyperinsulinemia in this population.²⁷⁻²⁹ In contrast, insulin clearance does not appear to be reduced in patients with PCOS.²³

Obesity characterizes 40-70% of patients with PCOS and is another key contributor to the pathogenesis of impaired glucose metabolism in this population.^{11,30,31} In a case-control study in 254 patients with PCOS and 80 age- and weight-matched controls, both BMI and waist/hip ratio (WHR) were independent predictors of IGT,⁶ while other studies have also reported higher BMI and WHR in patients with PCOS and IGT than in those with normal glucose tolerance.^{32,33} In prospective studies, obesity was also independently associated with increased incidence of IGT or T2DM in patients with PCOS.¹⁴ Obesity appears to exert a synergistic, independent, adverse effect on glucose metabolism, this accompanied by the added burden of intrinsic IR that characterizes patients with PCOS.²³ Body composition, including increased ratio of truncal/lower body fat and higher inter- and intramuscular adipose tissue also contribute to the aggravation of IR in this population.^{34,35}

Hyperandrogenism might also play a role in the pathogenesis of prediabetes in patients with PCOS. Indeed, patients with PCOS and hyperandrogenemia have more pronounced IR than patients without hyperandrogenemia.³⁶⁻³⁸ It has further been shown that treatment with androgens impairs insulin sensitivity, whereas antiandrogens improve insulin sensitivity,³⁹⁻⁴¹ while in addition it appears that IR aggravates obesity in patients with PCOS.^{42,43} Moreover, several studies reported that free testosterone levels are higher in patients with PCOS and IGT than in those with normal glucose metabolism.³³

Impaired glucose metabolism in patients with PCOS additionally appears to have a strong genetic background, since a positive family history of T2DM increases the risk for IR and prediabetes in this population.⁴⁴ Moreover, women with monozygotic twin sisters with PCOS have twice the risk of developing the syndrome.⁴⁵ In a number of studies, polymorphisms in several genes, including thyroid associated protein, DENN/MADD domain containing 1A and luteinising hormone/choriogonadotropin receptor, were associated with increased risk for PCOS.⁴⁴⁻⁴⁸ Developmental programming, i.e. changes in gene expression due to the presence of increased steroids, mostly androgens, during fetal development, also appears to increase the risk for IR, prediabetes and T2DM in offspring of patients with PCOS.⁴⁹

Emerging data suggest that the gut microbiome might also be implicated in the pathogenesis of impaired glucose metabolism in patients with PCOS.⁵⁰ In a recent pilot study, specific taxa of gut bacteria were associated with lower serum androgen levels and lower prevalence of oligo-amenorrhea.⁵¹

Muscle mitochondrial dysfunction has also been recently reported in patients with PCOS and might also play a role in the development of T2DM in this population.⁵²

SCREENING FOR PREDIABETES AND T2DM IN PATIENTS WITH PCOS

According to the recent guidelines of the American Association of Clinical Endocrinologists, the American College of Endocrinology and the Androgen Excess and PCOS Society, an oral glucose

tolerance test (OGTT) should be performed every 1 to 2 years in patients with PCOS based on a family history of T2DM and a BMI >30 kg/m², while this test should be performed every year in patients with PCOS and IGT.⁵³ A recent position statement of the PCOS Special Interest Group of the European Society of Endocrinology recommends performing an OGTT in all obese patients with PCOS as well as in lean middle-aged patients (>40 years), in the presence of a personal history of gestational diabetes or family history of T2DM.⁵⁴ In contrast, both Societies mention that measurement of fasting glucose levels and HbA_{1c} appears to have limited sensitivity in identifying prediabetes in patients with PCOS.^{12,13,55} The Endocrine Society recommends performing an OGTT in all patients with PCOS every 3-5 years or more frequently if central adiposity, substantial weight gain or symptoms of T2DM develop.⁵³ In patients unable or unwilling to perform an OGTT, measuring HbA_{1c} might be considered.⁵⁶ Moreover, the European Society of Endocrinology mentions that measurement of serum insulin and estimates of insulin resistance are not required for routine clinical management.⁵⁴

MANAGEMENT OF PREDIABETES AND T2DM IN PATIENTS WITH PCOS

Lifestyle changes, including diet, exercise and behavior modification, represent first-line treatment for all overweight and obese patients with PCOS.^{53,56,57} A hypocaloric diet (500-1000 kcal/d reduction) with reduced intake of saturated fats and increased intake of mono- and polyunsaturated fats, fiber, whole-grain breads, cereals, fruits and vegetables is recommended, along with at least 30 min of moderate-intensity physical activity daily.^{56,57} A reduced carbohydrate diet also appears to result in preferential loss of abdominal fat mass.⁵⁸ It is well established that diet improves IR in patients with PCOS,⁵⁹⁻⁶¹ while exercise also appears to improve IR and to reduce visceral fat in this population.^{62,63} Lifestyle changes reduced the risk of progression from IGT to T2DM in the general population^{64,65} and in patients with PCOS.⁶⁶

Additionally, the Androgen Excess and PCOS Society as well as the Endocrine Society suggest the use of metformin in patients with PCOS who have no improvement in IGT despite lifestyle changes and in

normal weight patients with IGT.^{56,57} Several studies showed that treatment with metformin improves IR and induces weight loss in patients with PCOS and that it might also induce reversion from IGT to normal glucose tolerance and prevent the development of IGT or T2DM.⁶⁷⁻⁷⁰ However, it should be noted that in the Diabetes Prevention Program study (n = 3,234 patients with IFG or IGT), metformin was less effective than lifestyle changes in reducing the incidence of T2DM (31 and 58% reduction, respectively).⁶² Importantly, the use of antiobesity agents is not recommended because of limited data on their safety and efficacy in patients with PCOS.^{57,61,71}

In patients with PCOS who are diagnosed with T2DM there are no specific recommendations for the choice of antidiabetic treatment.⁷² Accordingly, metformin and lifestyle changes are the treatment of choice, while any antidiabetic agent can be added in patients who do not achieve glycemic targets despite treatment with metformin (i.e. sulfonylureas, pioglitazone, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors or basal insulin).⁷² Among the available options, pioglitazone appears to improve insulin sensitivity to a similar degree as metformin, both agents exerting a synergistic effect on IR in patients with PCOS.^{73,77} However, safety concerns, including the risk of weight gain and edema, limit the use of pioglitazone in this population.⁵⁴ Limited data also suggest that glucagon-like peptide 1 analogues combined with metformin attenuate IR and reduce weight more effectively than metformin monotherapy.^{75,76} However, only insulin, metformin and glyburide can be safely used in pregnancy and therefore appropriate contraceptive measures should be implemented in patients receiving other antidiabetic agents.⁷⁷

CONCLUSIONS

Both prediabetes and T2DM are highly prevalent in patients with PCOS. Accordingly, regular screening is recommended in this population for the early identification of impaired glucose metabolism, particularly in overweight or obese patients and in those with a family history of T2DM. Prevention of T2DM in patients with IGT is primarily based on lifestyle

changes, whereas metformin might be considered in selected cases. Both diet and exercise have multiple beneficial effects on glucose metabolism in this population. The treatment of T2DM is similar in patients with and without PCOS but appropriate contraceptive measures should be implemented in patients receiving treatments other than insulin, metformin or glyburide.

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