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ORIGINAL ARTICLE *Reproductive endocrinology*

Assessment of impaired glucose tolerance prevalence with hemoglobin A_{1c} and oral glucose tolerance test in 252 Turkish women with polycystic ovary syndrome: a prospective, controlled study

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STUDY QUESTION: What is the prevalence of abnormalities in glucose metabolism in patients with polycystic ovary syndrome (PCOS) and controls in a Turkish population?

SUMMARY ANSWER: The total prevalence of glucose abnormalities in PCOS patients was 16.3% [impaired glucose tolerance (IGT) 14.3%; type 2 diabetes mellitus (T2DM) 2%] and was higher than in healthy subjects (IGT 8.5%; T2DM 0%, respectively).

WHAT IS KNOWN ALREADY: One of the most common markers of chronic glycemia is hemoglobin Alc (HbA_{1c}). However, little is known about whether the use of HbA_{1c} results in diagnosis of more cases of glucose intolerance in the PCOS population than the oral glucose tolerance test (OGTT) alone.

STUDY DESIGN, SIZE, DURATION: This was a prospective study, including 252 women with PCOS and 117 control women without PCOS.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study was carried out in the gynecological outpatient department of Namik Kemal University Hospital, Turkey, between 2010 and 2012. Women with PCOS ($n = 252$) were diagnosed according to Rotterdam criteria. The control group included 117 women (aged 17–45 years) who were selected randomly. BMI of participants ranged between 15.6 and 47.9 kg/m^2.

MAIN RESULTS AND THE ROLE OF CHANCE: Patients with PCOS were comparable to controls in terms of age (24.8 versus 25.9 years, respectively) and had higher BMI (26.1 versus 24.9 kg/m^2, respectively). Of 252 patients with PCOS, 41 had glucose intolerance (IGT 14.3%; T2DM 2%) when compared with 10 of the 117 control patients (IGT 8.5%; T2DM 0%; odds ratios = 2.08; $P = 0.045$) during the OGTT. When an HbA_{1c} value $\geq 5.6\%$ was used to divide the total population, the prevalence of abnormal glucose metabolism was 7.9% in the patients with PCOS, below the value detected in the control patients (8.5%), which showed that 20 of 41 patients with abnormal glucose tolerance would not have been diagnosed, if the HbA_{1c} alone had been used. When compared with the OGTT results, HbA_{1c} provided 52.4% sensitivity, 74.4% specificity, 67.1% positive and 60.9% negative predictive values with a threshold value of 5.6% in abnormal glucose tolerance. The receiver operating characteristic analysis suggested a threshold value of 5.35% in HbA_{1c} (75.6% sensitivity and 52.6% specificity) for the prediction of abnormal glucose tolerance.

LIMITATIONS, REASONS FOR CAUTION: This study did not involve weight-matched healthy subjects, which may cause a difference in prevalence of abnormal glucose metabolism between the groups, and the results are limited to an unselected population of patients who

have the full PCOS phenotype. In addition, the incidence of T2DM among the first-degree relatives and 2-h insulin levels could not be reported in full.

WIDER IMPLICATIONS OF THE FINDINGS: Further investigation of the efficacy of HbA_{1c} for the prediction of abnormal glucose tolerance should be undertaken in long-term prospective studies and in different geographic populations. At present, the only way to reliably detect abnormal glucose metabolism in Turkish women with PCOS appears to be using the OGTT.

STUDY FUNDING/COMPETING INTEREST(S): No financial support. The authors have no competing interests to declare.

TRIAL REGISTRATION NUMBER: Not applicable.

Key words: impaired glucose tolerance / diabetes mellitus / polycystic ovary syndrome / hemoglobin A_{1c}

