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Association between serum fructose level and insulin resistance in women with polycystic ovary syndrome: The effect of obesity

DOI: https://doi.org/10.32007/jfacmedbagdad.6421926.

Ameera H Jasim* **BSc, MSc**
Basil O Saleh** **PhD (clinical biochemistry)**
Afraa M Al-Naddawi*** **FIBoG, CABOG**

Abstract:

Background: Polycystic ovary syndrome (PCOS) women's most prevalent endocrinology condition is a mixture of environmentally and genetically adduced causing PCOS. The relationship between monosaccharide and PCOS is largely unknown.

Objective: This research was designed to investigate the relationship between blood levels of fructose, insulin resistance and androgen hormone in women with PCOS, and the effect of obesity on the obtained result, as well as studying the efficacy of serum fructose as a biomarker in the diagnosis of PCOS.

Cases and methods: This case-control research study was conducted at the Gynecology Clinic and Infertility Center, in Baghdad Teaching Hospital / Medical City between November 2021 to March 2022. It involved 120 women between the ages of 18-40 year. Fifty-nine women (cases) were newly diagnosed with PCOS by a gynecologist and 61 age and BMI matched healthy women (controls). PCOS women were subdivided according to their body mass index into four groups: lean, normal weight, overweight and obese. Investigations included serum measurements of fructose, luteinizing hormone (LH), follicular stimulating hormone (FSH), free testosterone, insulin, glucose, and calculated homeostasis model assessment- insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI).

Results: The mean ±SD values of serum fructose, glucose, insulin and HOMA-IR were significantly augmented in PCOS women as compared to controls ($p< 0.001$), while mean value of QUICKI was significantly decreased ($p<0.0001$). There was a significant positive correlation between BMI values and fructose levels in PCOS women. The result showed that serum fructose and free testosterone levels had the highest sensitivity and specificity in the differentiation between the PCOS group and the controls, with the area under curve values for free testosterone higher than area under curve values for fructose.

Conclusions: The fructose level can be used as an alternative biomarker for women with PCOS independent of insulin resistance. The majority of PCOS women are obese and overweight, and a minority are lean who are severely complicated by insulin resistance.

Keywords: PCOS, Fructose, HOMA-IR, free testosterone

JFac Med Baghdad 2022; Vol.64, No . 2
Received: June, 2022
Accepted: June, 2022
Published: July, 2022

Introduction:

Polycystic ovarian syndrome (PCOS) is a major cause of infertility in women (1). PCOS can have major repercussions, such as an increased chance of endometriosis and neoplasia (2). Insulin resistance (IR), metabolic disorders, and low-grade systemic inflammatory conditions are all additional symptoms of PCOS (3). Androgen exposure can impair hormones balance, causing Gonadotropin-releasing hormone (GnRH) pulse velocity to rise, altering the LH: FSH ratio and resulting in ovarian arrest and dysplasia (4). The role of IR and hyperinsulinemia in the development of PCOS is well recognized, and the molecular processes behind the androgen hypersecretion hallmark of PCOS are well understood as up to 70% of women with PCOS have insulin resistance (5). The many reasons are severely appertained to PCOS: Excessive embryonic androgen exposure, reactive oxygen species (ROSs), immunological, and endocrine disorders (6). Hyperandrogenism is the most important criterion in the diagnosis of PCOS development (7). Increased levels of insulin, an anabolic hormone, is adamant with insulin resistance and results in weight gain in turn, exacerbates this condition (8). A fallowing to adept, obesity combined with IR change the functionality of the hypothalamus and pituitary gland, resulting in increased production of androgen, which leads to PCOS (9). Fructose is a monosaccharide in the human diets that the body needs to metabolize. Monosaccharides are consumed in large amounts of

