Mini-Review

A Review on Glycosylated Hemoglobin in Polycystic Ovary Syndrome

Mohsen Rezaee MD [1], Nasrin Asadi MD [2], Yasna Pouralborz MD [1,*], Mahshid Ghodrat MD [1], Shaghayegh Habibi MD [1]

[1] *Student Research Committee, Fasa University of Medical Sciences, Fasa, Iran*
[2] *Maternal-Fetal Medicine Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

A B S T R A C T

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine disorders among women of reproductive age, with a variety of complications and consequences mostly due to hyperandrogenism and insulin resistance (IR). PCOS patients with IR are at risk for metabolic syndrome and diabetes mellitus (DM) along with its complications such as cardiovascular events. There are several methods for screening IR in patients with PCOS to predict DM and other complications. Fasting plasma glucose test, oral glucose tolerance test, and insulin and glycosylated hemoglobin (HbA1c) levels are some available screening tools for IR. The American Diabetes Association recommended HbA1c to screen for DM because HbA1c is not affected by day-to-day plasma glucose levels and reflects the plasma glucose status during 2-3 months before measurement. Some studies have evaluated the role of HbA1c as a screening method to predict DM in PCOS patients, however, there are still controversies in this matter. Also some studies reported that HbA1c has a correlation with complications of PCOS such as metabolic syndrome and cardiovascular events. We found that HbA1c could be a suitable screening test for IR in PCOS patients but more studies are recommended, omitting confounding factors that could affect IR in patients with PCOS, such as antihyperglycemic agents like metformin, or lifestyle modification, which can be effective in reducing IR in patients with PCOS.
Key Words: Polycystic ovary syndrome, Glycosylated hemoglobin, Review, Insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder among women of reproductive age that causes oligo- or anovulation, clinical and biochemical signs of hyperandrogenism, and special morphological features of the ovary in ultrasound examinations.[1] Insulin resistance (IR) is one of the pathophysiologic events that is presented in most patients with PCOS; IR worsens in some conditions such as adipose tissue dysfunction and because of genetic factors.[2,3] Patietns with PCOS are predisposed to consequences and complications of IR such as: cardiovascular and cerebrovascular diseases, hypertension, metabolic syndrome, and type 2 diabetes.[4–7] There are some methods for screening patients with PCOS to prevent related complications like type 2 DM, which occurs along with IR in PCOS. The current recommendation is to screen for type 2 diabetes in some patients with PCOS. Fasting plasma glucose (FPG) test and oral glucose tolerance test (OGTT) are performed in obese patients, and in lean women with age older than 40 years with a history of gestational diabetes.[8,9] Level of glycosylated hemoglobin (HbA1c) is another screening tool that reflects glycemic status during the previous 2-3 months.[10] It might be one of the accurate screening tests for complications mentioned previously. However, using this test in patients with PCOS as a screening tool is controversial because there are some confounding factors that affect IR and also HbA1c in patients with PCOS.

PCOS and IR

PCOS is one of the most common endocrine disorders among reproductive-aged women with various prevalence.[11] In some populations its prevalence has been reported as high as 25%.[12] This syndrome is associated with a wide spectrum of complications including hyperandrogenism, hirsutism, anovulation (in the absence of specific adrenal and/or pituitary disease), infertility, menstrual disturbance, and obesity.[2,11,13] Chronic anovulation often presents as oligomenorrhea, amenorrhea, abnormal uterine bleeding, and/or infertility, however, approximately 20% of patients with PCOS might describe normal menstrual cycles.[11]

PCOS can be diagnosed if the patients meet any 2 of 3 criteria after exclusion of other causes: (1) oligo-ovulation and/or anovulation; (2) clinical or biochemical hyperandrogenism; (3) polycystic ovaries detected using ultrasound.[14] Patients with hyperandrogenism might present clinically with hirsutism, acne, and/or male pattern alopecia. Hirsutism can be defined as the growth of coarse hair in a woman with a male pattern such as on upper lip, chin, chest, upper abdomen, back, etc. This is to be distinguished from hypertrichosis, which is more uniform and involves whole-body distribution of fine hair. Acne due to hyperandrogenism might be difficult to distinguish from normal pubertal acne in an adolescent with PCOS.[15] These patients

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* *Address correspondence to:* Yasna Pouralborz, MD, Student Research Committee, Fasa University of Medical Science, Fasa, Iran; Phone: +989173040538
E-mail address: Yasna.arztin90@yahoo.com (Y. Pouralborz).

