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Insulin Resistance in Obese and Non Obese PCOS Patients Using Homeostasis Model Assessment Insulin Resistant: A Comparison Study

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Abstract

Aim: this study was conducted to assess the insulin resistance in obese PCOS patients in comparison with non-obese PCOS women. Methodology: a comparative observational study was conducted on 165 Libyan PCOS women; 81 obese PCOS and 84 non-obese PCOS attending the out-patient clinic of Albayda Fertility Teaching Center and two private clinics in Albayda city/Libya, in the period between January 2021 and January 2023. All subjects undergone day 2 pelvic ultrasound scan, relevant hormonal assay and an overnight insulin and glucose levels were measured and used for insulin resistance calculation, using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula, 2.6 was used as a HOMA-IR cutoff value.

Result: of the total 165 PCOS women, 81 (49%) were obese with BMI ≥30 kg/m2 (study group) and 84 (51%) were non-obese (control group) PCOS. The prevalence of insulin resistance (IR) in all the included PCOS patients was 39% and the difference in prevalence of IR was non-significant between obese and non-obese PCOS (p=0.44). Insulin resistance was significantly higher among the obese PCOS (mean HOMA-IR =3) than non-obese PCOS group (mean HOMA-IR = 2.4) with P-value < 0.001. Insulin resistance had a significant positive correlation with fasting insulin and glucose levels but was not significantly correlated with BMI, age, LH, or with testosterone. Conclusion: both obese and non-obese PCOS women have insulin resistance, strengthening the aetiological role of Insulin resistance in PCOS pathogenesis. However, the insulin resistance was significantly higher among the obese PCOS accordingly life-style modifications might be beneficial in restoring PCOS pathogenesis.

Keywords: BMI, HOMA-IR, insulin resistance, obesity, PCOS

Introduction

Polycystic ovarian syndrome (PCOS) was first described by Stein and Leventhal in 1935 [1] and it is now considered as the commonest endocrine problem affecting women in reproductive age with a prevalence of 6-8% [2, 3].

PCOS is a heterogeneous endocrine disorder and the 2003 Rotterdam ESHRE/ ASRM sponsored PCOS consensus mandates presence of at least two of the three following criteria to make the diagnosis of PCOS:

chronic ovulatory disorder, clinical and/or biochemical hyperandrogenism and ultrasound picture of polycystic ovaries [4].

The aetiology of PCOS is unknown and it is multifactorial complex problem; however, insulin resistance (IR) is highly claimed in the pathogenesis of PCOS. About 40% of females with PCOS have insulin resistance which increases up to 70% in presence of obesity [5, 6]. It is assumed that all PCOS women have some degree of insulin resistance and compensatory hyperinsulinemia although IR is not included in the current Rotterdam criteria for the diagnosis of PCOS [5, 7-9]. This compensatory hyperinsulinemia leads to an amplified effect of insulin in other traditionally less insulin responsive tissues, including the ovarian theca cells resulting in increased androgen secretion [10].

Obesity is a risk factor for PCOS and it is also found to affect the prevalence and degree of insulin resistance (11). PCOS affect both obese and non-obese women and it is reported that, 30-70% of PCOS females are obese [6, 12]. Obesity and PCOS have a synergistic deleterious effect on glycaemic control [8].

Insulin resistance and the resulting hyperinsulinemia is a risk factor for reproductive [13] and a wide spectrum of long-term and life-threatening health problems such as; type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease [14, 15]. Moreover, studies have found higher insulin resistance, serum androgen levels, type 2 diabetes and cardiovascular diseases in the first-degree relatives of PCOS patients compared to the relatives of non PCOS groups [16, 17].

As mentioned in the literature; both PCOS and obesity are strongly associated with insulin resistance and insulin resistance is a risk factor for major health problems. Therefore, this research was conducted to assess the insulin resistance in obese PCOS women in comparison with non-obese PCOS using the Homeostasis Model Assessment – Insulin Resistant (HOMA-IR index).