*Dept. of Biochemistry, College of Medicine, University of Baghdad, e-mail: amyrthatm545@gmail.com.
**Dept. of Biochemistry, College of Medicine, University of Baghdad, e-mail: basil_omsal@comed.uobaghdad.edu.iq.
***Dept. of Obstetrics and Gynecology, College of medicine, University of Baghdad, e-mail: afraamn@yahoo.com

additive sugars in the diets, nearly half of which is fructose. Sucrose transforms to fructose and glucose by acidic hydrolysis in the stomach, and cleavage of sucrase and isomaltase in the intestine (10). Some tissues, for example, the hepatic, gut, fat, kidneys, and muscle, can transfer and process fructose without the need of insulin. Because most ingested fructose converts to glucose, glucose and fructose have similar metabolic fate. (11). It is worth noting that prolonged dietary fructose consumption has been linked to a variety of PCOS-related metabolic disorders (12, 13). The goal of this research was to investigate the relationship between blood levels of fructose with insulin resistance and androgen hormone in women with newly diagnosed PCOS.

Cases and methods

This case–control study was conducted at the Department of Biochemistry, College of Medicine, and University of Baghdad. It involved 120 women between the ages of (18-40 year) who were randomly collected from the Gynecology Clinic and Infertility Center, Baghdad Teaching Hospital/ Medical City, during the period from November 2021 to March 2022. Fifty-nine of them were diagnosed by a consultant gynecologist to have PCOS on the Rotterdam criteria (14) when at least two of the following criteria were met: Oligo-ovulation and /or amenorrhea, clinical and /or biochemical hyperandrogenism and polycystic ovaries by Ultrasonography. Sixty-one apparently healthy women, age and BMI matched with PCOS women served as the control group. Patients were subdivided according to their BMI into four groups: Lean: BMI < 18.5 kg/m^2, normal weight: BMI 18.5-24.9 kg/m^2, over weight: BMI 25-29.9 kg/m^2, and obese: BMI ≥ 30 kg/m^2 (15). Body Mass Index was calculated by dividing weight in kilograms on height in square meters. The waist hip ratio (WHR) was measured, and the waist circumference (WC) was measured. Women with the history of tobacco smoking; hormonal medication, pregnancy, lactation, endocrine abnormalities, and any known neoplastic diseases were excluded from the present study. Venous blood sample were taken and left to clot for 15-30 minute, and then separated at 2500 rpm for 10 min to obtain serum which stored at – 20 ^{a} C till the day of measurements of mannose [by enzyme linked immunosorbent assay (ELISA) using the kit proved by MybioSource/USA (16), LH, FSH, free testosterone and insulin (by ELISA), fasting glucose measure by spectrophotometer. Also, HOMA-IR calculates to following equation:

HOMA-IR = (glucose (mg/dl) * insulin (µU/ml) / 405

Normal Range HOMA-IR< 2.6 (17).

Also, quantitative insulin sensitivity check index QUICKI calculate to following equation:

QUICKI =1 / log (fasting insulin µU/mL) + log(fasting glucose mg/dl

QUICKI index < 0.339 indicate insulin resistance (17).

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 25.0 software. Frequencies, percentages, means and standard deviations were used to describe data. The ANOVA was used to evaluate the differences in mean level of numeric data between more than two variables. Pearson correlation regression r was used to evaluate correlations between numeric data. Receiver operating characteristic (ROC) was used to evaluate test reliability. The significance levels was chosen at $p \leq 0.05$.

Results

The results revealed that obese women represented (47%) of the studied PCOS women, overweight (22%), normal BMI (25%) and lean women (5%). The WHR was over 0.8 in (62%) and below 0.8 in (38%) of the cases. The mean ±SD values of age, BMI, and WHR of PCOS among the cases did not differ substantially from those among the controls (Table 1).

Table 1: Mean ±SD values of age, BMI, and WHR of cases and controls

Parameter	PCOS Cases (n= 59)	Controls (n=61)	P-value
Age (year)	25.4 ± 5.41	26.0 ± 5.43	0.56
BMI (kg/m^2)	26.5 ± 4.4	25.3± 4.99	0.18
WHR	0.8± 0.09	0.8 ± 0.05	0.36

The mean ±SD values of serum fructose of PCOS cases was (20.42 ± 5.65), significantly higher than that of controls (8.02 ± 2.29), p<0.001. The mean ±SD values of fasting serum glucose, insulin, and HOMA-IR for the PCOS cases were considerably greater than those of controls, while the mean value of QUICKI was significantly lower (p<0.001), as shown in Table 2.

