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Original

Determination of fasting plasma glucose cut-off valuefor the identification of abnormal carbohydratetolerance in women with polycystic ovarian syndrome.

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Abstract

Objective: To determine the predictive value of fasting glucose to identify abnormal carbohydrate tolerance in patients with polycystic ovary syndrome.

Materials and methods: 100 women diagnosed with polycystic ovary syndrome underwent a tolerance test toa 75 gdose of glucose.

Results: Sensitivity for a threshold value of 101 mg/dl was 41.7% (95% C.I.: 23% - 63%) and specificity 92.1% (95% C.I.: 83% - 97%); with a positive predictive value of 62.5% and a negative predictive value of 83.3%. The optimum cut-off value was 93 mg/dL, with a sensitivity of 75% (95% C.I.: 53% - 89%) and a specificity of 73.7% (95% C.I.: 62% - 83%). The optimum fasting plasma glucose cut-off value for intolerance in women with PCOS was 93md/dL.

Conclusions: The current recommendations for diagnosing abnormal carbohydrate tolerance in women with polycystic ovary syndrome are not appropriate.

Keywords: abnormal carbohydrate tolerance, polycystic ovary syndrome, screening.

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Abbreviations: ADA, American Diabetes Association; DM, Diabetes Mellitus; G2–HAL, Glucose two hours afterload; CIT, Carbohydrate intolerance; SM, Metabolic Syndrome; PCOS, Polycystic Ovary Syndrome.
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Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in womenin reproductive age, and affects approximate 5-20% of this population. Although usually are the manifestations of chronic anovulation and hyperandrogenism which make this patients to consult medical advice, the insulin resistance and the hyperinsulinemia are also common in them and have also an important etiologic role.

The prevalence of Carbohydrate Intolerance (CIT) in female with PCOS, Reaches up to 40%; five times the number expected in healthy women between 20-44 years all in the USA.With respect of Diabetes Mellitus type 2 (DM), its prevalence ranges between 8-12% in these population. These variations could be attributed to population differences corresponding to the patient´s origins, among others. In the same way, the association between CIT and metabolic Syndrome (MS), is clearly established.

The American Diabetes Association (ADA) indicates the screening guidelines for the CIT in dose persons with any risk factors to have DM type 2, like women with PCOS. It is proposed only, to realize glycemic testing two hours afterload 75g of glucose (G2–HAL), to identify CIT

in women with PCOS, when fasting glycemia is higher than 101 mg/dl (5,6 mmol/L). Similarly, The Canadian Diabetes Association recommends the use of these test when the fasting glucose is higher than 103 mg/dL (5,7mmol/L). However, even the evidence shows that measurement of fasting glucose is unreliable predictor to identify CIT in PCOS women, the Canadian and American Guidelines based on this screening test and therefore this test is performed in the same way here in Costa Rica.

The objective of this research was to determinate the predictive value of the thresholdcut number of 101 mg/dL (5,6 mmol/L) of fasting glycemia for CIT patients with PCOS and stabilized an optimal screening level for fasting glucose in this population.

Materials and methods

This prospective descriptive study, took as population patients with PCOS, captured in the Endocrine Gynecology consultation in the Women Hospital "Dr. Adolfo Carit Eva" (HOMACE) in the period of February 1st, 2009 to May 31st, 2010. The research protocol was approved by the Bioethics Local Committee of the HOMACE.

Inclusion criteria were based in the PCOS diagnose effectuated according under the guidelines established in 2003, by the European Reproductive and Embryology Society in Rotterdam, also called Rotterdam Criteria 1. Olygo or Anovulation, 2.Clinical and biochemical signs of hyperaldoteronism, 3. Polycystic Ovaries by pelvic Ultrasound. Of 109 women with the diagnosis of PCOS, nine met any of the exclusion criteria, adolescents with less than three years of filing menarche, women over 40 years old with menstrual cycle alterations, personal history of suprarenal Hyperplasia (no classical congenital), Hyperprolactinemiaor Hypothyroidism, secondary causes of hyperandrogenism (Cushing Syndrome o Androgen-Secreting tumors), and the use of oral contraceptives, sex hormones or any medication that affects the metabolism of glucose in the three months prior recruitment.

