Postprandial lipid profile and Androgen status in polycystic ovarian syndrome (PCOS)

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Abstract

Objectives: Polycystic ovary syndrome (PCOS) is an endocrinopathy that affects women of reproductive age. PCOS shares components with the metabolic syndrome and has broad health implications. Lipid abnormalities, including elevated low-density lipoprotein (LDL), triglyceride levels and decreased high-density lipoprotein (HDL), are often found in women with PCOS. It is clear that obesity, insulin resistance and hyperandrogenism coexist in PCOS, and have independent and interactive effects on dyslipidemia

Aim: To study the relationship between postprandial Triglyceride as predictor for cardiac disease and Testosterone in reproductive age women with PCOS.

Patinents and Methods: Postprandial lipid profile and Sex hormones level were measured in 40 PCOS patients and 35 control women without a known family history of PCOS. DRG-ELISA kit used to Testosteanone and Sex Hormone Binding globulin, Biomerieux- VIDAS kit used to Estradiol follicular stimulating hormone and luteinizing hormone, enzymatic methods used for postprandial lipid profile measurement.

Results: A statistically significant differences were found in serum levels of postprandial Triglyceride, HDL-C, LDL-size & atherogenic index between the two groups PCOS and healthy control women ($p \leq 0.05$). also there was a highly significant difference in luteinizing hormone(LH), follicular stimulating hormone (FSH), estradiol (E2), sex hormone binding globulin (SHBG)and in Free androgenic index (FAI) ($p \leq 0.001$) and there was no significant in the level of testosterone between PCOS women and healthy control ($p=0.56$). Serum Testosterone levels correlated significantly with Triglyceride ($p=0.034$), LDL-size ($p=0.021$), Atherogenic index ($p= 0.032$), BMI ($p=0.012$), Age ($p=0.016$) & it's reversely correlated with HDL-C ($p=0.043$) .Estradiol level correlated significantly with HDL-C ($p=0.032$) in dyslipidemic women with PCOS.

Conclusion: These results suggest that postprandial elevation of Triglyceride is a predictor of cardiovascular diseases in PCOS reproductive age dyslipidemic women.

Key Words: Polycystic ovarian syndrome, postprandial lipid profile, Testosterone, Sex hormone binding globulin and free androgenic index.

الخلاصـــــــــة

الأهداف:

داء تكيس المبايض (PCOS) هو من الامراض التي تحدث بسب اعتلال الغدد الصم التي تؤثر في النساء في سن مبكر. داء تكيس المبايض يشترك مع المتلازمة الايضية ببعض المكونات. فيؤدي الى مضاعفات صحية واسعة ففي اغلب الاحيان يجد أختلال في ايض الدهون عند النساء المصابات بداء تكيس المبايض كأرتفاع مستوى الدهون الثلاثية والدهون واطئة الكثافة مع انخفاض في الدهون عالية الكثافة. فمن الواضح حدوث السمنة ,مقاومة الجسم للانسولين و زيادة الصفات الثانوية الذكرية تتعايشُ في النساء المصابات بتكيس المبايض.ولها تأثيرات مستقلة وتفاعلية مع اضطراب الدهون .

الهدف: لدراسة العلاقة مابين الدهون الثلاثية بعد مرور ساعتين من الوقت على وجبة الافطار (كمتنبأ للامراض القلبية) والهرمون الذكري في النساء المصابات بتكيس المبايض.