Method and participants

The study was approved by the local ethical committee of the Albayda Fertility Teaching Center/Libya and a verbal consent for the participation was obtained from all the participants before the commencement of the study.

This comparative observational study was conducted on 165 Libyan PCOS women, selected on bases of the Rotterdam's criteria [4]. All the included patients were Libyan to avoid the effect of ethnicity on the insulin resistance [18]. The participants were PCOS women attending the out-patient clinic of Albayda Fertility Teaching Center/Libya and two private clinics in Albayda city in the period between January 2021 and January 2023.

In a prepared porforma, all the demographic data including age, BMI, the main compliant (menstrual irregularity, symptoms of hyperandrogenism, infertility), drug history and previous medical problems were recorded. Women on any insulin-sensitizing agent for at last 2 months preceding the start of the study, those having any medical or endocrine disorder likely to affect the glycaemia status of the participants were excluded.

Blood pressure was measured, weight (kilograms) in light cloths was measured, and height (centimeter) in upright posture without shoes using a stadiometer was recorded and used for calculation of the body mass index (BMI). The included participants were divided into two groups based on WHO classification [19]: study group (obese with BMI ≥30 kg/m2) and non-obese group (normal and overweight) with BMI < 30 kg/m^2.

Ultrasound scan was done for all the eligible participants on day 2 of the menstrual cycle to evaluate the ovaries; antral follicular count (AFC), to assess ovarian volume and to exclude any pelvic pathology. The circulating level for luteinizing hormone (LH), testosterone, prolactin and thyroid stimulating hormone (TSH) were measured.

An overnight fasting (12 hour) venous blood sample was obtained from each participant to determine fasting levels of insulin and glucose, and were used for calculation of insulin resistance using Homeostasis Model Assessment – Insulin Resistant (HOMA-IR) formula [20]. HOMA-IR has been shown to be a surrogate marker of IR as measured by the glucose clamp technique [21, 22] and cutoff value of 2.6 was used to identify individuals at risk of insulin resistance [23].
HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL)/405 [23, 24].

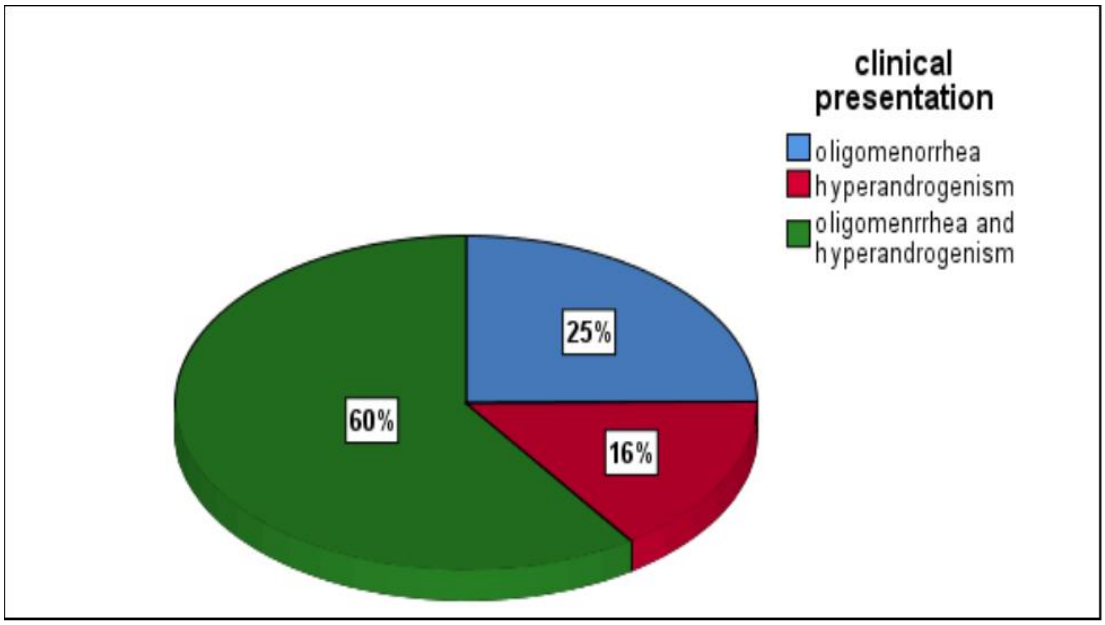
Statistical analysis
SPSS software, version 25 was used for data collection and analysis. Normality of quantitative data was checked by Shapiro–Wilk test. The quantitative variables including; age, body mass index (BMI), hormonal levels, fasting insulin, glucose and HOMA-IR were presented by mean and standard deviation. *t*-test was used to compare mean values among the two studied groups (obese and non-obese PCOS). The numbers and percentages were also computed for qualitative variables and Fisher' exact test used to compare the qualitative data. Pearson's correlation was used to assess the association between of HOMA-IR and relevant variables. Regression test done to test the most determinant factor for insulin resistance. *P* values < 0.05 were considered as significant.