The CIT and DM diagnosis was determined according to ADA guidelines, which defined as glycemic values between 140-199 mg/dl in a G2–HAL with 75g of glucose, and ≥ 200 mg/dL respectively. For all the participants blood samples were processed in la HOMACE Clinical Laboratory, in order to obtain plasmatic levels of fasting glucose and 2 hour postprandial glucose, glycosy lated hemoglobin A1c, fasting insulinemia, total cholesterol, high density lipoproteins (HDL), Low density lipoproteins (LDL), Triglycerides, free testosterone and total, dehidroepiandrostenedione sulfate (DHEAS), follicle stimulating hormone (FSH), Luteinizing hormone (LH), prolactin (PRL), thyroid stimulating Hormone (TSH) and thyroxin (T4). The blood chemistry (including lipids and glycemic) was processed with OLYMPUS AU400® equipment. The G2-HAL with 75g of glucose used 40% of dextrose, where 187.5 ml equivalent to 75g of anhydride dextrose, produces by Chemical Reactive Laboratory of the CCSS. The calculation of glycosylated hemoglobin was performed using BIORAD D10® unit, according to the chromatographic principle of high performance. The measurement of the hormonal tests used INMULITE 1000®, which underlines said immunological determination, by a chemiluminescent reaction.

We measurement and weighted each participant in the nursing cubicle on the HOMACE outpatient. Subsequently, as part of the physical medical exam, the specialist assistant of the Endocrinology Gynecology consult, had measurement the abdominal circumference (AC) with a metric standard tape of 1.50 m long, and took blood pressure, sitting, with the sphygmomanometer in the right arm.

The statistical analysis was realized with Stata 10.0 software. The variables were compared by means of estimation of the t student test for quantities variables and the homologue Chi square for qualities variables; was defined statically significant, a critical point of 0,05 ($p \leq 0,05$). The specificity, sensibility and the positive and negative predictive values were generated with a data or threshold number of 101 mg/dl. A ROC ("receiver operating characteristic") curve was elaborated to define the most adequate threshold of fasting glucose, to identify abnormal tolerance of glucose.

Results

The clinical and laboratory characteristics of the female participants are summarized in Table 1. In 24 of 100 women (24%), CIT was identified. Of these women, five showed enough alterations to realized DM type 2 diagnoses; two presented levels between 132 mg/dL to 147 mg/dL for fasting glycemia and postprandial between 202 mg/dL to 207 mg/dL, respectively. Other three women had showed fasting glycemic levels between normal limits, but G2-HAL with 75g of glucose higher or above 200 mg/dL(200 mg/dl, 203 mg/dl and 257 mg/dl, respectively). Sixteen of the 24 patients with CIT, meet the diagnosis criteria of MS, according to WHO (1999); corresponding a 16,0% of women with PCOS included in this research.

The mean systolic and diastolic pressure was 126,8 mmHg and 82,6 mmHg, respectively, for the same group, a small increase (Table 1) compared with patients without abnormalities in tolerance. Furthermore, the Hemoglobin Aic (means) and fasting insulinemia concentrations, were higher in CIT women, 5,2% vs 6,3% and 12,2%µUI/mlvs26,6 µUI/ml (normal values 5-15 µUI/ml) respectively.