المرضى وطرق العمل: بعد مرورو ساعتين على وجبة الافطار تم جمع نماذج الدم من النساء المصابات بتكيس المبايض وعددهم 40. ونساء مقاربات لهن في العمر. كمجموعة سيطرة ويبلغ عددهم 35. وذلك لقياس مستويات الدهون والهرمونات الجنسية الانثوية والذكرية وكذلك الهرمونات الجنسية المرتبطة بالبروتين(SHBG).
النتائج: اختلاف معنوي قد وجد في مستويات الدهون الثلاثية , الدهون العالية الكثافة , حجم الدهون الواطئة الكثافة وكذلك في معدل مقياس الجلطة القلبية. وقد لوحظ ان هناك فرق معنوي في مستوى الهرمونات الجنسية والهرمونات الجنسية المرتبطة بالبروتين ولا يوجد فرق معنوي في مستوى الهرمون الذكري بين مجموعتي الدراسة النساء المصابات بتكيس المبايض ومثيلاتهن من الاصحاء. كما وقد وجدت علاقة خطية ذات تناسب طردي بين كل من الهرمون الذكري و الدهون الثلاثية ,حجم الدهون عالية الكثافة ,مقياس الجلطة القلبية ,دالة كتلة الجسم .وعلاقة خطية عكسية مع الدهون عالية الكثافة. كما لوحظ ان هناك علاقة خطية طردية بين كل من الهرمون الانثوي والدهون عالية الكثافة.
الخاتمة: ان هذه النتائج تقترح ان قياس الدهون الثلاثية بعد مرور ساعتين من وجبة الافطار ممكن اعتمادها وذلك كمتنبأ مبكر للامراض القلبية في الاعمار المنتجة لدى النساء اللواتي يعانيين من اضطراب الدهون و المصابات بتكيس المبايض. الكلمات الافتتاحية:
تكيس المبايض, الهرمون الذكري, الهرمونات الجنسية, الهرمونات الجنسية المرتبطة بالابروتين .

Introduction

Polycystic ovarian syndrome (PCOS) consists of a group of symptoms and changes in hormone levels. The name comes from the fact that women with the condition often have many small painless cysts in the ovaries. Symptoms include irregular or absent menstrual periods, infertility, weight problems, acne, excess facial and body hair, thinning head hair, and brownish discoloration of the skin in the neck and upper chest (1,2). The exact cause of PCOS is unknown, but an imbalance of hormones is central. It has been called "ovarian androgen excess" because the ovaries produce male hormones (androgens) in increased amounts. Diagnosis is made on the basis of symptoms, measurement of hormone levels, and possibly ovarian ultrasound and measurement of blood glucose. Most women with PCOS have insulin resistance and many are overweight (3).

Historically, the associations between metabolic abnormalities and cardiovascular disease have been studied largely during fasting conditions. However, the important contribution of postprandial state to cardiovascular disease is increasingly being recognized, particularly in conditions of insulin resistance, PCOS and T2DM. The mechanisms of postprandial hyperglycemia, as well as its clinical importance (including cardiovascular) risk have been addressed in several excellent review articles (4).

Postprandial triglyceride concentrations often remain elevated throughout the day. Importantly postprandial triglyceride concentrations may in fact be a better predictor of cardiovascular events than fasting triglycerides. The adverse effect of postprandial triglycerides is thought to be mediated by proatherogenic lipolysis products of nascent triglyceride-rich lipoproteins, such as remnant lipoproteins and fatty acids, and even a transient increase in these factors may worsen vascular function(5-8).

Subjects and Methods

Subjects

- **Patients**

Forty patients with Polycystic ovarian syndrome aged between (25-39) years, and their (mean±SD) age were (30±7.2). They were recruited from High Institute For Infertility Diagnosis &Assisted Reproductive Technologies. The study conducted in April-2012.

- **Control group**

Thirty five apparently healthy women were involved as a control group with matching age to the patient group (mean±SD) age was (25±6.54). None of them have a history of thyroid disease, Polycystic Ovary Syndrome, Diabetes Mellitus, renal impairment, or any other severe illness or infection, and not taking any drug (including hormone replacement

and any estrogenic, anti hypertensive or lipid lowering medication or any operation on the ovary

Blood collection:-

Ten mls of blood were collected in to a plain test tube in postprandial state (2-3 hours after breakfast) at the morning. The serum was obtained after centrifugation at 3200 rpm for 10 min. then was divided into small aliquots.

a- Immediate measurement of serum glucose, lipid profile, was done using the enzyme colorimetric methods.

b- The rest was stored at (- 20 C°) until assayed for hormones analysis: luteinizing hormone (LH), follicular stimulating hormone (FSH), estradiol (E2), testosterone and sex hormone binding globulin (SBG).

Method

- **Determination of hormones**

A- Serum Estradiol(ES), Lutinizing hormone (LH), Follicular stimulating hormone (FSH) were estimated by miniVIDAS Kit (Biomerieux, France).

B- Serum testosterone and Sex hormone binding globulin were estimated by ELIZA Kit.

- Enzymatic methods were used for measuring: Triglycerides, Total cholesterol and High density lipoprotein.