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine condition that is usually diagnosed according to the criteria of the Rotterdam (ESHRE/ASRM, 2004). More than 50% of women with PCOS are insulin resistant, and it is estimated that they have a 5- to 8-fold increased risk of type 2 diabetes mellitus (T2DM), when compared with age- and weight-matched controls (Glintborg *et al.*, 2004; Glintborg and Andersen, 2010). The development of T2DM is affected by insulin resistance (IR) and β-cell dysfunction as a major pathogenesis. Therefore, women who have PCOS usually are at increased risk for impaired glucose tolerance (IGT) and T2DM (Lillioja *et al.*, 1993; Dunaif, 1997; Legro *et al.*, 1999). However, IGT can be underdiagnosed, even in populations at high risk, because the diagnosis of IGT needs an oral glucose tolerance test (OGTT) (Harris *et al.*, 1987; King and Rewers, 1993). According to a previous study, IGT and T2DM are present in 31–35% and 7.5–10%, respectively, of American women with PCOS (Ehrmann *et al.*, 1999). Although, in Europe, the prevalence of abnormal glucose metabolism was reported as being much lower than in American women with PCOS (IGT 12.4%, T2DM 1.7), it is significantly higher than in the general population (Legro *et al.*, 1999; Trakakis *et al.*, 2012). Thus, it is recommended that patients with PCOS are screened for diabetes using an OGTT (ESHRE/ASRM, 2004; Salley *et al.*, 2007). However, in daily practice, the performance of OGTT may be inconvenient and time-consuming because the patient has to be assessed while fasting and, therefore, needs to attend the clinic usually on two different days. Thus, a strategy that could decrease or replace the need for an OGTT would be useful.

Hemoglobin A_{1c} (HbA_{1c}) is a commonly used marker of chronic glycemia, and it reveals the average blood glucose levels over a 2- to 3-month period. The problem of the day-to-day variability of glucose values and the need for fasting and preceding dietary preparations can be avoided most of the time using HbA_{1c} instead of OGTT (ADA, 2011). Lately, an international expert committee composed of members of the European Association for the Study of Diabetes, the International Diabetes Federation and the American Diabetes Association (ADA) stated that HbA1c levels between 6 and 6.5% should lead to an OGTT, whereas HbA_{1c} levels of $<6\%$ indicate that no further tests are required (ADA, 2011).

The primary aim of this prospective study was to determine the prevalence of IGT and T2DM in a Turkish population of women with PCOS when compared with healthy women, to obtain data that will be representative of the Eastern Mediterranean region. We also evaluated whether the use of HbA_{1c} resulted in the diagnosis of more cases of glucose intolerance in our PCOS population than the OGTT alone.

Materials and Methods

Subjects

We prospectively studied 252 women with PCOS and 117 healthy (control) women, recruited from our gynecological outpatient department of Namik Kemal University Hospital, Turkey, between 2010 and 2012. The study was approved by the institutional review board of the hospital, and all participants gave written informed consent. PCOS was diagnosed when 2 out of the following 3 features were present: oligoovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination (the presence of 12 or more follicles measuring 2–9 mm in diameter and/or ovarian volume $> 10\ cm^3$) according to the criteria of the Rotterdam European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine-sponsored PCOS consensus workshop group (ESHRE/ASRM, 2004). Oligoanovulation was defined as the presence of oligomenorrhea (menstrual cycles of > 35 days) or amenorrhea (lack of a menstrual period for 6 months or more). Patients who had hyperprolactinemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's disease, hypertension, hypercholesterolemia, a history of neoplasm and those using medication (e.g. insulin-sensitizing drugs, oral contraceptives, antiandrogens, statins, aspirin, corticosteroids and GnRH agonists and antagonists) during the 90 days prior to enrollment were excluded. The control group included 117 women who were selected from patients who did not show any clinical and ultrasonographic signs of PCOS and were selected in a randomized manner. To avoid changing insulin action, control women did not engage in aerobic exercise. Controls also did not have a history of hypertension, a personal history of diabetes or a first-degree relative with diabetes. Patients with anemia and adrenal diseases were not included in this study to avoid any misinterpretation of HbA_{1c} levels (Eriksson *et al.*, 1989; DeFronzo and Ferrannini, 1991; Goodyear and Kahn, 1998).

Protocol

Routine evaluation of participants included medical history, clinical examination, transvaginal ultrasound, and fasting blood samples. Subjects were weighed on an electronic scale. BMI (kg/m^2) of each patient was calculated, and waist circumference was measured by accepting the lower rib and iliac crest as midway. The level of the major trochanters was the reference point for the hip circumference. The waist–hip ratio (WHR) was calculated as waist circumference divided by hip circumference. An investigator identified the presence or absence of hirsutism for every woman

with a modification of the Ferriman–Gallwey (mF–G score) method. Hirsutism was defined as an mF–G score > 7 (Coskun et al., 2011).

Fasting blood samples were drawn in the morning during the follicular phase (cycle days 2–8) in patients with a cycle length shorter than 3 months. Patients with cycle length > 3 months had the blood samples drawn on a random cycle day. Blood tests included the measurement of androgens [17-hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEA-S) and total testosterone], LH, FSH and prolactin.

