Echocardiography Measurements in Obese and Non-Obese Polycystic Ovarian Syndrome Women

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ABSTRACT

Background: Obesity andpretem lab insulin resistance (IR) may produce disorder of left ventricular (LV) function, obese polycystic ovarian syndrome (PCOS) women have many hormonal and metabolic abnormalities are thought to be increased cardiovascular risk.

Objectives: To explore the role of obesity and IR in the pathogenesis of early structural functional changes in echocardiographic parameters associated with PCOS.

Methods: The study was conducted at Department of Physiology, Medical College of Al-Mustansiriya University in cooperation with the unit of Infertility and echocardiography at Al-Yarmook teaching hospital in Baghdad during the period from December 2015 to March 2017. One hundred Iraqi women with PCOS (aged 16 to 45 years) were included in this study. The clinical and metabolic characteristics were done for all patients [body mass index (BMI), waist circumference, waist to hip ratio (WHR), FBS, fasting insulin, lipid profile and homeostasis model assessment of insulin resistance (HOMA-IR)]. Echocardiographic measurements both Pulsed-wave Doppler and tissue Doppler imaging (TDI) were done for all patients.

Results: One hundred women with PCOS were divided into two groups according to BMI < 30 kg/m^2 as not obese with 46% and > 30 kg/m^2 regarding as obese PCOS woman with 54%. And when we compared between two groups in clinical and metabolic characteristics, there were significant differences between two groups in BMI, waist circumference, WHR, fasting insulin, serum cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), low density lipoprotein/high density lipoprotein ratio (LDL/HDL) and HOMA-IR, were all higher in obese PCOS women. Echocardiographic measurement both (Conventional) pulsed-wave Doppler and TDI done for both groups and there were significant differences between obese and non-obese women with PCOS in peak early filling velocity (E), E/A ratio, lateral e΄, lateral e΄/a΄ ratio, medial a΄, medial e΄/a΄, e΄ average, were all lower in obese PCOS women, while a΄ average, deceleration time (DT), left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD) and interventricular septum thickness (IVS) were slightly higher in obese PCOS women. One patient with PCOS with BMI < 30 kg/m^2 has left ventricular diastolic dysfunction (LVDD) and ten women with PCOS with BMI > 30 kg/m^2 have LVDD as early asymptomatic subclinical LVDD diagnosed by both TDI and pulsed-wave Doppler.

Conclusion: PCOS women who have asymptomatic LVDD tend to be more obese by increased BMI, wider waist circumference and high waist to hip ratio and have high insulin level and HOMA-IR. Given the pivotal role to obesity and insulin resistance were play in the etiopathogenesis and progression of PCOS and its potential subsequent metabolic and cardiovascular complications.

Keywords: Polycystic ovarian syndrome, Insulin resistance, Body mass index, Tissue Doppler imaging, Left ventricular diastolic dysfunction.

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Polycystic ovarian syndrome (PCOS) is heterogeneous clinical syndrome. It is one of the widely common endocrine disorders in female during reproductive period between 16 and 44 years.

It affects (5-10%) of this age group[1]. PCOS being associated with other conditions like type 2 diabetes mellitus, dyslipidemia, obesity, hypertension, heart disease, obstructive sleep apnea, endometrial cancer and mood disorders[2]. Also, PCOS associated with metabolic syndrome. Androgen excess is the central

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defect in PCOS patients, yet it is triggered by other factors, obesity and insulin resistance being frequently involved. Insulin level, insulin resistance and homocysteine levels are elevated in PCOS women[3]. "Metabolic Syndrome" is characterized by a clustering of metabolic abnormalities which lead to increased cardiovascular disease and all-causes mortality[4]. Metabolic dysfunction is an important risk associated with PCOS, it can or seen at an early age. Although not all PCOS women are obese, about 20-50% of PCOS women are thin or normal in weight and the pathophysiology of the disease in these women may vary from that in obese women[5]. This appears as a tendency towards central obesity and symptoms associated with insulin resistance, this will lead to metabolic syndrome[1,5].

