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Prevalence of Elevated Glycated Hemoglobin Concentrations in the Polycystic Ovary Syndrome: Anthropometrical and Metabolic Relationship in Amazonian Women

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Abstract

Background: To determine the prevalence of elevated glycated hemoglobin (HbA1c) and to examine its relationship with other carbohydrate metabolic parameter among Brazilian women with polycystic ovary syndrome (PCOS).

Methods: A cross-sectional study including 288 PCOS patients was conducted. Anthropometrical, clinical, biochemical and endocrine parameters were evaluated.

Results: The mean age was 26.92 ± 5.51 years. HbA1c mean concentration was 5.83±1.34%. In 38.54% of patients, HbA1c was ≥ 5.7%. HbA1c was positively correlated with body weight (r = 0.142, P = 0.017), body mass index (P = 0.000), waist:hip ratio (P = 0.000), fat mass (P = 0.000), conicity index (P = 0.000), triglyceride (P = 0.001), C-peptide (P = 0.000), total testosterone (P = 0.003), free testosterone (P = 0.000), free androgen index (P = 0.006) and fasting insulin (P = 0.025). Using the oral glucose tolerance test, HbA1c showed positive correlation with glucose concentrations at any point in time (P < 0.05).

Conclusions: HbA1c was elevated in nearly 40% of PCOS patients and it showed positive correlation with several anthropometric and metabolic factors and androgen levels. The current study provides further evidence that HbA1C is higher in PCOS patients and may have a potential role in the prediction of dysglycemic disease in these women.

Keywords: Glycated hemoglobin; Impaired glucose tolerance; Polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, affecting up to 21% of patients [1]; its prevalence in Brazilian women was not determined yet. Compared with healthy women, patients with PCOS are at a higher risk for coronary heart disease (OR = 1.2 - 12.9), cerebrovascular disease (OR = 2.8 - 3.4), hypertension (OR = 1.4), dyslipidemia (OR = 2.9 - 3.2), myocardial infarction (OR = 2.6 - 4.2), impaired glucose tolerance (IGT) (OR = 2.5), metabolic syndrome (OR = 2.1) and central obesity (OR = 1.9 - 2.4) [2-5]. The risk for type 2 diabetes mellitus (T2DM) is also two- to four-fold higher in patients with PCOS (OR = 2.2 - 3.6). The current screening recommendations for T2DM in patients with PCOS include the measurement of fasting plasma glucose (FPG) and the use of an oral glucose tolerance test (oGTT, 75 g oral dextrose) in cases of obesity, advanced age, personal history of gestacional diabetes or family history of T2DM [6]. The measurement of glycated hemoglobin (HbA1c) is also commonly used to identify non-PCOS individuals at risk of IGT, prediabetes or T2DM [7]. As the use of HbA1c does not require fasting and provides a time-averaged estimate of blood glucose over the preceding 3 - 12 weeks [8], it may be a better indicator of overall glycemia than a glucose concentration at a single point in time [9, 10].

Elevated HbA1c concentrations have been associated with other risk factors for cardiovascular disease (CVD) and the presence of metabolic syndrome in several other non-PCOS clinical conditions and populations [8]. It seems that in patients with or without PCOS, a 1% increase in the absolute HbA1c concentration is associated with a 10-20% increase in CVD risk [8, 11]. The prevalence of elevated HbA1c in women with PCOS has not yet been established worldwide. Previous studies have reported that elevated HbA1c occurs in 10% of PCOS patients in Austria and Turkey [10, 12] and 31% of Korean patients [13]. Given the potential relationships between HbA1c and health-related outcomes in PCOS patients, and the fact that a very few studies have reported on the prevalence and of abnormal HbA1c concentrations in patients with PCOS, the current study aimed to determined the

prevalence of elevated HbA1c concentrations in knowledge Brazilian patients with this clinical condition.