An OGTT was performed at 8:00 a.m. on a random day of the cycle. Insulin and capillary blood glucose levels were measured at baseline and at 30, 60 and 120 min after oral ingestion of a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Abnormal glucose tolerance was defined as impaired fasting glucose (IFG) or IGT. According to the ADA guidelines, the IFG cutoff for diabetes was 5.6 mmol/L, and IGT was defined as 2-h glucose ≥ 7.8 mmol/L during the OGTT or HbA_{1c} > 5.6%, with diabetes diagnosed at a 2-h glucose ≥ 11.1 mmol/L or HbA_{1c} ≥ 6.5% (ADA, 2010).

IR, defined by the homeostasis model assessment IR index (HOMA-IR), was calculated with use of the following equation: HOMA-IR = fasting insulin (μU/L) × fasting glucose (mmol/L)/22.5 (Matthews et al., 1985).

Assays

Serum levels of LH, FSH, total testosterone, DHEA-S, estradiol and insulin were determined by enzyme-linked immunosorbent assay (Cobas 411, Roche Diagnostics, Mannheim, Germany). Glucose levels were measured by an autoanalyzer using standard enzymatic methods (Cobas 311, Roche Diagnostics, Mannheim, Germany). Hemoglobin A_{1c} was measured in venous blood by the D10 Hemoglobin testing system (BIORAD laboratories) that is based on cation exchange high-performance liquid chromatography.

Statistical analysis

Analysis was performed using the Statistical Package for the Social Sciences for Windows 11.5 program. Normal distribution of continuous variables was assessed by applying Shapiro–Wilk test, and data were expressed as mean ± SD or as median and 95% central range, as appropriate. The differences between groups were assessed using unpaired *t*-tests for parametric data and Mann–Whitney *U*-test for nonparametric data. Differences in frequencies were tested by χ^2 test. Correlations between variables were evaluated with the use of Spearman's correlation coefficient. To analyze the effects of PCOS on glucose parameters, analysis of covariance (ANCOVA) was applied with BMI as covariate. Partial correlation analysis was aimed to find correlations between 2-h glucose and clinical and biochemical parameters of subjects. A multiple regression analysis was performed to determine which variables predicted 2-h glucose levels in patients with PCOS. Receiver operating characteristic (ROC) curves were constructed to examine the diagnostic test performance of HbA_{1c} to identify abnormal glucose tolerance in PCOS patients. Odds ratios (OR) are presented with 95% confidence intervals (CIs). *P*-values <0.05 were considered statistically significant.

Results

The comparison of clinical and biochemical parameters between women with PCOS and healthy subjects is given in Table I. The mean age of women with PCOS was 24.8 ± 5.5 years that is comparable with the healthy subjects (25.9 ± 5.7). Patients with PCOS were heavier, with an increased BMI ($P = 0.03$) and WHR ($P = 0.001$) when compared with the control group. The total testosterone, DHEA-S, glucose parameters (including 2-h glucose levels), fasting insulin levels and HOMA-IR were also higher in the PCOS group than in control patients. To correct for the possible effect of BMI and age on these parameters, ANCOVA was performed, and the differences between groups remained significant.

Women with both PCOS and IGT were older than women with PCOS and normal glucose tolerance (NGT, 29.1 versus 25.6; $P = 0.001$). The 2 h-glucose, fasting insulin, HbA_{1c} and HOMA-IR in women with IGT-PCOS were significantly higher than those in NGT-PCOS and control groups. (Table 2). Of 252 patients with PCOS, 41 had glucose intolerance (IGT 14.3%; T2DM 2%) when compared with 10 of 117 control patients (IGT 8.5%; T2DM 0%; $\chi^2 = 4.00$; OR = 2.08 [95% CI 1.00–4.31]). The total prevalence of glucose abnormalities in our PCOS patients was 16.3% (IGT 14.3%; T2DM 2%) that was higher than in healthy subjects (IGT 8.5%; T2DM 0%) (Fig. 1).

In the PCOS group, 84.1% of the population was younger than 30 years old (212 out of 252). Similarly, in the control group, 74.3% of population was younger than 30 years old (87 out of 117). Of the 252 patients with PCOS, 66 (26.2%) were overweight (BMI ≥ 25 kg/m^2) and 23.8% were obese (BMI ≥ 30 kg/m^2), whereas 40.2% of control patients were overweight and 9.4% were obese. The prevalence of glucose intolerance increased significantly with an increase in BMI ($P_{\text{for trend}}$: 0.015) and age ($P_{\text{for trend}} < 0.001$) (Table 3).