Table 2: Mean ±SD values of serum fructose, glucose, insulin, HOMA-IR, and QUICKI of PCOS cases and controls

Parameter	Cases (n=59)	Controls (n=61)	p- value
Fructose (ng/ml)	20.4 ± 5.65	8.0 ± 2.29	0.001
Glucose (mg/dl)	79.2± 11.07	73.4 ± 12.04	0.001
Insulin (mIu/ml)	34.7 ± 9.10	13.9 ± 2.68	0.001
HOMA-IR	6.8 ± 1.93	2.4 ± 0.48	0.001
QUICKI	0.3 ± 0.01	0.3 ± 0.01	0.001

The mean values of serum LH, LH/FSH ratio and free testosterone in PCOS cases were significantly higher than their matched healthy controls (p < 0.001), as shown in Table 3.

Table 3: Mean ±SD values of free testosterone, LH, FSH, and LH/FSH ratios of PCOS cases and controls

Parameter	Cases (n=59)	Controls (n=61)	p-value
Free testosterone (Pg/ml)	41.8 ± 10.34	13.2 ± 6.41	0.001

LH (mIu/ml)	24.0 ± 9.51	4.1 ± 2.82	0.001
LH/FSH ratio	2.2 ± 0.54	0.7 ± 0.13	0.001

The mean serum fructose levels of obese and overweight women were substantially greater than lean women's (P < 0.001, P < 0.02 respectively). They were also substantially greater than those of normal weight (P< 0.001, P< 0.01 respectively). The mean serum fructose of obese women was significantly higher than that of overweight women (p < 0.03). Moreover, the mean value of insulin level of the obese group was significantly greater than that of overweight women (p<0.04), while there were no significant differences in the mean concentrations of insulin between other subgroups of PCOS women. There were no significant differences in the mean value of other measured parameters among the BMI-related subgroups of PCOS women as illustrated in Table 4.

Table 4: Mean (±SD) values of studied biochemical parameters according to BMI of PCOS women

Parameter	PCOS Cases – BMI (Mean ±SD)			
	Lean (n=3)	Normal (n=15)	Overweight (n=13)	Obese (n=28)
HOMA-IR^{NS}	7.2 ± 2.61	6.7 ± 1.58	7.4 ± 1.65	6.5 ± 2.17
QUICKI^{NS}	0.3 ± 0.01	0.3 ± 0.01	0.3 ± 0.01	0.3 ± 0.01
Insulin (mIu/ml)	40.3 ± 14.5	34.6 ± 8.15	31.7± 8.81	40.2±7.18 *
Glucose (mg/dl)^{NS}	72.3 ± 2.08	79.9 ± 8.74	75.1±12.23	82.54±11.49
Fructose (nmol/ µl)^{NS}	12.6 ± 1.28	16.0 ± 3.58	20.3 ± 5.28	23.8±4.48**, ***
F.testo (pg/ml)^{NS}	33.6 ± 10.65	44.6 ± 2.19	41.0±10.49	41.6 ± 9.11
LH (mIu/ml)^{NS}	20.6 ± 8.4	20.3 ± 7.33	28.0±11.23	24.5 ± 9.36
LH/FSH ratio^{NS}	2.2 ± 0.25	2.1 ± 0.51	1.9 ± 0.25	2.3 ± 0.64

ANOVA and t-test reveals * significantly higher mean insulin in obese than in overweight (p <0.004), ** significantly higher fructose in obese and overweight than in lean (p <0.001, p < 0.02 respectively) and normal weight (p < 0.001, p <0.01 respectively), *** significantly higher mean fructose in obese than in overweight (p< 0.03), NS: non-significant differences.

Serum fructose levels were significantly positively correlated to WC (r=0.45, p<0.0001) and BMI (r=0.61, p<0.0001) as shown in figure 1. In addition, a significant positive correlation was observed between HOMA-IR and serum insulin levels (r=0.85, p<0.0001), while it had a strong negative correlation with QUICKI (r=-0.89, p<0.0001), figure 2.

