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Insulin resistance and dysglycaemia in polycystic ovary syndrome patients

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathy occurring during women reproductive age marked by a large range of metabolic disorders and abnormalities.**Materials and Methods:** This study was conducted in Bouaké Teaching Hospital. The diagnosis of PCOS was confirmed according to the revised Rotterdam criteria. Firstly, we established the diagnosis of PCOS through the measurement of different hormonal parameters and on the basis of ultrasonography and disease's history. Secondly, we met patients to realize different tests aimed to explore glucose metabolism. The oral glucose tolerance test was performed each 30 minutes after administration of 75 g of oral glucose.**Results:** We noted that 17% of PCOS patients had a HOMA Insulin Resistant in contrary to 83% of patients with a HOMA insulin sensitive state and obesity was significantly more prevalent in the IR group. PCOS patients HOMA IR group had a mean BMI significantly higher than those of IS group. Out of 12 insulin-resistant PCOS patients, 01 had normal BMI and 11 were overweight or obese (91.70%) contrary to those in IS group within 47.45% had normal BMI and 52.54% were overweight or obese. In the subgroup of IR with high BMI, we noticed the higher values of glycaemia. The rate of dysglycaemia was more prevalent in this subgroup following by IS with high BMI group.**Conclusion:** The rate of PCOS patients with HOMA-IR was important and was correlated to anthropometric disorders and high level of LH and testosterone. To successfully handling this important endocrinopathy, it's strongly advised to early diagnosed PCOS.© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathy occurring during women reproductive age. It's characterized by clinical manifestation; such as oligo/anovulation, morphological abnormalities on ovaries and biochemical hyperandrogenism. PCOS affects 5% to 10% women of reproductive age.¹ PCOS is marked by a large range of metabolic disorders and abnormalities including hyperinsulinaemia, hyperglycaemia, glucose intolerance, dyslipidaemia, and obesity, which are regarded as the

hallmark components of metabolic syndrome (MetS).² The primum movens of these abnormalities seems to be due to insulin resistance (IR) which affects the health of PCOS patients and plunges them into type 2 diabetes mellitus (T2DM). This state is in link with defected lipid profile and exposing patients to metabolic syndrome

(MetS). It is estimated that 70% of women with PCOS have at least one abnormal lipid constituent.³ Among PCOS patients, those who are overweight or obese are more inclined to lipid disorders particularly elevated triacylglycerols (TG) and decreased high-density lipoprotein cholesterol (HDL-C).⁴ Thus, some studies highlighted the impact of weight on the level of HDL-C in

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PCOS women.⁵

MetS is a common metabolic state found in obesity and PCOS and resulting from many disorders precisely insulin resistance. IR also represents a common metabolic disorder prevalent in PCOS and obesity. Moreover, accumulating evidence indicates that women with MetS also exhibit hyperandrogenism, contributor to PCOS aetiology. Androgen in excess appears to affect independently the cardiometabolic aberrations in PCOS women.⁶

Our countries located in south-sahara, aren't in rest and particularly Côte d'Ivoire which facing a prevalence more and more important of obesity together with other metabolic disorders and endocrinopathy such as PCOS. PCOS known as a most frequent endocrinopathy women undergo is surely endemic in my country. However, too few data of literature are available and this hinders the process in order to better understand and treat PCOS patients. We are to launch into this axis and through this study, we hope to deem the prevalence of insulin resistant within a PCOS patients living in the centre of Côte d'Ivoire and on other side to establish the link between insulin resistant and body mass index (BMI).

2. Materials and Methods

2.1. Population

This cross-sectional study was conducted in 2016 in Bouaké Teaching Hospital. Seventy-one patients diagnosed with PCOS were recruited in this study. The research protocol was approved by the medical and scientific Director of the hospital. Written informed consent was obtained from all participants. The diagnosis of PCOS was confirmed according to the revised Rotterdam criteria,⁷ in which the presence of any two out of the three following criteria was required and exclusion of other aetiologies.

Any patients with a disease affecting metabolic parameters, including diabetes mellitus, thyroid disorders, and hypertension, were excluded from the study. Patients taking a month before the onset of the study were also excluded. Moreover, history of being on a special diet, such as weight-losing diet during the 3 months before the onset of the study, was regarded an exclusion criterion.