Results
The study included 165 PCOS women who were diagnosed with PCOS according to Rotterdam ESHRE/ ASRM sponsored PCOS consensus criteria [4].

The age of the eligible participants was ranged between 18 and 42 years, with a mean and standard deviation of 27.7 (5.6) years and the mean body mass index (BMI) of the included candidates was 30 (6.5) kg/m2 and ranged from 17 to 49 kg/m2. Of the eligible PCOS women; 81(49%) were obese and 84 (51%) were non-obese. All the participants were euthyroid with a mean TSH level of 2 (1.3) mIU/L and with a normal prolactin level; 21.7(15) mIU/L.

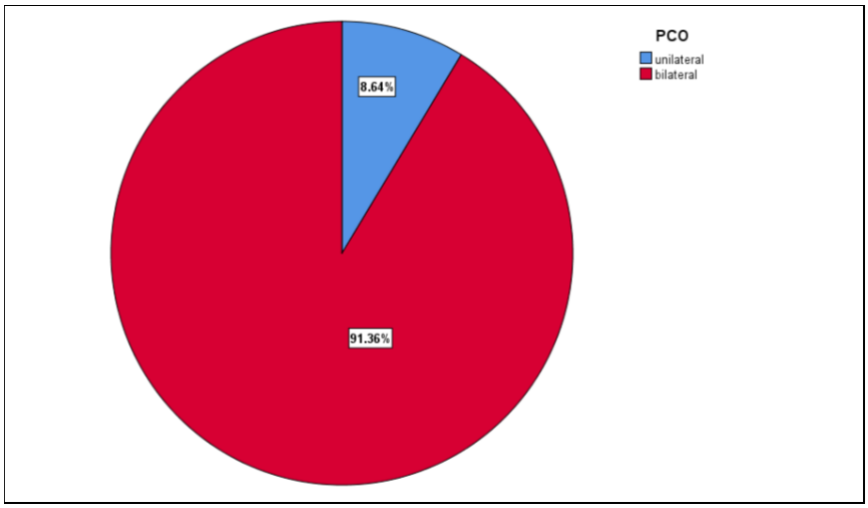
Almost all the patient were presented with history of primary or secondary infertility. 60% presented with both irregular menstrual cycle and symptoms of clinical hyperandrogenism (acne/ hirsutism or both). 25% were presented only with menstrual irregularity and 15% of the participants had only symptoms of hyperandrogenism (Figure 1).

Figure 1 The frequency of the presenting symptom.



A picture of polycystic ovaries was found in all the included PCOS women and as shown in Figure 2. An ultrasound picture of polycystic ovary was bilateral in 150 patients (91%) and unilateral PCO seen only in 9 (9%) patients.