Obesity and insulin resistance inherently linked to increased visceral adiposity which leads to metabolic and proliferative alternations in cardiac myocytes and interstitium produce disturbances in left ventricular functions[6]. Several studies identified the role of insulin resistance in the development of cardiac function disturbance[6,7].

A review published in 2010 revealed that PCOS women have a high prevalence of insulin resistance and type 2 diabetes, even with low body mass index[8]. Women with PCOS are more prone to gestational diabetes, especially if obese[5]. Obesity may be a good indicator of metabolic dysfunction than PCOS condition itself[9]. Also, obesity is a powerful magnifying factor of several aspects of PCOS, which are not limited to favorite the development of insulin resistance and hyperinsulinemia[10].

It has been reported that women who shows clinical criteria of PCOS have lower 5-years cardiovascular events free survival than women without criteria of PCOS[11]. Oxidative stress caused by reactive oxygen species (ROS) production in immune cells plays a fundamental role in the genesis and progression of endothelial dysfunction, which leads to the development of arterial hypertension and cardiovascular disease[12]. Furthermore, chronic inflammation and insulin resistance are two essential elements in the etiopathogenesis of metabolic syndrome and type 2 diabetes mellitus which in turn open the door for further complications for the overall health of women with PCOS[13].

Conventional echocardiography (C-Echo) is quick, inexpensive, non-invasive and radiation free method to assess and make accurate determination of left ventricular (LV) volume and ejection fraction (EF) is important for making clinical decision and follow up. LVDD in PCOS women can be detected by quantitative tissue Doppler image (TDI) before the onset of clinical signs of heart failure and before the appearance of traditional echocardiographic indices of systolic myocardial dysfunction. Application of tissue Doppler imaging might validate routine screening used for diastolic dysfunction to presume to have healthy heart[14].

The study aims to explore the role of obesity in the pathogenesis of early structural functional changes in echocardiographic parameters associated with PCOS by both conventional echocardiography and TDI.

Methods

The study was done at Department of Physiology, Medical College of Al-Mustansiriya university in cooperation with echo and infertility units of Al-Yarmook teaching hospital, during the period from December 2015 until March 2017.

One hundred women with PCOS are enrolled in the study diagnosed by Rotterdam criteria 2003 that indicated presence of PCOS if any two out of three criterion are present in the nonappearance of other diseases that might reason these results[1]:

1. Chronic anovulation and/or oligo-ovulation (oligomenorrhea or amenorrhea).

2. Hyperandrogenism (hirsutism, acne) clinical and/or biochemical.

3. PCOS by ultrasound (polycystic ovaries).

Exclusion criteria (type 2 diabetes mellitus, history of hypertension, systolic blood pressure ≥ 140 mm Hg and or diastolic blood pressure ≥ 90 mm Hg) at the time of visit or the use of antihypertensive drugs[15], valvular heart diseases, cardiac arrhythmia, thyroid disease and renal disease.

All females were between the age of 16 and 45 years were they informed and verbal consent obtained from all women after explanation of the aim of this study. History interview, general physical examinations were performed for all 100 PCOS women. Blood pressure measurement, body mass index (BMI) as measured with this equation:

BMI = Weight / Square Height = (kg/m^2)

Waist to hip ratio (WHR), blood sampling taken after an overnight fasting for oral glucose tolerance test (OGTT), lipid profile, fasting insulin level done by closed system called Automatic Biochemistry Analyser[16] and insulin by immunotech insulin level using immuno radio metric assay (IRMA) by gamma counter.

Echocardiography (echo) by the machine Philips CX50 ultrasound system USA 2009 with a transducer operating 3.5 MHz, echocardiography, conventional, 2-D echocardiography, Motion or M-mode, pulsed-wave Doppler, continuous-wave Doppler and tissue Doppler image done for all subjects.