The obtained data for medical history included social and anthropometric parameters. Subjects were weighed in light clothing without shoes. Height was measured to the nearest 0.1 cm, using a wall-mounted stadiometer. BMI was calculated as weight (kg) divided by the square of height (m).⁸

2.2. Laboratory measurements

After a 12-hour overnight fasting, 5 ml blood was obtained in the follicular phase of the menstrual cycle To explore the levels of hormonal parameters including progesterone, estradiol, LH, FSH and so on.⁹ In terms

of high progesterone level, the whole measurements were repeated after one or two week(s) for those that diagnosed PCOS patients we carried out exploration after one or two week(s) for exploring glucose metabolism through static measurement (fasting glucose and fasting insulin) and after oral glucose tolerance test (OGTT). The whole blood samples were centrifuged at 3,000 rpm for 5 minutes. The samples were analyzed either immediately or during the first week after conservation at -20 °C. The serum glucose was analyzed using the standard enzymatic method. Levels of Testosterone, LH, FSH and plasma Insulin levels were all measured using measured using enzyme-linked immune-sorbent assays (ELISAs) method.

2.3. Oral Glucose Tolerance Test (OGTT) / evaluation of IR

The standard oral glucose tolerance test (OGTT) was performed another day, after diagnosis, and after withdrawing a blood for fasting glucose and insulin. According to the protocol, we administered 75g of oral glucose for all patients⁹ and different prelevements were made at T30, T60, T90 and T120 for both glycaemia and insulinemia. The homeostasis model of insulin resistance (HOMA-IR) was calculated as (fasting plasma glucose concentration (mmol/L) × fasting serum insulin concentration (μ U/mL)/22.5). IR was defined as HOMA-IR value of ≥ 3.8 .⁹ Impaired glucose tolerance (IGT) was defined as an elevated fasting glucose ($110 \text{ mg/dL} \leq G0 \leq 125 \text{ mg/dL}$) or an elevated 2-hour glucose ($140 \text{ mg/dL} \leq G120 \leq 199 \text{ mg/dL}$). The patients were divided into insulin-resistant (IR) and insulin-sensitive (IS) groups. Firstly, variations of BMI and hormonal parameters were compared between the two groups, and then, the correlation of glucose profile with insulinemia into different subgroups was analyzed.

2.4. Statistical analysis

All the results were tabulated as mean and standard deviation. We used the SPSS 20.0 version for statistical analysis. The unpaired student t test was used to determine the statistical significance between the study groups. Pearson correlation was used for correlating different parameters. A P value of < 0.05 was considered to be statistically significant.

2.5. Ethical considerations

The study was approved by the Institutional Ethics Committee, Medical and Scientific Direction, teaching hospital of Bouaké, Côte d'Ivoire. Written and informed consent was obtained from the individuals who have participated in the study.

3. Results

The mean age of participants was 25.37 years old and regarding BMI of 28.82 Kg/m² that was higher than 24.99, the target value of normal BMI. The measurement of biological parameters gave the following means: LH (8.27 mIU/L) ; FSH (5.12 mIU/L) ; testosterone (0.58 nmol/L) and estradiol (49.90 pg/ml). PCOS patients underwent the oral glucose tolerance test during two hours within the peak of serum glucose and insulin reached at T₃₀ with respective values estimated to 7.39 mmol/L and 77.03UI/L (Table 1).

We also noted that 17% of PCOS patients have got a HOMA Insulin Resistant in contrary to 83% of patients with a HOMA insulin sensitive state. Obesity was significantly more prevalent in the IR group compared to the IS group. PCOS patients HOMA IR group had a mean BMI significantly higher than those of IS group (Table 2). Otherwise, the mean values of testosterone and LH were higher in the IR group as opposed to those of estradiol and FSH higher in the IS group. Thus, the ratio of LH/FSH (1.78) was higher in the IR group (Table 2).