Figure 2 Bilateral Vs. Unilateral PCO picture



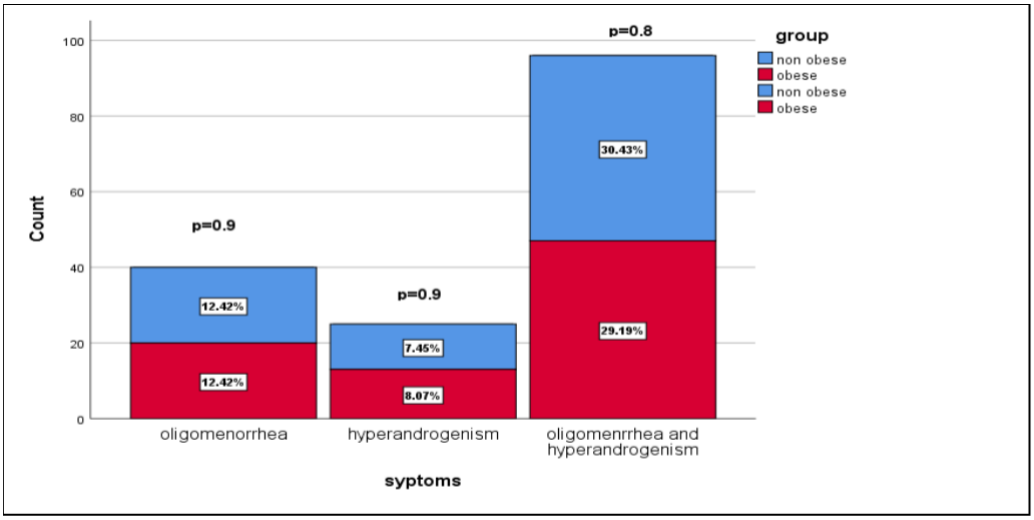
The obese women were having a significantly higher BMI ($P < 0.001$) than the non-obese and there was no significant difference in the age between the two groups and both groups had comparable serum LH and testosterone levels (Table 1).

Table 1 Demographics and biochemical data of the participation

Variable	Obese PCOS Mean (SD)	Non-obese PCOS Mean (SD)	*P* value
BMI	34.3(6)	25.4 (3.4)	0.001*
Age	28.4 (3.4)	27.4 (5)	0.3
LH	7.8(4)	9 (4.7)	0.1
Testosterone	0.62 (0.5)	0.66 (0.8)	0.7

Comparing the two groups with regard to clinical manifestation; there was no significant difference in the clinical manifestations between the obese and non-obese PCOS (Figure 3).

Figure 3 the clinical manifestation of PCOS in both groups



The prevalence of insulin resistance in the whole study population was 39% and there was no significant difference in the prevalence of HOMA-IR between the obese than the non-obese PCOS (*P*= 0.44).

Table 2 demonstrates the glycemic indices of the obese and non-obese PCOS groups. Fasting glucose among the obese PCOS group was higher than those for non-obese PCOS, however the difference was non-significant (*P*= 0.3). Whereas, the level of fasting insulin among obese PCOS was significantly higher than that of non-obese PCOS (*P*= 0.03). Insulin resistance assessed by using HOMA-IR formula was also significantly higher in obese PCOS subjects comparing to their non-obese counterpart (*P*= 0.02) as shown in Figure 4.

Table 2 Fasting blood glucose, fasting insulin and HOMA-IR in obese PCOS Vs. non-obese PCOS women

Variable	Obese PCOS Mean (SD)	Non-obese PCOS Mean (SD)	P value
FBS	87.3 (14)	85 (13.5)	0.3
FI	13.5 (9)	11 (5.3)	0.03*

HOMA-IR	3 (2)	2.4 (1.4)	0.02*

FBS: Fasting Blood Glucose FI: Fasting Insulin HOMA-IR: Homeostasis Model Assessment