Above investigations were done in Al-Yarmook teaching hospital, in infertility unit for diagnosing PCOS patients by ultrasound examination, echo unit for measurement of echocardiographic parameters and main lab for biochemical tests. Statistical analysis to the data was approved by using the available statistical package of SPSS-24 (Statistical Packages for Social Sciences, version 24). Data existed in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

Results

The results from this study divided the data into two groups according to the BMI above (> 30 kg/m^2) = 54% and below (< 30 kg/m^2) = 46%, (Figure 1). The study revealed the percentage of subclinical left ventricular diastolic dysfunction (LVDD) in asymptomatic women with PCOS was 11%, one out of 46 % with BMI < 30 kg/m^2 = 2.2% and 10 out of 54% with BMI > 30 kg/m^2 = 18.5%.

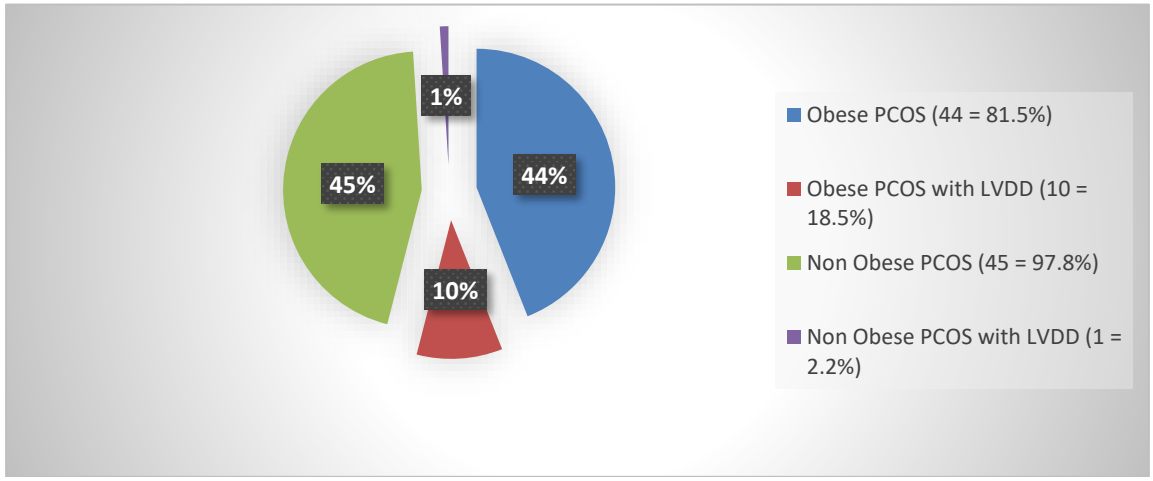

Figure 1: The relative frequency of LVDD in obese compared to non-obese PCOS

Regarding the clinical and metabolic characteristics, there were significant differences between two groups in BMI (kg/m^2), waist circumference (cm), WHR, fasting insulin (µu/ml), serum cholesterol (mg/dl), LDL (mg/dl), LDL/HDL and HOMA-IR. All were higher in PCOS women with BMI above than 30 kg/m^2 (obese women). While there were no significant differences between two groups in age (years), triglycerides (TG) and HDL, (Table 1). When we compared between two groups in the values are expressed as mean ± standard deviation (SD) with the range of each parameter.

Regarding echocardiographic characteristic (Table 2) showed the comparison between obese and non-obese women in M-mode measurement. There were slightly differences in LVEDD, LVESD and IVS between two groups.

Regarding the pulsed-wave Doppler parameters, there was significant difference in peak early filling velocity (E velocity) which is lower in obese PCOS women. There was no significant difference between two groups in peak late filling velocity (A velocity). There was slightly difference in E/A ratio between two groups, slightly lower in obese PCOS women. There was no significant difference between two groups in IVRT. There was significant difference between two groups in DT; it is higher in obese PCOS women, (Table 3).