Out of 12 insulin-resistant PCOS patients, only 01 had normal BMI and 11 were overweight or obese (91.70%) contrary to those in insulin-sensitive group within 47.45% had normal BMI and 52.54% were overweight or obese. In the subgroup of IR with high BMI, we noticed the higher values of glycemia precisely fasting, T₃₀, T₉₀ and T₁₂₀. The rate of dysglycemia was more predominant in this subgroup following by the subgroup of IS with high BMI patients. The ratio of fasting glucose/ fasting insulin was lower in the HOMA obese group with values under 0.21 at T₀ and a minimal value of 0.04 found at T₆₀ (Table 3).

4. Discussion

HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in T₂DM subjects but also for patients suffering from other endocrinopathy such as PCOS or metabolic diseases. Previous studies have indicated that insulin resistance plays an important role in the pathogenesis of polycystic ovary syndrome.¹⁰ Insulin would act synergistically with luteinizing hormone (LH), leading to increased production of androgens in the ovarian theca cells.¹¹ Wehr et al.¹² have reported that increased serum testosterone levels in PCOS women are associated with excess of visceral fat amount, insulin resistance and more frequent occurrence of impaired glucose tolerance. IR would be one of the most prevalent metabolic perturbations in women with PCOS, affecting 65-70% of all patients.¹³ As a consequence of the perturbed insulin action, a higher amount of insulin is required to attain its metabolic effects, which results in increased production and release of insulin from pancreatic β cells. This is why IR is frequently associated with compensatory hyperinsulinemia.^{13–15}

In our cohort, the degree of insulin resistance was estimated at the baseline by HOMA according to the method described by Matthews et al.⁶ In our trial, 17% of recruited PCOS patients displayed a case of HOMA-IR. In our cohort, the mean age and BMI was estimated at 25.37±5.47 years and 28.82kg/m², however, the value of BMI were widely lower to those of HOMA-IR. Indeed that argues metabolic disorders resulting from weight gaining and fat accumulating in adiposity cells before PCOS occurring. Our results were slightly lower than those reported by Ebrahimi-M. et al.¹⁶ respectively of 26.9±5.7 years and 31.4±3.8 kg/m²; in a study focused on association of insulin resistance in overweight or obese women with PCOS. Related to BMI, this discrepancy could be due to the criteria of recruitment focused on overweight and obese PCOS patients in their study.

Within PCOS patients with HOMA IR, the mean age was higher (25.50±5.64 years) together with BMI which was at 34.86±6.17 kg/m² by opposite to IS group with respectively 25.32±5.46 years and 27.59±8.42 kg/m². Thus, IR was more prevalent to PCOS patients more aged and presenting a higher value of BMI. This trend was in line with the report of literature.^{11,14} Thus HOMA-IR was significantly correlated with age, BMI, fasting glucose and fasting insulin. Clinical studies documented that women with PCOS showed increased global adiposity¹⁷ and thickness of the intraperitoneal and mesenteric fat compared with control women.¹⁸ However, the molecular mechanisms implicated in the increased abdominal adiposity induced by chronic exposure to androgens remain partially known and could be due to the hypersecretion of LH. To elucidate this point, a preclinical study of female mice conducted by Nohara et al.¹⁹ has been done. They suggested that androgen excess may perturb the ability of leptin to stimulate energy expenditure, which in turn may promote visceral fat accumulation.

Our results corroborate the findings reported by Sanchez et al.¹⁴ who found that the mean BMI and the prevalence of obesity were higher in the IR compared to the IS patients. In fact, abdominal obesity may result in higher insulin concentration.²⁰ Although unsteadily, IR occurs in obese as well as lean subjects with PCOS,²¹ any degree of obesity is liable to trigger reduced insulin sensitivity. In non diabetic as well as diabetic subjects, insulin resistance is related to several cardiovascular risk factors, including hyperglycemia, dyslipidemia, hypertension, etc. Previous studies^{22–24} confirmed that metabolic abnormalities are less severe in normoandrogenic women with PCOS in comparison to phenotypes with hyperandrogenism.

Consequently, insulin resistance might be regarded as an important factor in the pathogenesis of cardiovascular disease (CVD) in type 2 diabetes. Nonetheless, it is interesting to establish whether insulin resistance does contribute to atherosclerosis or cardiovascular disease. That

Table 1: Quantitative values of certain parameters explored in PCOS patients.