Figure 4 HOMA-IR in obese and non-obese PCOS

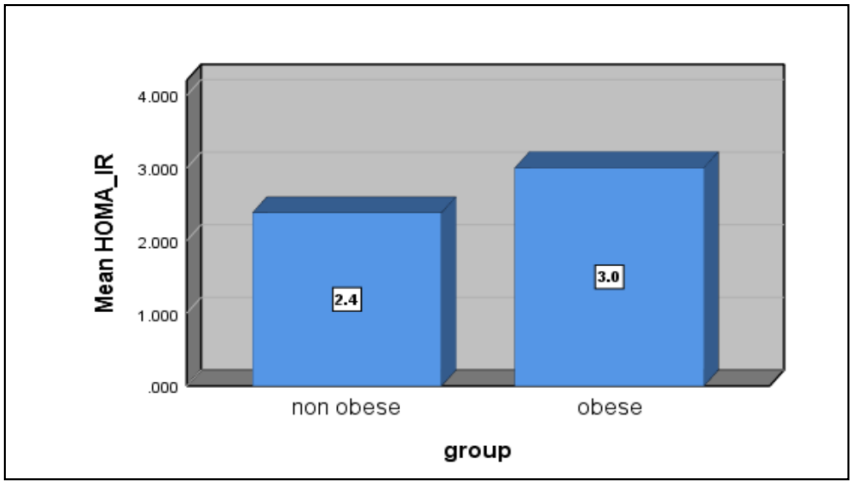


Table. 3 shows that Pearson's correlation between estimated insulin resistance and age, BMI, hormonal parameters and the glycemic indices in the study population showed that, no significant correlation was found between insulin resistance and either BMI, age, LH nor testosterone. However, HOMA-IR was positively correlated with fasting insulin and fasting glucose in the POCS patients.

Table 3 Correlation of HOMA-IR with BMI, age, LH, testosterone.

Variable	Pearson correlation	P value
BMI	0.04	0.56
Fasting glucose	0.43*	<0.001*
Fasting insulin	0.96*	<0.001*
Age	0.04	0.5
LH	0.05	0.53
Testosterone	0.14	0.07

Table 4 revealed that backward regression showed that insulin resistance had a non-significant correlation with BMI as illustrated in Figure. 4. Whereas; fasting glucose and fasting insulin were the most significant determinant of insulin resistance as illustrated in Figure 5& 6.

Table 4 Regression analysis

Independent variable	Standardized Coefficient β	Sig.	95% confidence interval	
BMI	0.001	0.9	-0.007	-0.008
Fasting insulin	0.91	<0.001*	0.22	0.23
Fasting glucose	0.21	<0.001*	0.25	0.03