Regarding tissue Doppler imaging parameters there was significant difference in lateral e′ (cm/sec) between two groups, slightly lower in obese PCOS women. There was no significant difference in lateral a′ (cm/sec) between two groups. There was significant difference in lateral e′/a′ ratio between two groups. There was no significant difference in medial e′ (cm/sec) between two groups. There was significant difference in medial a′ (cm/sec) between two groups. There was significant difference between two groups in medial e′/a′ ratio. Also, there was significant difference between two groups in e′ average and a′ average with P-value 0.011 and 0.020 respectively. There was no significant difference between two groups in E/lateral e′ ratio and E/medial e′ ratio, (Table 4).

Table 1: The clinical and metabolic characteristics of obese PCOS patient compared with non-obese PCOS women.

	PCOS Non-Obese No.=46 BMI(<30.0) Mean ±SD (Range)	**PCOS Obese** No.=54 BMI(≥30.0) Mean ±SD (Range)	P value
Age (years)	26.54±6.58 (16-43)	27.85±7.30 (16-45)	0.056
Body mass index (BMI) (Kg/m²)	25.18±3.04 (18.80-29.90)	34.59±3.68 (30.10-43.60)	0.001*
Waist circumference (cm)	80.35±6.93 (67-96)	94.70±8.22 (76-121)	0.001*
Waist-Hip Ratio (WHR)	0.79±0.05 (0.70-0.91)	0.86±0.08 (0.71-1.20)	0.001*
Fasting blood sugar (FBS) (mg/dl)	95.76±6.57 (83-110)	97.26±4.72 (86-106)	0.189
Fasting insulin (µu/ml)	14.20±2.87 (9.00-19.20)	17.66±2.87 (12.70-24.60)	0.001*
Serum cholesterol (mg/dL)	188.30±28.18 (135-278)	215.30±26.91 (165-312)	0.001*
Serum triglycerides (mg/dL)	147.43±34.29 (30-223)	153.63±33.86 (67-273)	0.367
HDL (mg/dL)	48.17±5.19 (33-60)	48.28±8.34 (30-67)	0.942
LDL (mg/dL)	119.09±22.03 (75-194)	135.13±25.36 (95-220)	0.001*
VLDL (mg/dL)	18.63±7.23 (6-35)	21.65±7.51 (10-45)	0.044*
LDL/HDL	2.50±0.60 (1.40-4.10)	2.85±0.67 (1.70-5.00)	0.008*
HOMAIR	3.26±0.73 (2.00-4.70)	4.12±0.72 (2.90-5.80)	0.001*

* P-value at 0.05 levels.

Table 2: The M-mode echocardiographic characteristics of obese PCOS patient compared with non-obese PCOS women.

	PCOS not Obese no.=46 BMI(<30.0)	PCOS Obese no.=54 BMI(=>30.0)	P value
LVEDD (mm)	41.37±4.10 (33-55)	44.24±3.94 (38-54)	0.001*
LVESD (mm)	27.02±2.84 (22-34)	28.78±3.23 (22-36)	0.005*
EF (%)	63.57±6.33 (51-79)	63.65±5.81 (53-77)	0.946
IVS Thick (mm)	8.39±0.86 (7-10)	8.83±0.99 (7-12)	0.020*
Aortic RD (mm)	22.91±3.16 (16-33)	24.17±4.06 (18-42)	0.092
LAD (mm)	29.07±4.86 (21-39)	30.22±3.62 (22-39)	0.176
RVD (mm)	27.33±3.84 (19-37)	28.00±2.49 (23-35)	0.294

Table 3: The Pulsed-wave Doppler parameters of both groups obese and non obese PCOS women.