The association between 2-h glucose levels and the determinants of IR in all subjects was tested. Two hour glucose levels significantly correlated with BMI ($r = 0.293$; $P < 0.000$), fasting glucose ($r = 0.447$; $P < 0.000$), HOMA-IR ($r = 0.217$; $P < 0.000$) and fasting insulin ($r = 0.307$; $P < 0.000$), HbA_{1c} ($r = 0.272$; $P < 0.000$), but not with total testosterone ($r = 0.042$, $P = 0.422$) and DHEA-S ($r = 0.022$;

Table I Clinical and biochemical parameters in women with PCOS and healthy controls.

Variable	PCOS (n = 252)	Controls (n = 117)	*P*-value
Age (years)[a]	24.8 ± 5.5	25.9 ± 5.7	0.098
BMI (kg/m^2)[b]	26.1 ± 5.7	24.9 ± 4.3	0.03
WHR[a]	0.83 ± 0.1	0.76 ± 0.1	<0.001
Total testosterone (nmol/L)[a]	39.0 ± 19.3	29.7 ± 11.6*	<0.001
DHEA-S(μmol/L)[a]	223.7 ± 109.7	200.6 ± 89.1	0.047
Fasting glucose (mmol/L)[b]	5.0 ± 0.6	5.0 ± 0.4	0.953
OGTT 2-h glucose (mmol/L)[a]	5.7 ± 1.7	5.3 ± 1.3	0.026
HOMA-IR[b]	2.2 ± 2.9	1.5 ± 1.2*	0.009
Fasting insulin (pmol/L)[b]	66.4 ± 24.0	49.5 ± 32.7*	0.003
HbA_{1c} (%)[a]	5.4 ± 0.5	5.4 ± 0.3	0.976

Data are shown as mean ± SD. $P < 0.05$ was considered statistically significant. WHR, waist–hip ratio; DHEA-S, dehydroepiandrosterone sulfate; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment IR index; Hb, hemoglobin.
[a]Tested by *t*-test.
[b]Tested by Mann–Whitney *U*-test.
*$P < 0.05$, after BMI adjustment.

Table II Clinical and biochemical parameters according to glucose status in women with PCOS and healthy controls.

	PCOS		Control	
	NGT ($n = 211$)	IGT ($n = 41$)	NGT ($n = 107$)	IGT ($n = 10$)
BMI (kg/m^2)	$25.6 \pm 5.4^{a,*}$	29.1 ± 6.3	24.5 ± 4.3^{b}	27.9 ± 3.4
Age (years)	$24.3 \pm 5.3^{a,*}$	27.4 ± 5.4	25.6 ± 5.7	28.0 ± 5.3
WHR	0.83 ± 0.5	0.83 ± 0.1	0.76 ± 0.1	0.75 ± 0.1
Total testosterone (nmol/L)	38.2 ± 18.8	43.1 ± 21.3	29.4 ± 11.5	32.3 ± 13.1
DHEA-S (μmol/L)	226.2 ± 110.8	210.7 ± 104.1	198.2 ± 92.2	222.0 ± 51.6
Fasting glucose (mmol/L)	$4.9 \pm 0.5^{a,*}$	5.7 ± 0.9	$4.9 \pm 0.3^{b,*}$	5.7 ± 0.3
OGTT 2-h glucose (mmol/L)	$5.2 \pm 0.9^{a,*}$	8.3 ± 2.3	$5.1 \pm 1.1^{b,*}$	7.3 ± 1.4
HbA_{1c} (%)	$5.3 \pm 0.4^{a,*}$	5.7 ± 0.7	5.40 ± 0.34	5.35 ± 0.26
HOMA-IR	$1.9 \pm 2.7^{a,*}$	3.7 ± 3.5	1.4 ± 1.1^{b}	1.9 ± 1.7
Fasting insulin (pmol/L)	$59.4 \pm 45.9^{a,*}$	102.8 ± 86.1	47.6 ± 31.3^{b}	65.8 ± 40.6

Data are mean ± SD. NGT, normal glucose tolerance; IGT, impaired glucose tolerance; *t*-test and Mann–Whitney *U*-test were used.
[a]$P < 0.05$ PCOS patients with IGT when compared with PCOS patients with NGT.
[b]$P < 0.05$ non-PCOS patients with IGT when compared with non-PCOS patients with NGT.
*$P < 0.01$, after BMI adjustment.