The dependent variable: HOMA-IR

Figure 5 Relationship between HOMA-IR and BMI in infertile PCOS women

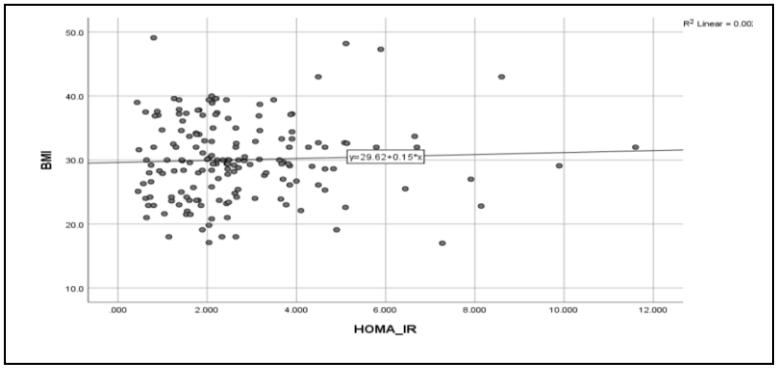


Figure 6 Relationship between HOMA-IR and fasting insulin in PCOS women

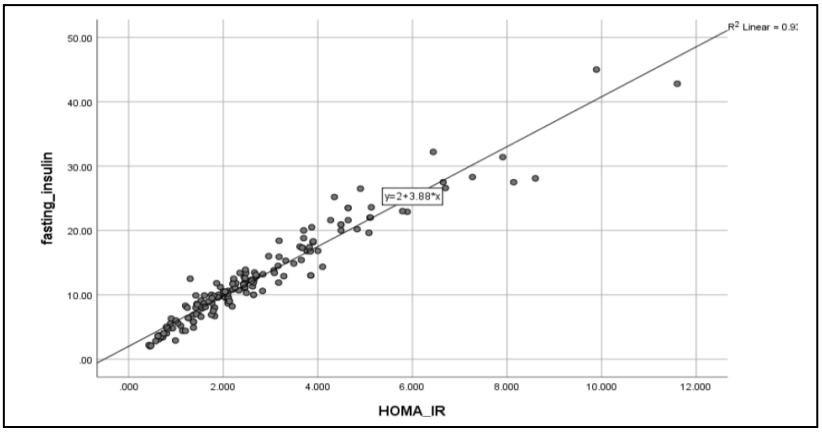
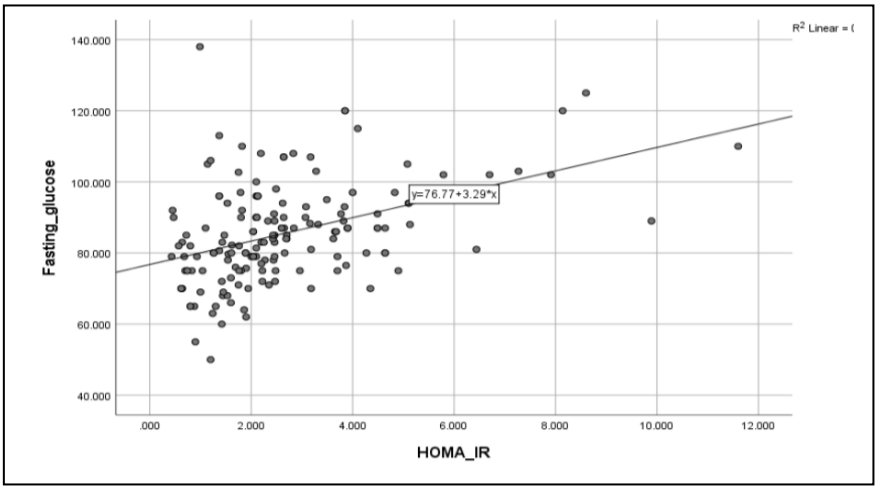


Figure 7 Relationship between HOMA-IR and fasting glucose in PCOS women



Discussion:

PCOS is probably the most prevalent endocrinological disorder affecting females in the reproductive age [2, 3]. Insulin resistance is highly implicated in the pathogenesis of PCOS [5, 6] and is reported to affect both obese and non-obese PCOS women [6, 12].

165 PCOS Libyan women were eligible for participation in the study. The prevalence of obesity in PCOS women in this study was 49% and this was in accordance with [25]. However, a much lower prevalence of obesity (26.56%) in PCOS women was reported [26]. In contrast, Shirazi *et.al* (2021) reported a higher incidence of obesity (75.6%) among the PCOS women and this could be attributed to the BMI used for categorizing the patients as obese if BMI≥24.39% [27]. Whereas in our study a BMI ≥30% was used to define obesity. So, obesity per-se is not a pre-requisite for PCOS but is likely to exacerbate insulin resistance [11] and insulin resistance is a major risk factor for many life-threatening health problems [14, 15].

The mean age (standard deviation) of the patient in present study was 27 (4) years and all were Libyan to avoid the effect of ethnicity on insulin resistance [18]. Almost all patients were presented with infertility; the second most common complaint was both oligomenorrhea and symptoms of hyperandrogenism and the third presenting complain was oligomenorrhea only and the least percentage of PCOS women were complaining of clinical hyperandrogenism only. In previous study, oligomenorrhea was the main presenting symptom [26]. Most of our participants were recruited for infertility clinic, and this could explain the higher percentage of infertility in the present study.