Materials and Methods

The sample consisted of PCOS patients in whom HbA1c levels were measured attending either the Endocrinology or the Reproductive Units at the Julio Muller University Hospital and Tropical Institute of Reproductive and Menopause in Cuiaba, Brazil, until July 2013. The sample size was estimated using an imprecision (i) value of 5%, a mean expected effect of 14% (based on scarce previous studies reporting on the proportion of PCOS patients with an elevated HbA1c) and an alpha level of 5% [10, 14, 15]. Written informed consent was obtained from each patient, as approved by the local Committee for Ethics in Research. Patients were excluded for any of the following reasons: use of sex steroids or insulin-sensitizing drugs over the previous 6 months; thyroxin-stimulating hormone (TSH) concentration ≥ 4.2 µUI/mL and prolactin (PRL) concentration > 25 ng/mL (1,086 nmol/L). Non-classic 21-hydroxylase, 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase (3β-HSD) were excluded as published elsewhere [15].

PCOS diagnosis was performed according to the National Institutes of Health and Rotterdam criteria [1, 15]. Clinical hyperandrogenism was defined as a dichotomous variable using the presence or not of hirsutism in the following body areas: upper lip, chin, chest, upper or lower back, upper or lower abdomen, upper arms and thighs [16]. The free androgen index (FAI) was estimated as total testosterone (nmol/L)/sex hormone-binding globulin (SHBG; nmol/L) × 100. The free estrogen index (FEI) was calculated as follows: 100 × estradiol (nmol/L)/272.1 × SHBG nmol/L) [17]. Ovary transvaginal ultrasound examination was performed using a Voluson machine (Voluson®E8, GE Health Care, England) and PCO morphology defined as previous recommendation [18].

Anthropometric measures

Subjects were weighed on an electronic scale, and height was measured using a Harpender stadiometer (Holtain Limited, Crymych, Dyfed, UK). The waist circumference (WC) was measured at the midway point between the lower rib margin and the iliac crest, and the hip was measured at the widest circumference (location of the greater trochanters). Body mass index (BMI) was calculated as body weight (kg/height $(m)^2$). Obesity was defined as BMI ≥ 30 (kg/m^2) [4]. Lean body mass (LBM) was calculated using the James equation: (1.07 × weight (kg)) - 148 × $(weight^2/(100 \times height\ (m))^2$ [19]. Fat mass (FM) was calculated as: body weight - LBM. Abdominal adiposity was estimated using the conicity index (C index): WC (m)/(0.109 × square root of body weight (kg)/height (m)) [20].

Biochemical analysis

Triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) were measured after a 12-h overnight fast using an enzymatic assay (Wiener Laboratories, Rosario, Argentina). Low-density lipoprotein cholesterol (LDL-C) was calculated as TC - (HDL-C + TG/5) [21]. On a different day, blood was collected for the biochemical and endocrine measurements, followed by a 3-h oGTT and samples obtained basally and at 30, 60, 90, 120 and 180 min after dextrose ingest. Blood samples were drawn between days 3 and 5 in patients with oligomenorrhea or, in amenorrheic patients, in a random day, including progesterone measurement to certify that the blood was collected in follicular phase. The plasma glucose concentration was analyzed using the glucose oxidase technique (Beckman Glucose Analyses, Fullerton, CA, USA). HbA1c was measured using a turbidimetric assay (Wiener Laboratories, Rosario, Argentina). The criteria of elevated HbA1c concentration (≥ 5.7%) with a threshold of ≥ 6.5% to diagnose T2DM were used as recommended by the American Diabetes Association [7]. IGT or prediabetes were defined by a single abnormal parameter as follows: FPG between 100 mg/dL (5.5 mmol/L) and 126 mg/dL (6.99 mmol/L); 2-h oGTT glucose value between 140 mg/dL (7.8 nmol/L) and 199 mg/dL (11.0 nmol/L) [7]. Insulin resistance was defined using fasting insulin levels > 12.2 µU/mL (84.7 pmol/L) [22]; and/or homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 2.8 [23]. The homeostatic model for insulin resistance and tissue sensitivity to insulin (HOMA-IR) was calculated using a free online program [23]: (glucose (nmol/L) × insulin (µU/mL))/22.5.