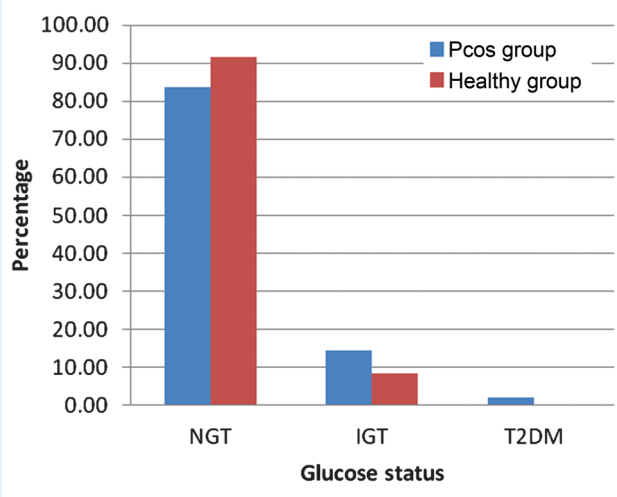

Figure 1 Prevalence of glucose abnormalities in women with PCOS and in healthy controls. Comparison of abnormal glucose tolerance prevalence in women with and without PCOS ($P = 0.045$), tested by χ^2 test. NGT, normal glucose tolerance; IGT, impaired glucose toleranceT2DM, type 2 diabetes mellitus.

$P = 0.671$). Using multiple regression analysis, fasting glucose and BMI were found to be significant independent determinants of 2-h glucose concentrations (adjusted $r^2 = 0.276$; $P < 0.000$).

In the PCOS group, 41 of 252 patients had abnormal glucose tolerance during OGTT. If we defined abnormal glucose tolerance as an HbA1c ≥ 5.6%, the prevalence of abnormal glucose metabolism decreased to 7.9% in PCOS patients, still below the value in control patients (8.5%). In addition, we conducted analysis in the higher risk group for impaired glucose metabolism according to the anthropometric characteristic of BMI > 25 kg/m^2. In the overweight/obese patients with PCOS, 29 of 126 patients had abnormal glucose tolerance during OGTT. Of 29 patients with IGT, 20 had HbA1c levels > 5.6%. When HbA1c level > 5.6% was used, the prevalence of abnormal glucose metabolism was 7.9%.

The ability of HbA_{1c} to discriminate women with PCOS and NGT from those with PCOS and abnormal glucose metabolism was then tested. According to the ROC curve analysis, HbA_{1c} was suitable for discrimination between normal and abnormal metabolism in women with PCOS, although it was not in controls (Fig. 2). However, when we determined a cutoff as 5.35%, for HbA_{1c} with highest specificity and sensitivity, 14 (34.1%) of 41 patients with abnormal glucose metabolism diagnosed by OGTT still remain below the cutoff level. Then, we applied the same cutoff to the whole population, and we found that 16 of 51 patients with abnormal glucose metabolism diagnosed by OGTT remain below this cutoff level. In comparison to the OGTT results, HbA_{1c} provided 68.6% sensitivity, 49% specificity and 17.7% positive and 90.6% negative predictive values, with a threshold value of 5.35 in abnormal glucose tolerance in the population. When we defined an abnormal OGTT as an outcome with IGT or T2DM, the sensitivity of HbA_{1c} ≥6.5% as a diagnostic marker decreased to 9%, and the specificity was 99% in women with PCOS.

Discussion

To date, this is the first controlled study of Turkish women with PCOS to estimate the prevalence of abnormalities of glucose metabolism (IGT, T2DM) and that assesses the ability of screening tests to predict these abnormalities within this population. Our data indicated that the prevalence rate of abnormal glucose tolerance in Turkish women with PCOS (IGT 14.3%; T2DM 2%) was significantly higher than that of the healthy controls (IGT 10.3%; T2DM 0%). This prevalence rate is similar to that reported from cohort of Mediterranean women with PCOS and was lower than in American and Chinese women (Legro *et al.*, 1999; Gambineri *et al.*, 2004; Chen *et al.*, 2006).

As well as having different exercising habits, the Mediterranean diet and varying genetic and personal factors might be reasons for the lower prevalence of glucose abnormalities in the Mediterranean and

Table III The age- and BMI-stratified prevalence of glucose intolerance in women with PCOS and controls.