Statistical analysis:

The data of the research were stored in Microsoft Excel Spread sheet and analyzed on the computer using Microsoft Excel program (2010) and SPSS (v.15). All values were expressed as mean± standard deviation (M±SD).Statistical analysis were performed using student's T-Test to estimate the difference between the groups, and correlation regression taking ($P< 0.05$) as the lowest limit of significance.

Results

A- Postprandial lipid profile in reproductive age women with PCOS

Postprandial lipid profile in reproductive age women was measured and compared with healthy control women this study show highly significant elevation in Triglyceride, Atherogenic index and LDL-size. And highly significant reduction in HDL-C. With p-value 0.0001 in dyslipidemic women with PCOS and there was no significant difference in the mean of total cholesterol and LDL-C as shown in table (1).

B- Sex hormones and Free Androgenic Index (FAI) in reproductive age Women with (PCOS)

As shown in table (2) there was significant elevation in luteinizing hormone (LH) in dyslipidemic women with polycystic ovarian syndrome (PCOS) p- value 0.001.

Follicular stimulating hormone (FSH) and Estradiol (E2) highly significant reduction in mean of their levels was found in reproductive age dyslipidemic women with PCOS when compared with healthy control p- value (0.001)& (0.0001) respectively.

Testosterone were not significant in dyslipidemic women with PCOS when compared with reproductive age healthy control group p- value (0.56)

Sex hormone binding globulins (SHBG) highly significant differ in PCOS when compared with healthy control women p- value (0.0001).

And there was highly significant difference in mean of free androgenic index (FAI) in reproductive age dyslipidemic women with PCOS p- value (0.001).

Table 1. Postprandial lipid profile in both control and dyslipidemic reproductive age women.

Parameters	Dyslipidemic women	Control

	with PCOS Mean±S.D	
N	40	35
Age (year)	30±7.2	25±6.54
t- test P-value*	0.63	□
Triglyceride (mmol/l)	2.75±0.54	1.81±0.74
t- test P-value*	H.S	□
total cholesterol (mmol/l)	4.85±0.44	4.53±0.81
t- test P-value*	0.21	□
HDL-C(mmol/l)	0.88 ±0.21	1.18±0.28
t- test P-value*	H.S	□
LDL-C(mmol/l)	2.72±0.54	2.52± 0.85
t- test P-value*	0.097	□
Atherogenic index (LDL-C/HDL-C)	3.28±1.12	2.27±0.97
t- test P-value*	H.S	□
LDL size index (TG/HDL-C)	3.27±0.91	1.61±0.76
t- test P-value*	H.S	□

- Significant p value at 0.05 or less.
- H.S (Highly Significant) when P-value ≤ 0.0001.

Table 2. Sex hormones & FAI in both control and dyslipidemic Reproductive age women.

Parameters	Dyslipidemic women with PCOS Mean±S.D	Control
N	40	35
LH (miu/ml)	5.46±2.87	4.09±1.74
t- test P-value*	H.S	□
FSH (miu/ml)	4.26±1.98	6.36±2.29
t- test P-value*	H.S	□
E2(pg/ml)	52.90±7.75	97.67±23.49
t- test P-value*	H.S	□
Testosterone (nmol/l)	1.59±0.53	1.23±0.53
t- test P-value*	0.56	□
SHBG (nmol/l)	41.52±9.60	80.13±15.67
t- test P-value*	H.S	□
FAI	3.83±0.69	1.74±0.55
t- test P-value*	H.S	□

- Significant p value at 0.05 or less.
- H.S (Highly Significant) when P value ≤ 10^{-3}