	Min.	Mean	S.D	Max
Age (yrs)	15	25,37	5,47	41
Weight (Kg)	40,0	77,82	22,24	123,0
Height (m)	1,26	1,64	0,08	1,80
BMI (Kg/m ²)	15,0	28,82	8,51	46,68
Testosterone (nmol/L)	0,12	0,58	0,26	1,50
LH (mIU/L)	0,56	8,27	5,07	25,0
FSH (mIU/L)	1,30	5,12	1,60	8,50
Estradiol (pg/ml)	12,0	49,90	47,37	227,0
Fasting glycaemia (mmol/l)	3,60	4,76	0,75	9,80
Fasting insulinemia (UI/L)	0,53	10,43	8,67	42,0
Glycaemia T ₃₀ (mmol/l)	4,40	7,39	1,59	10,90
Insulinemia T ₃₀ (UI/L)	0,73	77,03	61,88	298,0
Glycaemia T ₆₀ (mmol/l)	3,10	6,93	2,41	12,1
Insulinemia T ₆₀ (UI/L)	1,20	72,73	74,66	462,0
Glycaemia T ₉₀ (mmol/l)	2,20	5,97	2,18	12,30
Insulinemia T ₉₀ (UI/L)	2,60	59,66	71,35	500,0
Glycaemia T ₁₂₀ (mmol/l)	2,70	5,53	1,59	10,40
Insulinemia T ₁₂₀ (UI/L)	4,30	59,16	73,54	422,0

T: Testosterone; E2: Estradiol; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

Table 2: Mean values of Age, anthropometric and hormonal parameters in two different groups

	HOMA Insulin resistant group n= 12 (17%)				HOMA Insulin sensitive group n= 59 (83%)			
	Mean ±SD	Min.	Max.	P	Mean ±SD	Min.	Max.	P
Age	25.50±5.64	15	37	0.888	25.32±5.46	15	41	0.658
BMI (kg/m ²)	34.86±6.17	24.80	46.68	0.606	27.59±8.42	15	46	0.000*
Testosterone (nmol/L)	0.76±0.36	0.15	1.50	0.795	0.55±0.21	0.12	1.10	0.835
Estradiol (pg/ml)	35.91±13.47	13.00	56.00	0.929	52.77±51.23	12	227	0.857
LH (mIU/L)	8.66±3.12	3.90	12.00	0.032*	8.22±5.41	0.56	25	0.838
FSH (mIU/L)	4.86±1.10	3.70	7.60	0.280	5.11±1.74	1.30	8.50	0.935

*:Significant correlation.

evidence would be of great clinical value, because it might strongly justify and encourage the use of therapeutic options, including drugs able to improve insulin sensitivity, with the aim of reducing the cardiovascular risk. Standing the role of hyperinsulinemia as a pathogenic factor for the development of hyperandrogenism and PCOS, a variety of studies demonstrated that intervention with oral diabetic drugs such as metformin or thiazolidinediones (TZDs) reduces circulating insulin and androgen levels, increases SHBG levels, and improves ovarian function in women with PCOS.^{25–27}

Our results related to glucose metabolism in link with OGTT showed that the mean values of fasting glucose among different subgroups were normal. Nonetheless, based on the value after two hours, we noticed in the HOMA IR with high BMI subgroup that the serum glucose was at 21.54 mmol/l; outlined glucose intolerance and also insulin resistance. This fact reveals a disturbance in serum glucose regulation which could rise as this pathology growing up. As previously outlined, women with PCOS frequently

exhibit insulin resistance associated to hyperinsulinemia and a high propensity for developing Type 2 Diabetes. While the effect of androgen excess on systemic insulin sensitivity has been extensively explored, less attention has been paid to assessing the impact of hyperandrogenism on β cell function and insulin release. However, some evidence suggests that androgen excess may contribute to impairing glucose tolerance and β cell function in women with PCOS.^{28,29} However, the mechanisms underpinning this androgenic effect on the pancreas remain poorly understood.