Hormone assays

Hormones were measured as described elsewhere [18]. In short, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH, estradiol, PRL, SHBG and total testosterone levels were measured by electrochemiluminescence assays (Elecsys 2010, Roche Diagnostics GMBH, Mannhein, German). Free testosterone and insulin were measured using a chemiluminescence assay (Siemens Medical Solution Diagnostics, CA, USA) with sensitivity and intra- and inter-assay coefficients of variation as the following: 0.002 pmol/L, 7.0-8.4% for free testosterone and 2 µUI/mL, 4.9-6.4% for insulin.

Statistical analyses

Data were examined for Gaussian distribution using the Kolmogorov-Smirnov-Lilliefors goodness of fit test, and, where necessary, data were log transformed prior to analysis and

Table 1. Sociodemographic and Clinical Characteristics of Brazilian Polycystic Ovary Syndrome Patients

Parameters	N (288)	%
Age (years)		
14 - 19	28	9.72
20 - 24	64	22.22
25 -29	100	34.72
30 - 34	76	26.38
35 - 39	17	5.90
≥ 40	3	1.04
Social habits		
Etilism	81	28.12
Smoking	18	6.25
None	189	65.62
Physical activity		
Walking	41	14.23
Biking	1	0.34
Other	4	1.39
None	230	79.87
Not recorded	12	4.17
Clinical features		
Infertility	148	51.38
Amenorrhea	57	19.79
Oligomenorrhea	166	57.63
Polymenorrhea	16	5.55
Acne	126	43.75
Hirsutism	149	51.73
Acanthosis nigricans	67	23.26
Striaes	17	5.90
Ultrasound features		
Normal ovary	56	19.44
Polycystic ovary	232	80.56

*One or more clinical feature per patient.

Table 2. Distribution of Normal and Abnormal Anthropometrical Characteristics of Polycystic Ovary Syndrome Patients

Variable	n/N	%	Test Z	P*
BMI (kg/m^2)				
< 30	147/264	56.68		
≥ 30	117/264	44.32	2.611	0.009
Fat mass (%)				
< 32	146/265	55.10		
> 32	119/265	44.90	2.345	0.018
Waist (cm)				
< 88	129/254	50.79		
≥ 88	125/254	49.21	0.354	0.726
W:H ratio				
< 0.80	191/252	75.80		
≥ 0.80	61/252	24.20	11.581	0.000
Conicity index				
< 1.25	112/150	74.67		
≥ 1.25	38/150	25.33	8.544	0.000

*P, two-tailed Z proportion test.

subsequently retransformed into the original units for reporting. Anthropometrical, biochemical and endocrine data, presented as mean and standard deviation (SD), were analyzed using the Welch test because equality of variance was not tested. The Z test was used to compare HbA1c status in obese and non-obese PCOS patients. The prevalence rate with 95% confidence intervals (95% CI) was used to compare HbA1c status and other markers of glucose metabolism. The relationships between the HbA1c concentration and anthropometrical, endocrine and metabolic variables were examined using Pearson's correlation coefficient. Stratified analyses for confounding variables were performed using the Mantel-Haenzel χ^2 test. All analyses were performed using SPSS for Windows, version 18 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P \leq 0.05$.