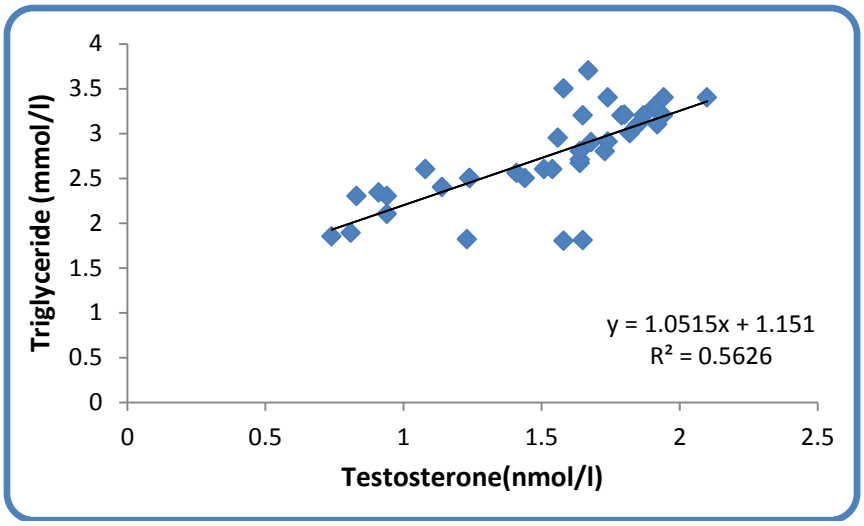

Figure 1. Correlation between testosterone level and Triglyceride in PCOS patients

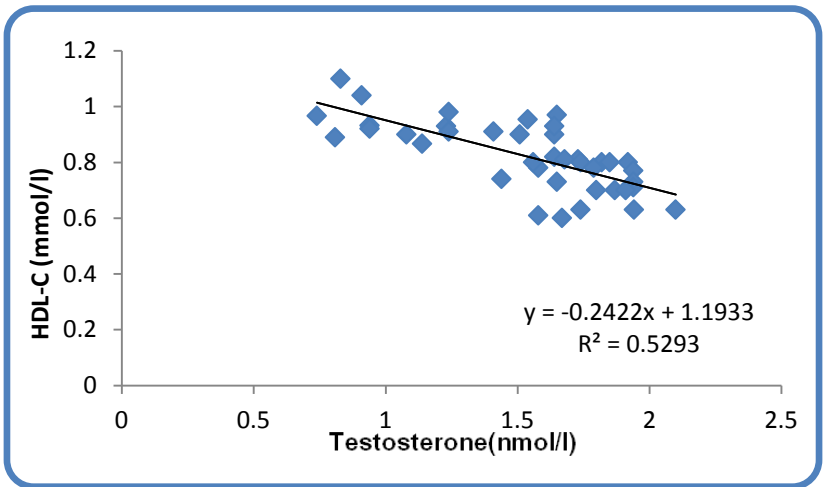

Figure 2. Correlation between testosterone level and HDL-C in PCOS patients.

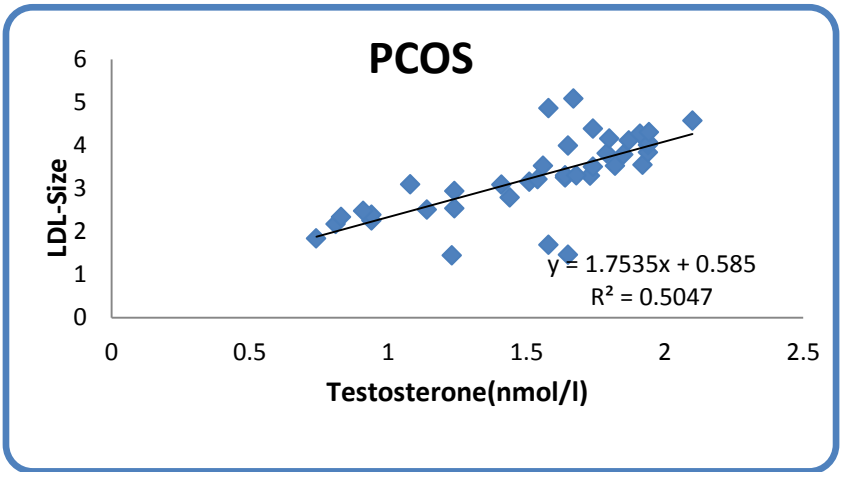

Figure 3. Correlation between testosterone level and LDL-sizein PCOS patients.