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also have dyslipidemia such as elevated triglyceride (TG) and low-density lipoprotein cholesterol levels and low high-density lipoprotein cholesterol levels.[16,17] When clinically evaluating a patient with PCOS, it is also important to search for the presence of signs of IR.[11]

IR is one of the hallmarks of this reproductive endocrine disease and an important component in etiopathogenesis of PCOS, associated with central obesity, acanthosis nigricans, hirsutism, and early pregnancy loss.[16] IR can also increase the risk of type 2 DM by 5-10 times. Some evidence supports the association between PCOS and the region near the insulin receptor gene. IR causes compensatory hyperinsulinemia, which results in hyperandrogenism by stimulating ovaries and increasing free androgen in blood by suppressing liver production of sex hormone binding globulin.[12]

Any 3 or more of the following criteria are diagnostic for the IR syndrome (or so-called metabolic syndrome) in women: waist circumference > 88 cm, TG > 150 mg/dL, high-density lipoprotein cholesterol <50 mg/dL, blood pressure > 130/85 mm Hg, and fasting glucose > 110 mg/dL.[11,18] Approximately 75% of patients with PCOS are found to have IR.[12]

Screening for IR in Patients with PCOS

There are many helpful methods to evaluate IR but none of the tests are extremely sensitive or specific.[11] The measurement of fasting serum insulin is a simple and inexpensive method. However, it should be noted that fasting insulin levels might be in the normal range in up to 40% of women with PCOS who have impaired glucose tolerance diagnosed using the OGTT.[19]

Impaired fasting glucose is defined by an elevated FPG level (>100 and <126 mg/dL), which is considered prediabetes.[20] The OGTT is on the basis of venous plasma glucose before and 2 hours after a 75-g oral glucose load.[21] Impaired glucose tolerance is defined by an elevated 2-hour plasma glucose level (>140 and <200 mg/dL) in the presence of an FPG concentration <126 mg/dL.[22,23]

The glucose/insulin (G/I) ratio is easy to calculate, with lower values depicting higher degrees of IR.[19] When viewed as a screening test for IR in patients with PCOS, a value of the fasting G/I ratio of less than 4.5 is viewed as abnormal; the sensitivity and the specificity of a fasting G/I ratio is 95% and 84%, respectively.[24]

Recently, the American Diabetes Association suggested that HbA1c might be considered a screening tool because of its advantages over fasting glucose and OGTT, such as greater convenience (fasting is not required) and less day-to-day variability during periods of stress or illness.[25,26]

HbA1c in PCOS

HbA1c is formed as a result of slow reactions taking place during the lifespan of red blood cells. The reactions involve a ketoamine linkage between glucose molecule and β-chains of hemoglobin.[27] Although the current clinical use of HbA1c is mainly to assess chronic glycemic control in diabetes, some studies have evaluated the efficacy of HbA1c as a means of screening for diabetes.[28,29] Regarding a cutoff for HbA1c level, the American Diabetes Association has included an HbA1c level of 5.7% or higher and 6.5% or higher as criteria for diagnosis of prediabetes and DM, respectively.[10]

As mentioned, the level of HbA1c is highly dependent on the blood glucose levels over the previous 2-3 months before its measurement, therefore, treating individuals with antihyperglycemic agents such as metformin lowers HbA1c levels as it controls blood glucose levels.[30]

However, some data suggest that, independent of glycemia, some factors might influence the levels of HbA1c. Examples for these confounding factors would be: hemoglobinopathies, anemia, aging, and ethnicity.[31]

The elevated HbA1c level has been shown to be associated with increased risk of cardiovascular complications and metabolic syndrome in several conditions.[32] Cigarette smoking is related to higher HbA1c levels in patients with PCOS and results in increased risk of metabolic syndrome.[33]

Recently there has been a growing interest to apply HbA1c for screening and diagnosis of prediabetes and DM in women with PCOS because it has certain advantages over the 2-hour OGTT. Furthermore, HbA1c level provides a better estimate for healthcare providers regarding chronic glycemic control.[3,34,35]

At least half of patients with PCOS are estimated to suffer from IR and thus are prone to prediabetes and eventually DM.[36] Up to now, several studies have been performed to evaluate if HbA1c is a sufficient screening tool and results are controversial.

In a cohort study involving 252 Turkish patients with PCOS, results showed that HbA1c is not a reliable tool for screening for prediabetes compared with the OGTT. In this study the best sensitivity and specificity was reached when the cutoff of HbA1c was considered 5.35% or higher but even in that condition the OGTT was still a more reliable test.[25] A cross-sectional study performed on 671 young and nonobese women with PCOS in Austria (2006-2012) did not support using HbA1c or FPG as screening tools for prediabetes in the studied population but revealed a good correlation between these tests and type 2 DM.[37] Results from a retrospective cohort study including 68 adolescents with PCOS suggested that compared with the OGTT, HbA1c has moderate sensitivity and specificity for screening dysglycemia.[38] One study surprisingly suggested that in pregnant women with PCOS, levels of HbA1c concentration might be a better predictor for preeclampsia than for gestational DM.[39]

In contrast, several studies have shown beneficial aspects in using HbA1c for screening of PCOS complications such as metabolic and cardiovascular diseases. A positive correlation existed between an HbA1c level of 5.7% or higher with androgen level, anthropometrical measures like waist/hip ratio, metabolic profiles, and body mass index (BMI) in a study carried out in Brazil.[32] Another cross-sectional study, which was done in nondiabetic patients with PCOS, confirmed greater IR and increased risk factors for cardiovascular disease with an HbA1c level of 5.7% or higher.[40] A model suggested to evaluate the risks of metabolic and vascular diseases in women with PCOS includes evaluation of HbA1c as a component along with BMI and free testosterone levels.[41]