Table 1. Clinical and Laboratory characteristics of women with Polycystic Ovary Syndrome, in general form and according to glucose tolerance

	Normal Glucose Tolerance		Abnormal Glucose Tolerance		Patient total		
Characteristic	**Results**	**Number of patients**	**Results**	**Number of patients**	**Results**	**Number of patients**	**p Value**
Age, media, years (SD)	25.2(5.2)	76	29.7(6.5)	24	26.3(5.9)	100	<0.001
Familiar History (+) DM type 2, no. (%)	54.0	41	37.5	9	50.0	50	0.16
Body mass Index, media, kg/m2 (SD)	32.2(6.8)	76	35.9(6.8)	24	33.1(6.9)	100	0.02
Blood pressure, media, mmHg (SD)							
BP Systolic	117.7(13.5)	76	126.8(20.2)	24	119.9(15.8)	100	0.01
BP Diastolic	77.5(9.7)	76	82.6(10.2)	24	78.7(10.0)	100	0.03
Glycemic control, media, mg/dL (SD)							
Fasting	88.4(7.8)	76	100.8(15.6)	24	91.3(11.5)	100	<0.001
G2-HALwith 75 g of glucose	102.0(17.2)	76	170.6(28.2)	24	118.5(35.7)	100	<0.001
Hemoglobin A1C, media, % (SD)	5.2(0.4)	76	6.3(2.8)	24	5.4(1.5)	100	<0.001
FastingInsulinemia, media, µUI/mL (SD)	12.2(7-8)	76	26.6(20.6)	24	15.7(13.5)	100	<0.001
Lypid control, media, mg/dL (SD)							
Cholesterol							
HDL	40.9(8.7)	76	38.3(12.2)	24	40.2(9.7)	100	0.26
LDL	108.1(24.2)	76	114.8(31.9)	24	109.7(26.2)	100	0.27
Triglycerides	167.4(180.5)	76	223.2(187.7)	24	180.8(182.8)	100	0.19
Androgens							
Testosterone, media, ng/dL (SD)12	38.5(29.4)	42	25.4(23.9)	12	35.6(28.6)	54	0.16
Free Testosterone, media, ng/dL (SD)	3.2(9.9)	35	2.0(1.8)	12	2.9(8.6)	47	0.66
DHEASO4, media, µg/mL (SD)	154.9(79.1)	76	162.8(91.7)	24	156.8(81.9)	100	0.68
Thyroid function							
Free T_4, media, µUI/mL (SD)	1.2(0.2)	76	1.2(0.2)	24	1.2(0.2)	100	0.96
TSH, media, ng/dL (SD)	2.0(0.8)	76	2.1(0.8)	24	2.0(0.8)	100	0.75

SD: Standard deviation. Source: Investigation Unit. Women´s Hospital Dr. Adolfo Carit Eva, 2010

The comparison of the other characteristic showed significant differences between the groups of normal and abnormal tolerance for all the measurements; except for the presence of family history of DM, Lipids levels, androgens and thyroid function(p> 0,05; Table 1).

Determining the optimal threshold cutoff number of fasting glucose for the CIT screening in women with PCOS, was 93 mg/dl, with sensitivity of 75,0% (IC 95%: 53% - 89%) and specificity of 73,7%,(IC 95%: 62% - 83%), as shown in Figure 1. It was exposed that a cut threshold fasting glucose of 101mg/dl had a sensibility of 41,7%, (IC 95%:23% - 63%) and a specificity of92,1%, (IC 95%: 83% - 97%), with a positive and negative predictive value of 83,3% (IC 95%:73% - 90%) and 62,5%, (IC 95%: 36% - 84%), respectively. Table 2 summarizes the others sensitivity and specificity values, according to the cut threshold fasting glycemia.