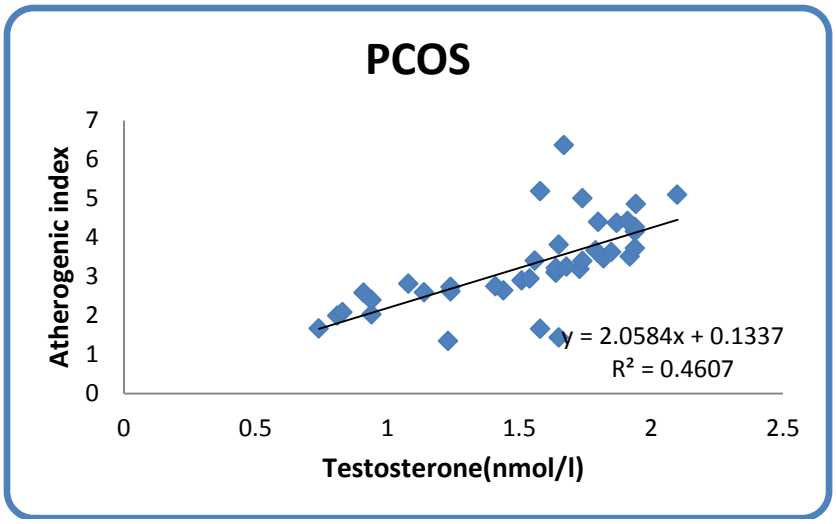

Figure 4. Correlation between testosterone level and atherogenic index in PCOS patients.

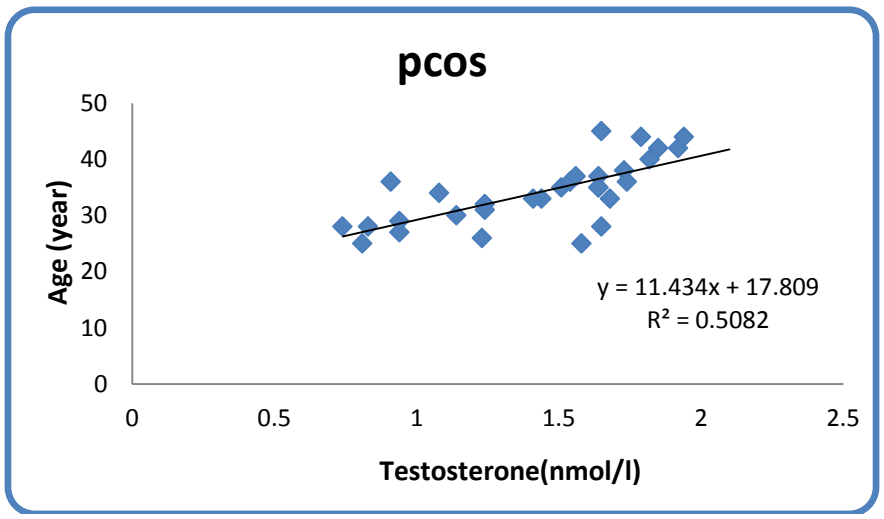

Figure 5. Correlation between testosterone level and the age in PCOS patients.

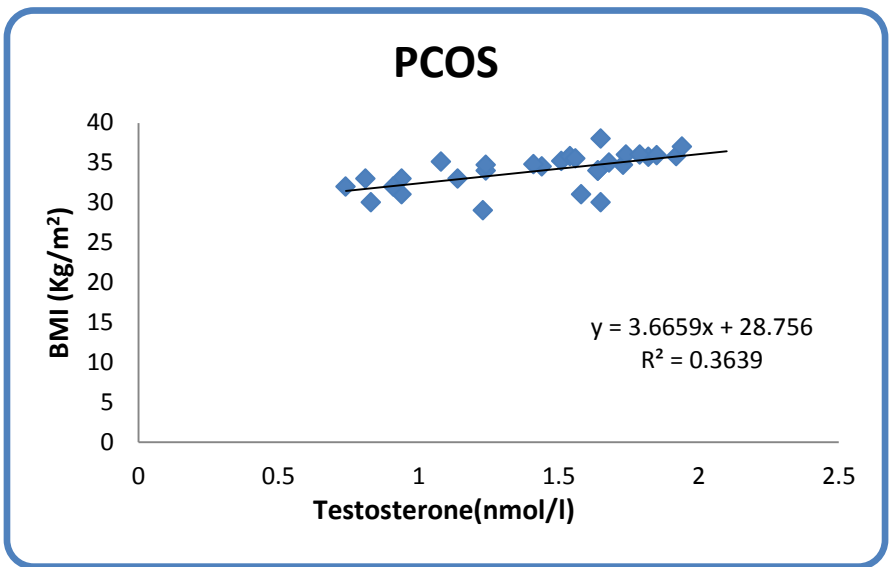

Figure 6. Correlation between testosterone level and BMI in PCOS patients.