	PCOS not Obese no.=46 BMI (<30.0)	PCOS Obese no.=54 BMI (≥30.0)	P value
E (cm/sec)	85.03±11.82 (67.20-119.00)	78.16±12.03 (50.40-105.00)	0.005*
A (cm/sec)	58.11±9.83 (39.60-78.00)	61.07±16.47 (39.60-118.00)	0.288
E/A ratio	1.49±0.24 (1.00-2.50)	1.35±0.35 (0.45-2.02)	0.035*
IVRT (ms)	59.17±16.08 (36-94)	59.22±14.73 (40-90)	0.988
DT (ms)	120.76±9.05 (90-162)	139.39±23.16 (99-199)	0.001*

Table 4: Tissue Doppler imaging (TDI) parameters of both groups obese and non-obese PCOS women.

	PCOS Not Obese No.=46 BMI (<30.0)	PCOS Obese No.=54 BMI (≥30.0)	P value
Lat é (cm/sec)	16.71±3.34 (9.40-24.90)	14.94±3.15 (6.70-22.80)	0.008*
Lat á (cm/sec)	10.64±2.42 (7.20-18.20)	11.27±3.05 (7.28-18.20)	0.262
Lat é/á ratio	1.60±0.28 (1.00-2.29)	1.42±0.45 (0.55-2.41)	0.021*
Med é (cm/sec)	12.98±2.39 (8.00-18.50)	12.06±2.56 (5.13-17.60)	0.067
Med á (cm/sec)	8.57±1.66 (5.20-12.40)	10.02±2.43 (6.10-16.10)	0.001*
Med é/ á ratio	1.54±0.29 (1.00-2.30)	1.27±0.37 (0.42-1.98)	0.001*
é average (cm/sec)	14.85±2.57 (9.70-20.60)	13.51±2.59 (6.05-18.60)	0.011*
á average (cm/sec)	9.61±1.76 (6.20-14.65)	10.65±2.47 (7.00-16.50)	0.020*
E/Lat é ratio	5.25±1.16 (3.43-8.96)	5.42±1.20 (3.60-8.60)	0.480
E/Med é ratio	6.69±1.19 (4.40-9.40)	6.71±1.50 (4.30-10.40)	0.922

*P-value at 0.05 levels.

Discussion

Several studies have suggested that degrees of cardiovascular risk are increased in young or middle aged women with PCOS, like endothelial dysfunction, arterial stiffness, carotid intima-media thickness and myocardial dysfunction[17]. But so difficult to explain how much of this risk is due to PCOS itself and how much to obesity, which is present in PCOS and itself obesity associated with major vascular risk[18]. A new study assessing extra fat accumulation and left ventricular function revealed that the accumulation of triglyceride in the myocardium of moderately obese subject is significant which may result from fatty acid overflow to the heart[19].

This study is the first one done on Iraqi women with PCOS to evaluate cardiovascular risk by echocardiography technology both pulsed-wave Doppler and tissue Doppler imaging (TDI) and

correlated it with clinical and metabolic characteristic (fasting blood sugar, fasting insulin level, HOMA-IR, lipid profile, BMI, waist circumference and WHR).

We divided the data in this study into two groups according to the BMI, above 30 kg/m^2 represented 54% and below 30 kg/m^2 represented 46%, (Figure 1). This study showed that the percentage of subclinical LVDD in asymptomatic women with PCOS was 11%, one out of 46% with BMI below 30 kg/m^2 = 2.2% and ten out of 54% with BMI above 30 kg/m^2 = 18.5%. This result means that the PCOS women who showed an increase LVDD were weight dependent.

These findings are consistence with preceding reports viewing relations between left ventricular diastolic dysfunction and different clinical and metabolic measures of insulin resistance, obesity and dyslipidemia[10]. The results are in agreement with the previous studies done by Tíras MB, et al[20] and Yarali H, et al[21] were they also reported diastolic dysfunction in PCOS women.

Table 1 showed the clinical and metabolic characteristics of two groups obese and non-obese PCOS women. There was significant difference between two groups in BMI, waist circumference, WHR, fasting insulin, serum cholesterol, LDL, LDL/HDL and HOMA-IR. All were higher in obese PCOS women.