Discussion

The proportion of women with PCOS and abnormal tolerance of carbohydrates was 24% (n: 24), within the expected rate, according to previously reports. This metabolic alteration occurred in an early age in the study (29,7 years

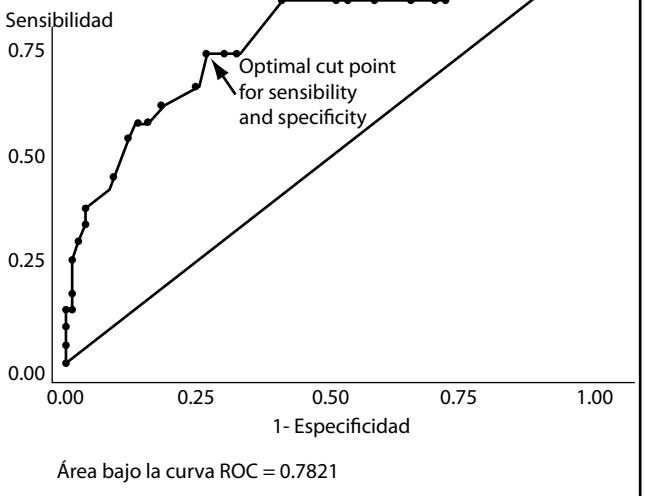

Figure 1. ROC Curve of fasting glycemia and abnormal glycemic tolerance association. The optimal threshold cutoff value of fasting glycemia (the graphic point [on the chart] closest to the left superior corner) was 93 mg/dl (sensibility of 75% and specificity of 73,7%).
Source: Investigation Unit. Women´s Hospital. Dr. Adolfo Carit Eva, 2010

Table 2. Sensibility and Specificity variability, as the threshold cut of fasting glucose, according glucose tolerance in PCOS patients

Cut off threshold of fasting glucose (mg/dl)	Sensibility (%)	Specificity (%)
≥ 93	75,0	73,7
≥ 94	66,7	75,0
≥ 95	62,5	81,6
≥ 96	58,3	84,2
≥ 98	58,3	86,8
≥ 99	54,2	88,2
≥ 100	45,8	90,8
≥ 101	41,7	92,1
≥ 102	37,5	96,1
≥ 103	33,3	96,1

Source: Investigation Unit. Women´s Hospital Dr. Adolfo Carit Eva, 2010

old), joining others publications that show that metabolic abnormalities begin at early ages in females with PCOS. 14 patients of the 24 diagnosed with CIT, presented fasting glycemic levels below the cutoff number proposed by the ADA of 101 mg/dl. Using this cutoff threshold number value, would not be diagnosed the glucose intolerance in 58,3% of women who had it, of the absence of the G2-HAL with 75g of glucose; this due to the low sensibility of this cutoff threshold fasting glucose in the sample (41.7%).

Consider the fact is very important, because it warns about the possibility of not identifying PCOS patients and carriers with CIT when they get a fasting glycemia within normal limits, because an early tolerance diagnosis offers the possibility to take actions to prevent development of DM type 2.

Furthermore, there was a clear increase of glycosylated hemoglobin levels, and specially fasting insulinemia, statistically significant in the glucose intolerance group, adding the evidence that shows that PCOS patients present with a steady state of insulin resistant. These findings, together with the significant differences in BMI and tensional numbers for women with CIT and PCOS, reiterate to both pathologies as predisposing to suffer a higher risk of cardiovascular disease.

Regarding independent predictive parameters for carbohydrates intolerance in women with PCOS, according to the research results, the family history of DM should not be consider predictive factors, because not reflect any relationship between their presence and CIT in women with PCOS.

Furthermore, the ROC Curve identified a number of 93 mg/dl as optimum cutoff threshold with a sensibility of 75% and specificity 73,7%. This sensibility number falls below the ideal 80% for a screening test. Furthermore, using this cut for realize the G2-HAL in women with PCOS, still yields an unacceptable 25% of intolerant women not diagnosed. Also, to reach the 80% sensibility, would have to accept a threshold cut of fasting glycemia of 90mg/dl, generating the possibility of raise the positive false percentage, and unnecessary waste of recourses.

In conclusion, just as has been demonstrated in several publications with another type of populations, the fasting glycemia is not an important predictor factor for the carbohydrate intolerance identification in PCOSpopulation,what makes adequate contemplate benefit-cost of realize an G2-HAL to diagnose PCOS and then do it regularly, in order to prevent de development abnormal tolerance to carbohydrates or Diabetes type 2.

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