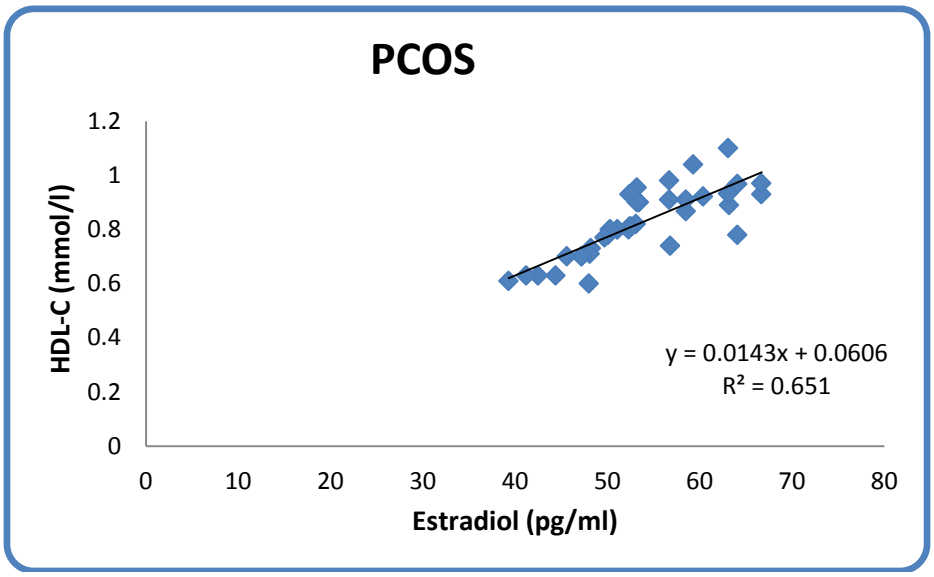

Figure 7. Correlation between Estradiol level and HDL-C in PCOS patients.

Discussion

Dyslipidemia is common in women with PCOS. They often have increased levels of LDL cholesterol. Overweight women with PCOS may also have low levels of HDL cholesterol and high levels of triglycerides, which are typical of insulin resistance. These lipid disorders put women with PCOS at increased risk for cardiovascular disease later in life. PCOS is not curable, but its effects are manageable with medications and changes in diet and exercise (9).

This study deals to mention the important of postprandial lipid profile especially postprandial elevation of triglyceride in patient with PCOS is a good predictor for cardio vascular disease (CVD). Significantly increase of postprandial TG, Atherogenic index and LDL-size. With a significant reduction in HDL-C was seen in this study. This contributed to irregular lipid metabolism in women with PCOS when compared to healthy women. Studies related these abnormalities in lipid profile in PCOS women to the insulin resistance. And this causes elevation in luteinizing hormone (LH) and testosterone and reduction of follicular stimulating hormone (FSH), estradiol and SHBG. The LH stimulates theca cells resulting in production of testosterone and androstenedione, whereas the FSH stimulates aromatase in the granulose cells, resulting in aromatization of androgens into oestrogens (10). The reduction in SHBG in PCOS related to insulin resistance (that develops with weight increases) due to the ability of insulin to inhibit hepatic SHBG synthesis (11). This loss in circulating SHBG, which preferentially binds androgens, leads to greater bioactivity of circulating androgen levels in PCOS women and this could be seen from the calculated value of free androgenic index (FAI) as shown in table 2.

Data for the relationship between SHBG and CVD have been mixed. Low SHBG levels, which are sometimes considered an androgenic marker in women, have been associated with low HDL cholesterol as well as increased risk of diabetes (12) In case-control studies, low plasma levels of SHBG were associated with higher likelihood of atherosclerosis on angiography and carotid intimal-medial thickness(13); however, another angiographic case-control study failed to find an association.(14)

In this study we found significant positive correlation between testosterone

and triglyceride (p=0.034), LDL-size (p=0.021), Atherogenic index (p= 0.032), BMI (p=0.012), Age (p=0.016) & it's reversely correlated with HDL-C (p=0.043) .Estradiol level correlated significantly with HDL-C (p=0.032) in dyslipidemic women with PCOS.

Many observational studies show that CHD risk increases with increases in total and LDL cholesterol levels and decreases with increases in HDL cholesterol levels in both genders, but the relative importance of these lipoprotein fractions might differ by gender (15-17). Levels of HDL cholesterol and triglycerides appear to be more closely related to CHD risk among women than men, whereas LDL cholesterol appears to be a more potent predictor among men (18, 19). Non-HDL cholesterol appears to be a better measure of CHD risk in women than in men (20). Although the relative risk of CHD due to lipid abnormalities is higher in younger than older women, the attributable risk is higher in the older age groups (21).