It has been mentioned that PCOS diagnosis does not always necessitate the presence of polycystic ovaries as only 60.93% of PCOS women had ultrasound evidence of PCOS [26]. However, in the present study, ultrasound evidence of PCOS was found in all included PCOS women and it was bilateral in 91% and unilateral PCO seen in 9% of patients. The ultrasound picture of polycystic ovaries was reported in 80 – 100% of women with PCOS as mentioned before [28] and this was similar to our result. Another study reported much lower percentage (60.93%) of PCOS patients had ultrasound evidence of polycystic ovary [26].

In the current study, the studied hormonal parameters were not significantly different in the PCOS individuals with various BMI groups and this was reported before [29]. HOMA-IR was used to estimate insulin resistance and 2.6 was used as cut-off value to identify people at risk of insulin resistance. The mean and standard deviation of HOMA-IR in this study was 2.7 (1.8). Previous research reported a lower mean level of HOMA-IR 2.46 (1.30) in PCOS patients [29]. On contrary, other researchers [30] reported a higher HOMA-IR 4.8 (4.2) in their PCOS patients and this could be explained by the higher BMI of their participants 36.4 (9.6) whereas, the mean BMI of the included subjects in the current study was 30 (6.2).

The prevalence of insulin resistance (IR) in all the included PCOS patients in the present study was 39% and this result was in accordance with a result of a study conducted on Congolese women with PCOS as IR evaluated by the HOMA-IR was detected in 39.3% of PCOS women [31]. Others reported that only 20% of PCOS women had insulin resistance [29] and this could be explained by a higher HOMA-IR cutoff value (> 3.820%). In contrast, a higher prevalence of insulin resistance (64%) was reported [30] and this higher prevalence could be due to the use of higher BMI and a variety of races of their participants. Even a higher incidence of insulin resistance (68% to 76%) was reported by other workers [32] who used a different way for estimation of insulin resistance and this might explain this higher incidence. In these two studies [30, 32] there was no difference in insulin resistance by race.

There was no significant difference in prevalence of HOMA-IR between the obese and non-obese PCOS women in our study, in contrast, others reported a higher prevalence of IR in obese PCOS women [5, 6].

So, form the forementioned, IR is not a universal finding in all PCOS patients, regardless of the sophistication of the test used for assessment of IR. It could be suggested that milder forms of IR may reduce insulin sensitivity only at the level of adipose tissue but not at the level of muscle [33] or IR may truly be absent in a minority of PCOS patients, and the syndrome may evolve in absence of IR.

The obese PCOS in this study were having a significantly higher HOMA-IR: 3 (2) than non-obese PCOS: 2.4 (1.4) with a P value of 0.02. In contrast others reported a non- significant difference in insulin resistance between obese and non-obese PCOS patients [29].

Estimated insulin resistance was not significantly correlated with BMI in PCOS patients and this was inconsistent with previous reports [11, 34]. It was reported that age and race affect insulin resistance [18, 35], contrary to that, others reported [30, 32] that; neither age nor race have any effect on insulin resistance. In the present study, all the participants were Libyan to avoid the effect of ethnicity on IR and there was no significant correlation between IR and age, and these data were in agreement with previous reports [30]. This could be explained by the relatively narrow age window for the included subjects (all were in reproductive age) in our study and in the study conducted by [30].

HOMA-IR had a significant positive correlation with fasting glucose and fasting insulin and this was in accordance with a result mentioned before [31]. Using a backward regression, fasting insulin and glucose levels were found to be the most significant determinant of IR in the women with PCOS and this data were also in agreement with those reported by [31] who showed that fasting insulin was the most significant determinant of insulin resistant.

It was reported proven clinical benefits in proportion of women with PCOS after lifestyle modification and pharmacological therapy with insulin-sensitizing agents [36, 37]. These measures might have potential implications for the future prevention and management of the metabolic syndrome. Therefore, clinical evaluation and management of obesity is still an important issue in PCOS women.

CONCLUSION

The presence of insulin resistance in both obese and non-obese PCOS patients strengthening the aetiologic role of insulin resistance in PCOS pathogenesis. However, the higher level of insulin resistance among obese PCOS women necessitates the importance of clinical evaluation and management of obesity in PCOS women in restoring PCOS pathogenesis.

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