	PCOS (n = 252)				Control (n = 117)			
	n	NGT (%)	IGT (%)	T2DM (%)	n	NGT (%)	IGT (%)	T2DM (%)
BMI (kg/m^2)								
<25	126	90.5 (114)	8.7 (11)	0.8 (1)	59	94.9 (56)	5.1 (3)	0
25–30	67	77.6 (52)	19.4 (13)	3 (2)	47	93.6 (44)	6.4 (3)	0
>30	59	76.3 (45)	20.3 (12)	3.4 (2)	11	63.6 (7)	36.4 (4)	0
Age (years)								
<25	145	89.7 (130)	9 (13)	1.3 (2)	62	95.2 (59)	4.8 (3)	0
25–30	67	82.0 (55)	14.9 (10)	2.9 (2)	25	88 (22)	12 (3)	0
31–35	27	55.5 (15)	40.7 (11)	3.7 (1)	22	90.9 (20)	9.1 (2)	0
36–40	12	83.3 (10)	16.6 (2)	0	7	71.4 (5)	28.6 (2)	0
>40	1	100 (1)	0	0	1	100 (1)	0	0

Number of patients are in parentheses, tested by stratified trend test.

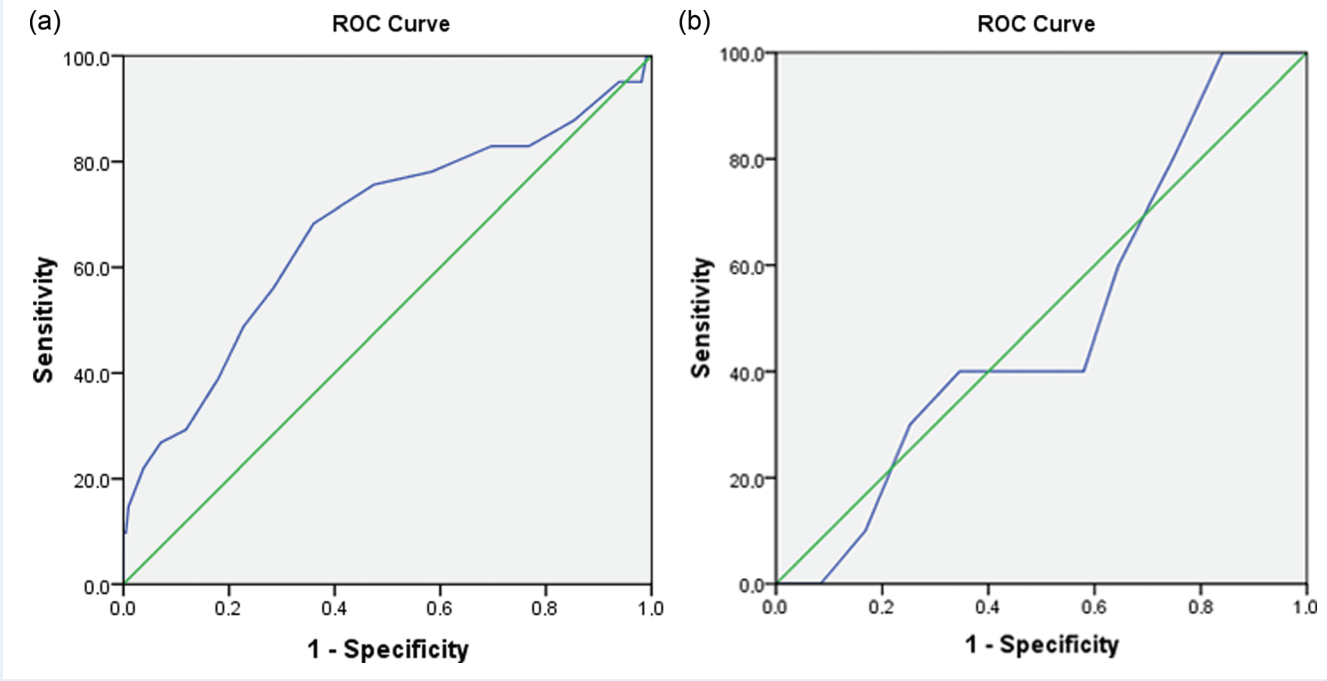

Figure 2 **a**. ROC curve for HbA_{1c} in patients with PCOS (AUC: 0.673; CI: 0.573–0.772; $P < 0.001$). **b**. ROC curve for HbA_{1c} in controls (AUC: 0.495; CI: 0.326–0.663; $P = 0.957$). *$P < 0.05$ is considered to be statistically significant. AUC, area under curve; CI = 95% CI.

the Turkish population (in this study) when compared with American and Asian populations (Abate and Chandalia, 2001).