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References

1. Bulun SE, Adashi EY. The physiology and pathology of the female reporductive axis. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. Williams Textbook of Endocrinology. 11th ed. Philadelphia, Pa: Saunders Elsevier; 2008:chap 16.
2. Radosh L. Drug treatments for polycystic ovary syndrome. Am Fam Physician. 2009;79:671-676.
3. Lobo RA. Hyperandrogenism: Physiology, etiology, differential diagnosis, management. In: Katz VL, Lentz GM, Lobo RA, Gershenson DM, eds. Comprehensive Gynecology. 5th ed. Philadelphia, Pa: Mosby Elsevier;2007:chap 40.
4. ACOG Practice Bulletin Number 108, October 2009. Accessed March 31, 2010.
5. Erica T. Wang, MD, Ronit Calderon-Margalit, MD MPH, Marcelle I. Cedars, MD, Martha L. Daviglus, MD PhD, Sharon S. Merkin, PhD, Pamela J. Schreiner, PhD, et. al. Polycystic Ovary Syndrome and Risk for Long-Term Diabetes and Dyslipidemia J Clin Endocrinol Metab 2011 January; 117(1): 6–13.
6. Adashi, E.Y. (1994) The climacteric ovary as a functional gonadotropin- driven androgen-producing gland. Fertil. Steril., 62, 20-27.
7. Arlt, W.; Justl, H.G.; Callies, F.; Feincke, M.; Hubler, D.; Oettel, M.; Ernst, M.; Schulte, H.M. and Allolio, B. (1998) Oral dehydroepiandrosterone for adrenal androgen replacement: Pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy female after dexamethasone suppression. J. Clin. Endocrinol. Metab., 83, 1928-1934.
8. Haffner SM, Moss SE, Klein BE. Sex hormones and DHEA-SO4 in relation to ischemic heart disease mortality in diabetic subjects: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care. 1996;19:1045–1050.
9. Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. J Clin Endocrinol Metab. 2006 Apr; 91(4): 1357–1363
10. Haffner SM, Valdez RA, Morales PA. Decreased sex hormonebinding globulin predicts noninsulin-dependent diabetes mellitus in women but not in men. J Clin Endocrinol Metab. 1993;77:56–60.
11. Reinecke H, Bogdanski J, Woltering A. Relation of serum levels of sex hormone binding globulin to coronary heart disease in postmenopausal women. Am J Cardiol. 2002;90:364.
12. Hauner H, Bognar E, Blum A. Body fat distribution and its association with metabolic and hormonal risk factors in women with angiographically assessed coronary artery disease: evidence for the presence of a metabolic syndrome. Atherosclerosis. 1994;105:209–216.
13. Lapidus L, Lindstedt G, Lundberg PA. Concentrations of sexhormone binding globulin and corticosteroid binding globulin in serum in relation to cardiovascular risk factors and to 12-year incidence of cardiovascular disease and overall mortality in postmenopausal women. Clin Chem. 1986;32:146–152.
14. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality30 years of follow-up from the Framingham Study. JAMA 1987;257:2176-2180.

15. Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levelsthe Framingham Study. JAMA 1986;256:2835-2838.
16. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein (a), apolipoproteins A-I and B, and HDL density subfractionsthe Atherosclerosis Risk in Communities (ARIC) study. Circulation 2001;104:1108-1113.
17. Brunner D, Weisbort J, Meshulam N, et al. Relation of serum total cholesterol and high-density lipoprotein cholesterol percentage to the incidence of definite coronary eventstwenty-year follow-up of the Donolo-Tel Aviv Prospective Coronary Artery Disease Study. Am J Cardiol 1987;59:1271-1276.
18. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women Arch Intern Med 1993;153:2209-2216
19. Gordon DJ, Rifkind BM. High density lipoproteinthe clinical implications of recent studies. N Engl J Med 1989;321:1311-1316.
20. Cui Y, Blumenthal RS, Flaws JA, et al. Non–high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality Arch Intern Med 2001;161:1413-1419.
21. Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and womenreview of an NHLBI Workshop. Ann Epidemiol 1992; 2: 161-176.