Results

Of the 288 PCOS patients enrolled, 197 (68.4%) were Caucasian, 41 (14.2%) were African descendants, 41 (14.2%) were of "other" races and nine (3.1%) did not declare their ethnicity. The mean age was 26.92 ± 5.51 years. Sociodemographic and clinical characteristics are shown in Table 1. The BMI was 29.94 ± 7.0 kg/m^2, FM 30.3 ± 12.54 kg, waist circumference 88 ± 16.31 cm, waist:hip ratio 0.81 ± 0.08 and conicity index 1.16 ± 0.11. The stratified anthropometric features are depicted in Table 2. The overall mean HbA1c concentration was 5.83±1.34%. HbA1c values ≥ 5.7% were present in 111/288 (38.54%), in which 102 (35.4%) had HbA1c between 5.7% and 6.4% and nine (3.12%) had HbA1c ≥ 6.5%. In 177/288 (61.46%), the HbA1c were < 5.7%. After stratification, the associations between HbA1c and other glucose metabolic parameters are shown in Table 3. Overall FPG levels presented mean of 5.11 ± 0.78 mmol/L; its levels were < 5.55 mmol/L in 234/282 (82.9%) patients, between 5.55 mmol/L and 6.99 mmol/L in 39/282 (13.8%) and > 6.99 mmol/L in 9/282 (3.19%) patients. Fasting insulin presented mean of 87.70 ± 2.69 and the levels were > 85 nmol/L in 142/265 (53.5%) patients. The mean HOMA-IR was 1.93

Table 3. Analysis of the Association of Glycated Hemoglobin Concentrations With Other Carbohydrate Metabolism Parameters in Polycystic Ovary Syndrome

Variable	HbA1c		Total (n)	PR* (95% CI)	P**
	≥ 5.7 (n)	< 5.7 (n)			
Fasting glucose (nmol/L)					
≥ 5.55	35	13	48		
< 5.55	76	158	234	2.24 (1.68 - 2.76)	0.000
Total	111	171	282		
Fasting insulin (nmol/L)					
≥ 85	69	73	142		
< 85	37	86	123	1.61 (1.16 - 2.27)	0.003
Total	106	159	265		
Pep-C (nmol/L)					
≥ 1.17	26	17	43		
< 1.17	60	112	172	1.73 (1.19 - 2.32)	0.003
Total	86	129	215		
HOMA-IR					
≥ 2.8	31	26	57		
< 2.8	75	127	202	1.46(1.04 - 1.95)	0.022
Total	106	153	259		
HOMA % β					
≥ 155	41	52	93		
< 155	65	101	166	1.12(0.81 - 1.53)	0.510
Total	106	153	259		

*PR: prevalence ratio. **P, two-tailed Z proportion test.

± 1.21 and the levels were > 2.8% in 57/259 (22.0%) patients, the mean HOMA-β was 128.73 ± 1.52 and < 155% in 166/259 (64.1%) and the C-peptide concentrations were 0.82 ± 0.39 nmol/L and > 1.17 nmol/L in 43/215 (20%) patients.

HbA1c concentrations were positively associated with several anthropometrical (body weight, r = 0.142, P = 0.017; BMI, r = 0.265, P = 0.000; waist:hip, r = 0.271, P = 0.000; FM, r = 0.215, P = 0.000); endocrine (C-peptide, r = 0.238, P = 0.000; total T, r = 0.179, P = 0.003; free testosterone, r = 0.447, P = 0.000; FAI, r = 0.1711, P = 0.018; FEI, r = 0.167, P = 0.055); and metabolic (TG, r = 0.207, P = 0.001) variables. HbA1c was correlated with glucose in the fasting state and any time point after the glucose load (Fig. 1, panel A) but was not correlated with insulin at any of the oGTT time points (Fig. 1, panel B). The distribution of HbA1c levels according the age and BMI is presented in Table 4.