In this study, patients with PCOS were heavier than the controls. However, they were comparable in terms of age. Even after adjustment for BMI, patients with PCOS still had elevated glucose parameters and a higher HOMA-IR index. Glucose tolerance has been associated with increasing BMI and age in most studies (Ehrmann *et al*., 1999; Legro *et al*., 1999). Likewise, in our study, there was an association between glucose abnormality and increasing age and BMI.

The increasing number of obesity cases is, in part, contributing to the increased prevalence of PCOS and diabetes throughout the world (Yildiz *et al*., 2008; ADA, 2009). Because diabetes is one of the main causes of death and disability, it is essential to screen women at high risk of T2DM such as women with obesity, prediabetes and/or IR, PCOS. A survey reported that not all women with PCOS were screened for diabetes at the first visit, and a large proportion are never rescreened. This situation has been accepted as a fact even by obstetrics and gynecology specialists and by

reproductive endocrinology and infertility (REI) sub-specialists who are interested in reproductive medicine (Abdel-Rahman *et al.*, 2012). The same survey showed that obstetricians, gynecologists and REI sub-specialists who care for women with PCOS currently use different approaches to screen for diabetes in women with PCOS (Abdel-Rahman *et al.*, 2012).

It was reported previously that most of the women with PCOS and glucose intolerance had normal fasting blood glucose (FBG), and this suggested that the OGTT test was the best screening measure for glucose intolerance and diabetes in women with PCOS (Lee *et al.*, 2009).

In 2010, HbA_{1c} was recommended by the ADA instead of FBG and the OGTT as the preferred diabetes screening and diagnostics test for the general population. The diagnosis for pre-diabetes and T2DM patients was an $HbA_{1c} > 5.6\%$ and $HbA_{1c} \geq 6.5\%$, respectively (ADA, 2010).

HbA_{1c} is favorable because it is a single blood test and fasting is not required. However, it has been perceived as a more expensive and imprecise test for women with PCOS, in part based on a small study published almost two decades ago (Holte *et al.*, 1994). When compared with OGTT, it is clear that HbA_{1c} is easier and more convenient, so the rate of periodic observance of women with PCOS in the future might improve. Finally, use of the HbA_{1c} test might change the recommendations about how to observe these high-risk women (Gillett, 2009). On the other hand, our data demonstrate that using HbA_{1c} we may not be able to detect 51.2% cases of abnormal glucose tolerance in our subjects with PCOS because only 20 out of 41 cases with IGT and T2DM had $HbA_{1c} > 5.6\%$. Beside these findings, 2 out of 5 subjects with T2DM displayed $HbA_{1c} < 6.5\%$, in which women with diabetes would remain undetected solely by HbA_{1c} testing. Hence, our current findings reveal that the OGTT is the best screening method for glucose intolerance, and diagnosis of diabetes and HbA_{1c} cannot be used reliably to predict IGT or T2DM, at least in Turkish women with PCOS. Our findings were also in accordance with a previous report which revealed that the clinical benefit of HbA_{1c} for diagnosing IGT and T2DM in PCOS in daily usage was low (Velling *et al.*, 2011), despite the ADA recommendation of HbA_{1c} evaluation in low-risk patients (ADA, 2010). When further analysis was conducted in higher risk group for impaired glucose metabolism according to the anthropometric characteristics, in the obese PCOS women, 29 of 126 patients had abnormal glucose tolerance during OGTT. Of 29 patients with IGT, 20 had HbA1c levels $> 5.6\%$, which increased the prevalence of abnormal glucose metabolism to 15.8% and suggested that HbA1c evaluation can be useful in a high-risk group of women with PCOS.

In our study, the ability of HbA_{1c} to distinguish women with PCOS who have normal metabolism from those with abnormal glucose metabolism was tested. When we selected the cutoff as 5.35%, for HbA_{1c} with the highest specificity and sensitivity, 14 of 52 patients with abnormal glucose metabolism who were diagnosed by the OGTT remained below the cutoff value. Thus, the only way to reliably detect abnormal glucose metabolism in Turkish women with PCOS appears to be using the OGTT.

A weakness of this study was that it did not include weight-matched healthy subjects and was limited to an unselected population of PCOS patients, mostly meeting all 3 criteria (204 out of 252) that may cause differences in prevalence of abnormal glucose metabolism between the groups. Therefore, more studies with age-matched and weight-matched subjects are needed to reproduce our results. Another potential weakness of our study was that the incidence of T2DM among the first-degree relatives and 2-h insulin levels could not be reported in our study population.

