Effects of metformin on the lipid profilein polycystic ovarian syndrome patients

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Abstract:

Background

Polycystic ovary syndrome (PCOS) is the most common and prevalent endocrinopathy in women, and the most common cause of anovulatory infertility. An altered lipid profile is common in polycystic ovary syndrome (PCOS) and is usually characterized by increased total cholesterol, triglycerides, low-density lipoproteins and very low density lipoprotein levels with low high-density lipoprotein. PCOS is associated with a higher frequency of cardiovascular disease because of dyslipidemia. Which are potent markers for cardiovascular risk factors. Metformin, is a widely used antihyperglycemic agent. It decreases insulin resistance and reduces hyperglycemia through a reduction of the hepatic glucose production.

Objectives

Determine the beneficial effect of metformin in PCOS patients in reducing lipid profile and subsequently reduction in cardiovascular disease.

Method

Measurements and analysis levels of total cholesterol, triglycerides, low-density lipoproteins, very low density lipoprotein and high-density lipoprotein were samples collected at the Institute of embryo research and infertility treatment, Al-Nahrain University. PCOS patients were recruited at the consultant clinic Patients: forty three women with PCOS were studied. Anthropometric data, lipid profile, were evaluated, before oral metformin (500mg/twice daily) treatment and after three months of use.

Results

Patients with PCOS after oral metformin treatment, revealed a significant lowering serum concentrations of total cholesterol, triglyceride, low-density lipoproteins and very low density lipoprotein and elevated high-density lipoprotein compared to before treatment.

Conclusions

dyslipidemia is common finding in PCOS women, in this study we found that the use of oral metformin tablets 500mg/ twice daily for three months will correct lipid profile level (cholesterol, triglyceride, LDL, VLDL and HDL) which is considered as cardiovascular risk factors and this lead to reduce risk of cardiovascular diseases.

Key word: - Polycystic ovarian syndrome, lipid profile and metformin

Introduction

Polycystic ovary syndrome (PCOS) is the most common and prevalent endocrinopathy in women (1) and the most common cause of anovulatory infertility, affecting 5-10% of the population (2,3) and represent 40% of infertility causes also it is responsible for 30% of miscarriage (4). PCOS is a heterogeneous condition (clinically and biochemically), affected women presenting in clinical practice seeking treatment for reproductive disorders such as menstrual cycle disturbances (oligomenorrhoea, amenorrhoea), infertility, hirsutism or acne (5). The menstrual irregularity of PCOS patients typically begins at menarche and although amenorrhea may occur (6). The endocrine profile of women with PCOS is characterized by high plasma concentrations of ovarian and adrenal androgens, gonadotropin abnormalities, a relative increase in estrogen levels (especially estrone) derived from conversion of androgens, reduced levels of sex hormone binding globulin (SHBG), and often high levels of prolactin (PRL)

and insulin (7). In addition, women with PCOS are thought to be at increased risk for endometrial cancer (through chronic anovulation with consequent estrogen exposure unopposed by progesterone of the endometrium) (5), breast and ovarian cancer (8). However, it has recently become clear that PCOS is also linked to a number of metabolic disturbances, including type 2 (non-insulin-dependent) diabetes mellitus (T2DM), possibly cardiovascular disease (CVD) and dyslipidemia (9, 10). Obesity is a common feature of women with PCOS, and it represents an important risk factor for both CVD and diabetes (11). The primary etiology of PCOS is unknown (12). However, insulin resistance with compensatory hyperinsulinaemia is a prominent feature of the syndrome; Hyperinsulinaemia stimulates both ovarian and adrenal androgen secretion directly and suppresses sex hormone-binding globulin synthesis from the liver, resulting in an increase in free, biologically active androgens. This excess in local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation along with the other clinical manifestations of hyperandrogenism such as hirsutism and acne (13).

Metformin, is a widely used antihyperglycemic agent (14). It decreases insulin resistance and reduces hyperglycemia through a reduction of the hepatic glucose production, it is an insulin-sensitizing agent represents a safer treatment alternative (15) and has been used successfully as the first-line drug to induce ovulation in women with PCOS (16). It may be added to clomiphene citrate in women with clomiphene resistance who are older and who have visceral obesity, combination with clomiphene citrate may increase ovulation rates and pregnancy rates (17) and its use before or during assisted reproductive technique (ART) cycles improved live birth or clinical pregnancy rates (18). Metformin reduce long-term consequences of insulin resistance in PCOS women, such as T2DM and CVD (19).