The higher value of serum glucose has been observed at the 30th minutes after oral glucose tolerance test (7.39 mmol/L). The peak of glycemia also aroused an important secretion of insulin which reached a value of 77.03 UI/L. This trend has also been registered for both subgroup namely for HOMA IR group and HOMA IS group. Nonetheless, the most important peak has been observed in the HOMA IR with high BMI group.

Consequently, all environmental factors that can lead to overweight or obesity and alter insulin action may

Table 3: Values of glycemia and insulinemia regarding BMI during oral glucose tolerance test (OGTT) in two different groups.

	HOMA Insulin-resistant group N = 01 (03.45%)				HOMA Insulin-sensitive group N = 28 (96.55%)			
	Glycaemia		Insulinemia		Glycaemia		Insulinemia	
Normal BMI	G ₀	04.20	I ₀	21.00	G ₀	04.65 P= 0.623	I ₀	05.27 P= 0.001*
	G ₃₀	05.10	I ₃₀	20.00	G ₃₀	07.56 P= 0.824	I ₃₀	36.15 P= 0.390
	G ₆₀	03.80	I ₆₀	14.40	G ₆₀	06.28 P= 0.780	I ₆₀	49.87 P= 0.875
	G ₉₀	03.80	I ₉₀	16.00	G ₉₀	05.69 P= 0.101	I ₉₀	30.74 P= 0.025*
	G ₁₂₀	04.50	I ₁₂₀	30.00	G ₁₂₀	06.15 P= 0.108	I ₁₂₀	33.52 P= 0.036*
High BMI (overweight and obese)	N = 11 (26.20%)				N = 31 (73.80%)			
	Glycaemia		Insulinemia		Glycaemia		Insulinemia	
	G ₀	05.34 P= 0.027 *	I ₀	24.81 P= 0.370	G ₀	04.71 P= 0.157	I ₀	08.66 P= 0.377
	G ₃₀	08.01 P= 0.827	I ₃₀	111.6 P= 0.296	G ₃₀	07.47 P= 0.620	I ₃₀	72.02 P= 0.561
	G ₆₀	07.34 P= 0.538	I ₆₀	155.2 P= 0.828	G ₆₀	07.48 P= 0.740	I ₆₀	61.68 P= 0.451
	G ₉₀	09.00 P= 0.432	I ₉₀	139.3 P= 0.751	G ₉₀	06.80 P= 0.745	I ₉₀	56.38 P= 0.514
	G ₁₂₀	21.54 P= 0.343	I ₁₂₀	123.9 P= 0.738	G ₁₂₀	06.23 P= 0.308	I ₁₂₀	56.74 P= 0.352

*: Significant correlation.

be involved in the etiology of this endocrine disorder. Diet and lifestyle are the main factors that may cause or exacerbate the metabolic and reproductive abnormalities of PCOS.³⁰ Sedentary lifestyle and inadequate dietary habits may promote obesity and insulin resistance and contribute to worsening the metabolic and reproductive features of PCOS. Supporting the role of these environmental elements in the pathogenesis of PCOS, it has been documented that an improvement in insulin sensitivity through lifestyle and diet modifications is sufficient to ameliorate some indexes of reproductive perturbations in obese women with PCOS such as anovulation and menstrual cycle irregularities.^{31,32}

One limitation of the present study is a relatively small number of participants representing different PCOS phenotypes. Another limitation is the use of HOMA-IR to estimate insulin resistance. The gold standard in the assessment of the whole-body insulin sensitivity is hyperinsulinemic euglycemic clamp; however, it is time-consuming and difficult to perform.³³

5. Conclusion

The rate of PCOS patients with HOMA-IR was important and was correlated to anthropometric disorders and high level of LH and testosterone. This clinical state is the cornerstone of metabolic disorders namely dysglycaemia which leads to type 2 diabetes. To facing this important endocrinopathy and handling its issue, It's strongly advised

to early diagnosed PCOS in order to adopt the necessary actions to treat and prevent weigh gaining, primum movens of disturbances registered. It'll be advisable to implement such study within different study groups in accordance with our lifestyle to appreciate the real impact of insulin resistance in our population and act upstream to prevent/reduce metabolic diseases.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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