In conclusion, IGT was found significantly more often in women with PCOS in comparison with healthy controls. In addition to this finding, when compared with the OGTT, HbA_{1c} has some potential weakness for IGT and T2DM screening in women with PCOS. Therefore, diabetes screening guidelines should be reevaluated following long-term prospective studies according to different populations.

Authors' roles

C.C. is the principal investigator for this project. Designed, analyzed data, wrote and edited manuscript. All authors contributed significantly as same degree in data collection and the interpretation of findings.

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Conflict of interest

None declared.

References

Abate N, Chandalia M. Ethnicity and type 2 diabetes: focus on Asian Indians. *J Diabetes Complications* 2001;**15**:320–327.

Abdel-Rahman MY, Jackson LW, Rodewald KJ, Abdellah MA, Ismail SA, Hurd WW. Polycystic ovary syndrome and diabetes screening: a survey of gynecologists and reproductive endocrinologists. *Eur J Obstet Gynecol Reprod Biol* 2012;**162**:178–181.

ADA. Standards of medical care in diabetes–2009. *Diabetes Care* 2009; **32**:S13–S61.

ADA. Standards of medical care in diabetes–2010. *Diabetes Care* 2010; **33**:S11–S61.

ADA. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; **34**:S62–S69.

Chen X, Yang D, Li L, Feng S, Wang L. Abnormal glucose tolerance in Chinese women with polycystic ovary syndrome. *Hum Reprod* 2006; **21**:2027–2032.

Coskun A, Ercan O, Arikan DC, Ozer A, Kilinc M, Kiran G, Kostu B. Modified Ferriman-Gallwey hirsutism score and androgen levels in Turkish women. *Eur J Obstet Gynecol Reprod Biol* 2011;**154**:167–171.

DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;**14**:173–194.

Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997;**18**:774–800.

Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999;**22**:141–146.

Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L. Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 1989;**321**:337–343.

ESHRE/ASRM R. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41–47.

Gambineri A, Pelusi C, Manicardi E, Vicennati V, Cacciari M, Morselli-Labate AM, Pagotto U, Pasquali R. Glucose intolerance in a

large cohort of mediterranean women with polycystic ovary syndrome: phenotype and associated factors. *Diabetes* 2004;**53**:2353–2358.

Gillett MJ. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Clin Biochem Rev* 2009;**30**:197–200.

Glintborg D, Andersen M. An update on the pathogenesis, inflammation, and metabolism in hirsutism and polycystic ovary syndrome. *Gynecol Endocrinol* 2010;**26**:281–296.

Glintborg D, Henriksen JE, Andersen M, Hagen C, Hangaard J, Rasmussen PE, Schousboe K, Hermann AP. Prevalence of endocrine diseases and abnormal glucose tolerance tests in 340 Caucasian premenopausal women with hirsutism as the referral diagnosis. *Fertil Steril* 2004;**82**:1570–1579.

Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med* 1998;**49**:235–261.

Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20–74 yr. *Diabetes* 1987;**36**:523–534.

Holte J, Bergh T, Berne C, Berglund L, Lithell H. Enhanced early insulin response to glucose in relation to insulin resistance in women with polycystic ovary syndrome and normal glucose tolerance. *J Clin Endocrinol Metab* 1994;**78**:1052–1058.

King H, Rewers M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. *Diabetes Care* 1993;**16**:157–177.

Lee H, Oh JY, Sung YA, Chung H, Cho WY. The prevalence and risk factors for glucose intolerance in young Korean women with polycystic ovary syndrome. *Endocrine* 2009;**36**:326–332.

Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999;**84**:165–169.

Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *J Clin Endocrinol Metab* 1993;**329**:1988–1992.

Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;**28**:412–419.

Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome–a position statement of the Androgen Excess Society. *J Clin Endocrinol Metab* 2007;**92**:4546–4556.

Trakakis E, Basios G, Peppa M, Simeonidis G, Labos G, Creatsa M, Misailidou M, Boutati E, Vaggopoulos V, Panagopoulos P *et al.*. The prevalence of glucose metabolism abnormalities in Greek women with polycystic ovary syndrome. *Gynecol Endocrinol* 2012;**28**:867–870.

Velling ML, Mumm H, Andersen M, Glintborg D. Hemoglobin A1c as a tool for the diagnosis of type 2 diabetes in 208 premenopausal women with polycystic ovary syndrome. *Fertil Steril* 2011; **96**:1275–1280.

Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;**93**:162–168.