Dyslipidemia and PCOS have reported on cholesterol levels and triglycerides. The lipid profile that is found in women with PCOS consists of elevated triglycerides levels, together with low levels of high-density lipoprotein (HDL) (20). These changes are consistent with the lipid profile that is typically found in association with insulin resistance. Increased secretion of very low-density lipoprotein (VLDL) particles by the liver results in elevated plasma triglycerides concentrations. Subsequently, triglycerides are exchanged for cholesteryl ester by the activity of cholesteryl ester transfer protein. This process results in triglycerides -enriched HDL particles that are catabolized more rapidly, and cholesteryl ester -enriched VLDL particles that are converted into small dense low-density lipoprotein (LDL) particles (21). As a consequence, insulin resistance contributes to decreased plasma levels of HDL (22).

Patients and Methods

PCOS - patients

Forty three PCOS patients (diagnoses made on base of clinical, hormonal and ultrasound examination) were obtained from the consultant clinic of embryo research and infertility treatment institute; of age group 18-38 years (25.9 ± 5.9) were involved in the study. The history were taken from the patients, they have no other medical illness other than infertility due to PCOS. Twelve hour fasting blood samples were obtained at the beginning before starting treatment and then metformin tablets 500mg /twice daily for three months were given and then other twelve hour fasting blood samples were taken.

Blood sampling

Blood samples (3ml) were withdrawn from patients after overnight fasting before test. Samples then transferred to plastic centrifuge tubes. Blood samples were left to clot for one hour, and then centrifuged at 1000×g for 10 min.(Centrifuge model A116 universal).

Lipid profile test

Using spectrophotometer (Cecil Ce 1011 Cambridge England), serum cholesterol, triglyceride, LDL, VLDL and HDL levels were determined for patients according to the manufacture recommended procedure, by using Biotic Kit (England). Statistical analysis: The results measured statistically by using student t-test

Results

Serum Lipid profile levels were measured for polycystic ovarian syndrome patients before and after treatment with metformin tablet 500mg /twice daily. As shown in figure (1), the mean serum Cholesterol in PCOS patients after treatment was found to be equal to (182 ± 25.56) mg/dl which was highly significant lower ($p<0.01$) than before treatment (233.05 ± 62.35) mg/dl. In figure (2), the mean serum level of Triglyceride in PCOS patients after treatment was found to be equal to (111.7 ± 26.43) mg/dl which was highly significant lower ($p<0.01$)than before treatment (142 ± 29.4) mg/dl

. In figure (3), the mean serum level of LDL in PCOS patients after treatment was found to be equal to (112 ± 30.12) mg/dl which was highly significant lower ($p<0.01$)than before treatment (157 ± 24) mg/dl. In figure (4), the mean serum level of VLDL in PCOS patients after treatment (22.07 ± 5.13) mg/dl was highly significant lower ($p<0.01$)than before treatment (29.625 ± 6.31) mg/dl. In figure (5), the mean serum level of HDL in PCOS patients after treatment was (44.77 ± 4.34) mg/dl was significantly higher ($p<0.05$)than before treatment (42.89 ± 3.78) mg/dl.