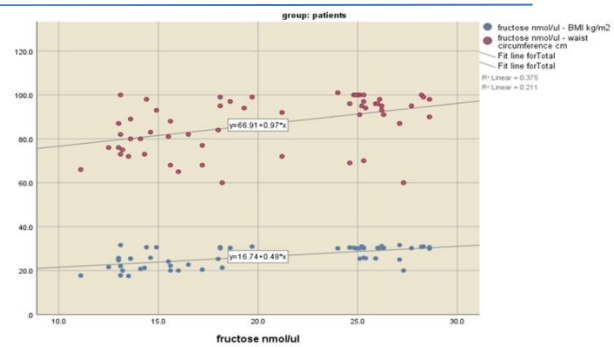

Figure 1: Correlation between fructose levels with BMI and WC in the PCOS group

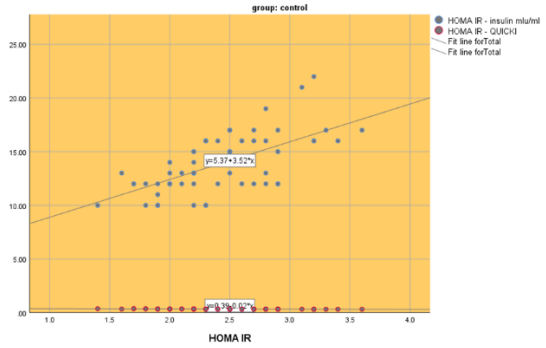

Figure 2: Correlation between HOMA-IR with insulin and QUICKI in the PCOS group

The ROC of this study found that measuring of serum fructose and serum free testosterone had the same sensitivity and specificity, fructose was (AUC=0.998), while free testosterone was (AUC=1.000). Fructose was the novel biomarker for distinguishing between PCOS and healthy women independent of insulin resistance, as shown in Table 5.

Table 5: ROC test result of free testosterone, fructose and HOMA IR

Test variable	AUC	P value	Cut-off value	Sensitivity	Specificity
Free testosterone	1.000	0.0001	20.6	100%	78.7%
Fructose	0.998	0.0001	10.4	100%	78.7%
HOMA-IR	0.999	0.0001	3.0	100%	88.5%

Discussion

The results of this research showed that PCOS patients had greater levels of fasting serum glucose, insulin, and HOMA-IR than controls, which is consistent with an earlier study from Iraq (18). The higher mean free testosterone level in the PCOS group as compared to control group is consistent with the findings of Rosenfield and Ehrmann indicating that PCOS women frequently have higher levels of total and free testosterone, which can prevent regular periods and fertilization even with a small increase (19). The significantly higher mean fructose level in PCOS cases compared to control group and the significant increase in obese PCOS women than in

overweight, normal and lean PCOS women is consistent with the results of a study from China in Medical College University's Shengjing Hospital on 157 Chinese women (67 control and 90 PCOS women). The latter study aimed to explore the link between blood fructose level and PCOS, and found that increased plasma fructose levels are linked to PCOS in Chinese women of fat and impaired insulin. Fructose levels are higher in the follicular fluid from PCOS women than that from normal controls, according to an on PCOS patient and controls who were grouped into overweight and lean subgroups (20). Another study from China on 1454 adolescents, found out that excessive fructose consumption was linked to higher fasting insulin levels and central obesity (21). LH secretion is frequently elevated in PCOS women; high levels of LH and insulin levels play a role in the high levels of male hormones such as testosterone produced from the ovaries (22). The present study found a significant positive correlation between fructose levels and BMI. Rising fructose used in sweetened foods and drinks, may trigger a hormonal reaction in the body that encourages excess weight and may have a higher obesogenic tendency than other sugars (23). Among serum metabolites, fructose was the novel biomarker in differentiating between PCOS women and healthy women independent of insulin resistance.

Conclusions

The majority of PCOS women are fat and overweight, with just a small percentage being lean and suffering from insulin resistance. Increased blood fructose levels, which are independent of insulin resistance, are a new diagnostic tool for assessing women with PCOS.