So our findings are in agreement with many studies done and viewing relations between left ventricular systolic and diastolic dysfunction and various measures of HOMA-IR and lipid profile. Although some, not all, studies have shown increased total cholesterol concentrations level in PCOS women[6].

Also, Guzick DS, et al[22] mentioned that PCOS women may have an increased risk of subclinical atherosclerosis. Jialal I, et al[23] said that insulin resistance was prominent abnormality in both obese and lean women with hyperandrogenism and PCOS. Also, dyslipidaemia has been reported in PCOS women with higher serum triglyceride and lower serum HDL values[9]. Insulin is a major positive controller of lipoprotein lipase which is implicated in the pathway of HDL production. So that dyslipidaemia is reasoning to be secondary to insulin resistance[10]. The present study is consistence with Tekin A, et al[24] who found that PCOS patients were had higher LDL, cholesterol and an increase body mass index (BMI) than other women without LVDD.

Regarding echocardiographic measurements in both obese and non-obese PCOS women in M-mode measurement there was a slightly difference in LVEDD, LVESD and IVS thickness between two groups but still within normal range, (Table 2), so it is considered normal.

Table 3 showed pulsed-wave Doppler parameters of 2 groups obese and non-obese PCOS women. There was a significant difference in peak early filling velocity (E), lower in obese PCOS women. Also, there was slightly difference in E/A ratio between two groups, lower in obese PCOS women. There was significant difference between two groups in DT, higher in obese PCOS women. But there was no significant difference between two groups in peak late filling velocity (A) and IVRT.

Table 4 showed tissue Doppler imaging parameters of obese and non-obese PCOS women. There was significant difference in lateral e′ (cm/sec) and lateral e′/a′ ratio between two groups, both they are lower in obese PCOS women. There was no significant difference in lateral a′ (cm/sec) and medial e′ (cm/sec) between two groups. There was significant difference in medial a′ (cm/sec); it's higher in obese PCOS women. Also there was significant difference in medial e′/a′ ratio; it's lower in obese PCOS women.

The results are consistence with study done by Ercan Erdoğan, et al[25] that there were no significant differences in M-mode parameters in PCOS women than control

group. Two studies done by Tekin A, et al[24] Selcoki Y, et al[26], they concluded that there were no significant differences in echocardiographic parameters between PCOS women and control group.

Brutsaert DL, et al[27] who reported that LVDD is an early indicator of cardiomyopathy and related to cardiovascular disease, endothelial dysfunction, hypertension correlated with insulin resistance and oxidative stress.

Yarali H, et al [21] consistence with our study who they found that PCOS women had lower mitral E velocity, lower mitral E/A ratio and decrease in IVRT than other healthy control group. So they suggested that left ventricular diastolic dysfunction was impaired in PCOS women.

This finding is consistence with the study done by Wojciech Kosmala, et al [28] who concluded that "a systematic impairment of left ventricular function in young women is associated with obesity and insulin resistance rather than the sex hormone disturbances associated with polycystic ovaries".

Another study done by Rees E, et al[29] was in agreement with this study "Suggested that both central adiposity and insulin resistance contribute to arterial stiffness and impaired diastolic function but that PCOS status does not confer additional risk".

The body fat distribution is considered as a significant factor in LVDD as "central adiposity" was found more closely associated to abnormal left ventricular diastolic chamber function than has BMI. "Central obesity, especially visceral adiposity" has been manifested to be associated with cardiovascular risk. An increased adipose tissue deposition could be promoting the production of interleukin-6 which raises the secretion of acute-phase proteins like C-reactive protein (CRP) by the liver[30].

In conclusion, PCOS women who have asymptomatic LVDD be liable to be more obese by increased BMI, wider circumference and high waist to hip ratio and have high insulin level and HOMA-IR. Given an important role to obesity and insulin resistance were play in the progression of PCOS and its potential subsequent metabolic and cardiovascular complications like LVDD as an early signal.

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