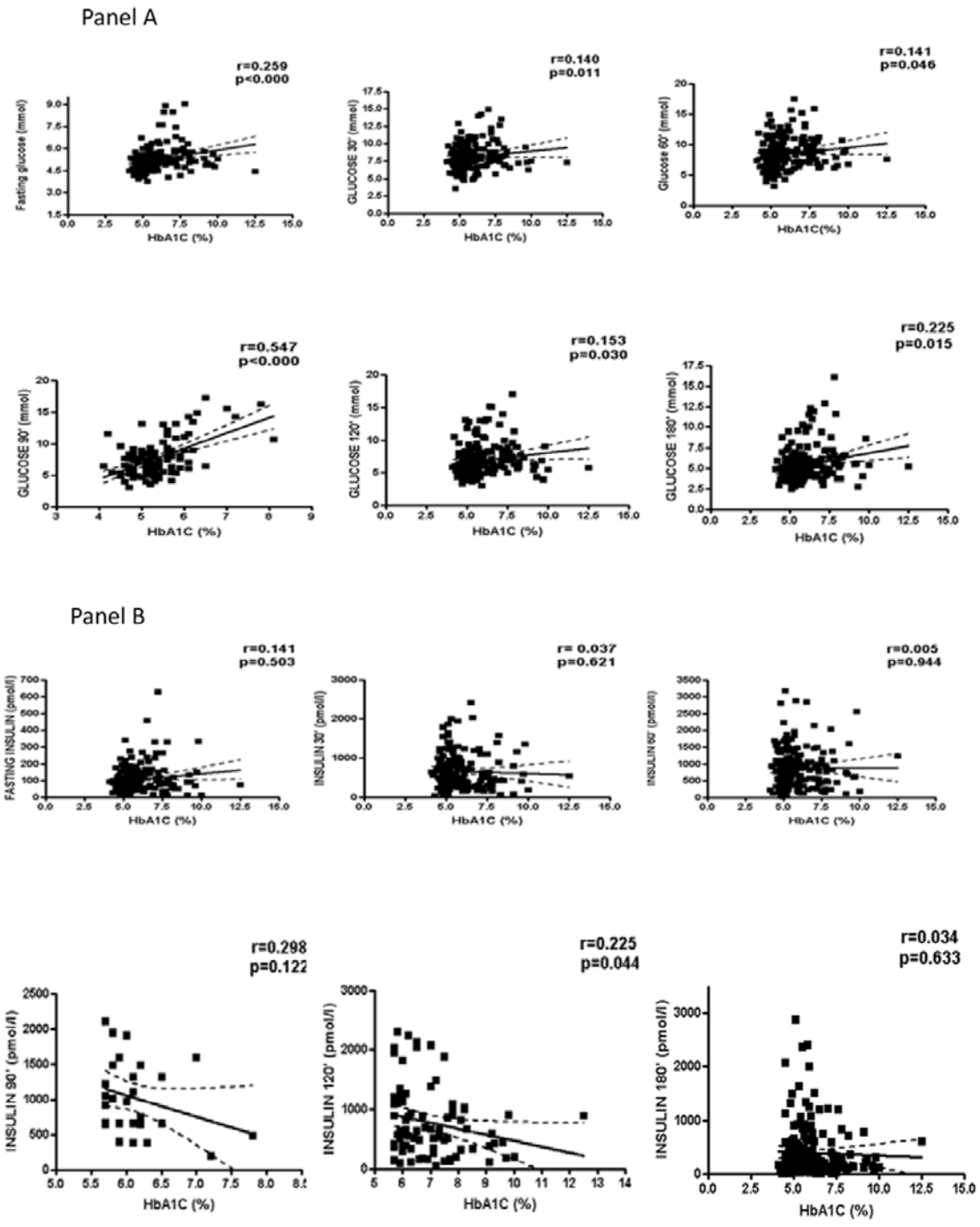

Figure 1. Correlation of glycated hemoglobin (HbA1c) with glucose and insulin.