Authors' Contributions:

Ameera H Jasim: student
Prof.Dr. Basil O Saleh: supervisor
Dr. Afraa Mahjoob Al-Naddawi: supervisor

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العلاقة بين مستويات مصل الفركتوز مع مقاومة الانسولين عند النساء المصابات بمتلازمة تكيس المبايض

الكيمياوي الاختصاص أميرة حاتم جاسم
الاستاذ الدكتور باسل عويد محمد صالح
المدرس الدكتورة عفراء محجوب نفل

الخلاصة:
الخلفية: متلازمة المبيض المتعدد الكيسات (PCOS) هي حالة الغدد الصماء الأكثر انتشارًا لدى النساء هي مزيج من العوامل البيئية والوراثية المسببة لمتلازمة تكيس المبايض. العلاقة بين السكاريد الأحادي ومتلازمة تكيس المبايض غير معروفة إلى حد كبير.
الهدف: تم تصميم هذا البحث لمعرفة العلاقة بين مستويات الفركتوز في الدم ومقاومة الأنسولين وهرمون الأندروجين لدى النساء المصابات بالـ PCOS ، وتأثير السمنة على النتيجة التي تم الحصول عليها ، وكذلك دراسة فاعلية سكر الفركتوز في الدم كمؤشر حيوي في تشخيص متلازمة تكيس المبايض.
الحالات والطرق: أجريت هذه الدراسة البحثية في عيادة أمراض النساء ومركز العقم في مستشفى بغداد التعليمي / المدينة الطبية بين نوفمبر 2021 إلى مارس 2022. وشملت 120 امرأة تتراوح أعمارهن بين 18 و 40 عامًا. تم تشخيص 59 امرأة (حالة) حديثًا مع متلازمة تكيس المبايض من قبل طبيب أمراض النساء وعمر 61 وكان مؤشر كتلة الجسم متطابقًا مع النساء الأصحاء (الضوابط). تم تقسيم نساء متلازمة تكيس المبايض وفقًا لمؤشر كتلة الجسم إلى أربع مجموعات: النحيلة ، والوزن الطبيعي ، والوزن الزائد ، والسمنة. تضمنت التحقيقات قياسات مصل الفركتوز وهرمون اللوتين (LH) وهرمون تحفيز الجريبات (FSH) وهرمون التستوستيرون الحر والأنسولين والجلوكوز وتقييم نموذج التوازن المحسوب - مقاومة الأنسولين (HOMA-IR) ومؤشر فحص حساسية الأنسولين الكمي (QUICKI).
النتائج: تم زيادة متوسط قيم ± SD لفركتوز المصل والجلوكوز والأنسولين و HOMA-IR بشكل كبير في النساء المتلازمة (PCOS) مقارنةً بالضوابط ($p < 0.001$) ، بينما انخفض متوسط قيمة QUICKI بشكل ملحوظ ($p < 0.0001$). كان هناك ارتباط إيجابي معنوي بين قيم مؤشر كتلة الجسم ومستويات الفركتوز لدى نساء متلازمة تكيس المبايض. أظهرت النتائج أن مستويات الفركتوز والتستوستيرون الحر في الدم كانت لها أعلى حساسية وخصوصية في التمايز بين مجموعة متلازمة تكيس المبايض والضوابط ، حيث كانت المنطقة الواقعة تحت قيم منحنى لهرمون التستوستيرون الحر أعلى من المنطقة الواقعة تحت قيم منحنى الفركتوز.
الاستنتاجات: يمكن استخدام مستوى الفركتوز كمؤشر حيوي بديل للنساء المصابات بمتلازمة تكيس المبايض بشكل مستقل عن مقاومة الأنسولين. غالبية النساء من متلازمة تكيس المبايض يعانين من السمنة وزيادة الوزن ، وأقلية من النحيفات واللواتي يعانين بشدة من مقاومة الأنسولين.
الكلمات الرئيسية: متلازمة تكيس المبايض ، الفركتوز ، HOMA-IR ، هرمون التستوستيرون الحر