Discussion

Elevated HbA1c concentrations were found in 38% of PCOS patients, and, after stratification, its levels were not significantly influenced by age or BMI. HbA1c was correlated with a number of variables that are associated with the metabolic syndrome, including fasting glucose and glucose response after oGTT at any point in time. The proportion of PCOS patients with elevated HbA1c levels in the current study was higher than those found in previous reports in other populations. In Korean PCOS patients, also using HbA1c $\geq$ 5.7% to discriminate normal and high levels, 31% of the patients had elevated HbA1c, which was significantly higher than the

Table 4. Stratified Analysis of Glycated Hemoglobin Status According to Age and Body Mass Index in Polycystic Ovary Syndrome

Age (years)	BMI ≥ 30 (n)	BMI < 30 (n)	Total (n)	χ^2_{mh}	P
HbA1c < 5.7%					
< 30	18	31	49		
≥ 30	35	78	113	0.512	0.474
Total	53	109	162		
HbA1c ≥ 5.7%					
< 30	31	10	41		
≥ 30	33	28	61	4.806	0.028
Total	64	38	102		
Total					
< 30	49	41	90		
≥ 30	68	106	174	5.653	0.017
Total	117	147	264		

χ^2_{mh}: Mantel-Haenszel qui-square.

results observed in healthy controls (6.6%) [11]. Meanwhile, only 7.6% of Turkish PCOS patients had HbA1c > 5.6% [12], and 8.6% of an older group of Danish PCOS patients presented HbA1c ≥ 6% [24]. Interestingly, 20% of the non-obese patients with PCOS had elevated HbA1c levels in the Korean study, compared to only 6% of the obese PCOS patients [11]. In contrast, the current study found that the levels were twofold higher in obese than non-obese PCOS patients. This difference was no longer present when the sample was stratified according to the HbA1c levels. At this time, it is difficult to determine if the differences between the Korean, Danish, Turkish and Brazilian patients are due to ethnicity or other sample characteristics.

Elevated HbA1c levels have been associated with a more adverse metabolic profile, in PCOS patients in the current study and in the study conducted in Denmark [24]. Although no relationships between HbA1c and insulin either in fasting or after oGTT in the current study was found, such relationships have been reported in the Danish population of PCOS patients [24]. Certainly, more studies are required to confirm the clinical relevance of these data. Significantly higher FAI and free testosterone levels have been reported in women with PCOS and T2DM compared to PCOS women with prediabetes or normal glucose tolerance [10], and significant correlations between HbA1c and FAI and free testosterone have been reported in women with reduced fertility [25]. The study conducted in Danish PCOS patients reported conflicting findings; total testosterone and FAI were not positively correlated with HbA1c levels. The authors suggested that the combination of high HbA1c and low SHBG levels could be better as markers for CVD risk in PCOS patients, based on the presence of inverse relationships between SHBG and HbA1c levels in their sample. Therefore, the influence of age, BMI and endocrinological features on HbA1c concentrations should be examined in future studies and in different populations.

Increased HbA1c levels could potentially be used as a marker of cardiovascular risk in individuals without diabetes [26]. The significant correlations between HbA1c levels and several established anthropometrical predictors of CVD risk in the present study are in agreement with the reported cardiovascular risk in other non-PCOS populations with central obesity, IFG, increased carotid to femoral pulse wave velocity, or low fecund ability rate [5, 27-30]. Within the PCOS

population, a recent study reported associations between elevated HbA1c concentrations, larger waist circumferences and higher BMIs in an older group of PCOS patients [24].

One possible limitation of the current study is that social habits that may also affect glycemic status, such as smoking, alcohol use and physical activity, were not completely examined. Second, the study enrolled women who were attending tertiary institutions, and this may have resulted in selection bias and limited the generalizability to the general community. Finally, most of the patients included in the present study met all three Rotterdam criteria for PCOS diagnosis, and this may explain the high prevalence of elevated HbA1c in this sample. In conclusion, HbA1c was elevated in at least one-third of PCOS patients and was positively associated with weight, BMI, waist:hip ratio, FM and androgen levels in the current study. Future clinical studies should be conducted to better understand the potential role of HbA1c as a dysmetabolic variable and a marker of elevated CVD risk in PCOS patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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