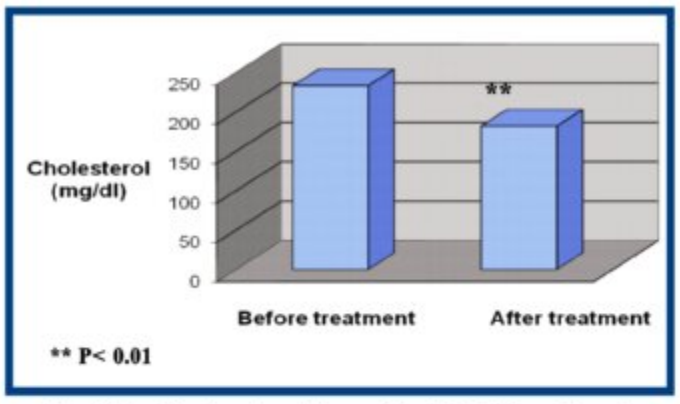

Fig.(1):-Cholesterol level in PCOS patients before and after treatment with

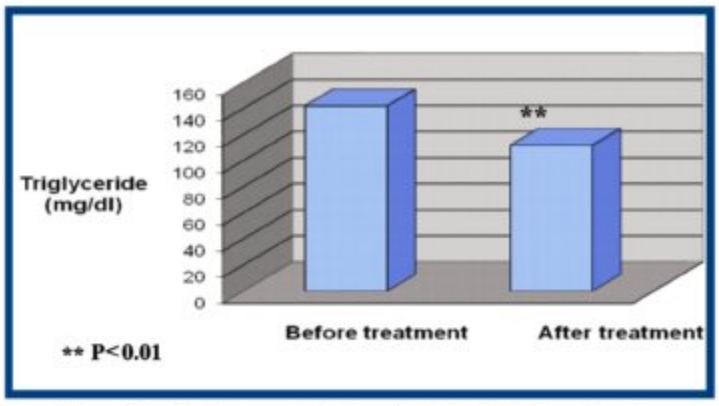

Fig.(2):-Triglyceride level in PCOS patients before and after treatment with metformin

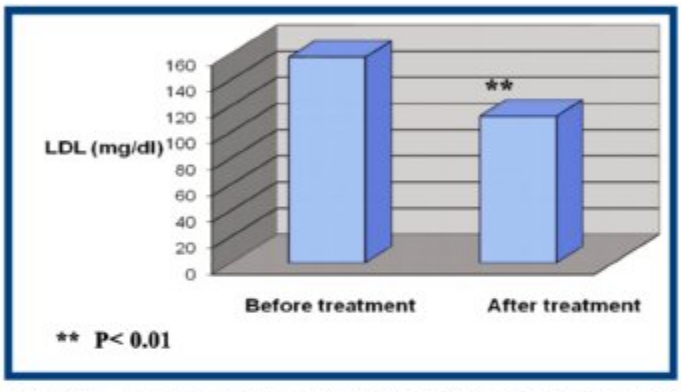

Fig.(3):- LDL level in PCOS patients before and after treatment with metformin

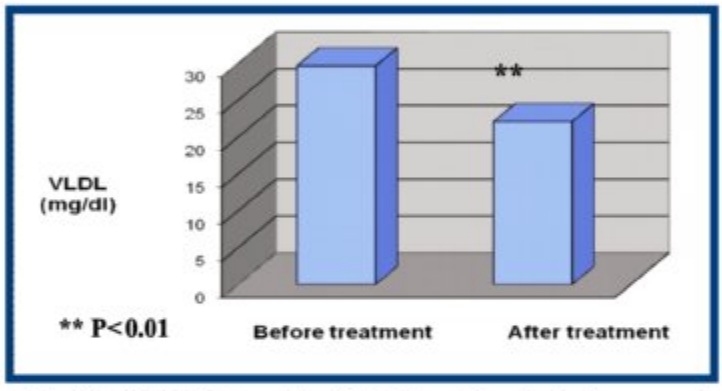

Fig.(4):-V LDL level in PCOS patients before and after treatment with metformin

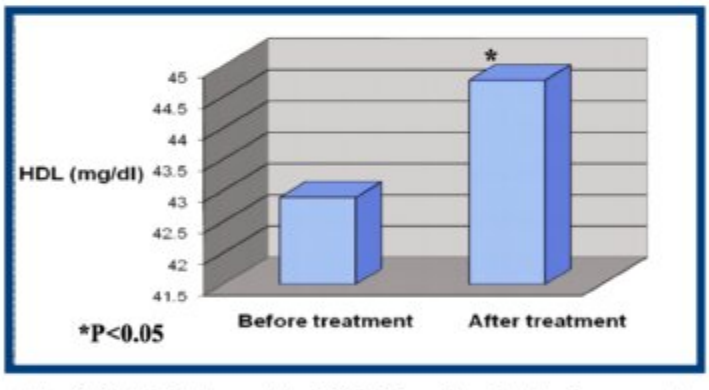

Fig.(5):-HDL level in PCOS patients before and after treatment with metformin

Discussion

Metformin now commonly used in the treatment of PCOS (18), it was of particular interest to examine its effects on the lipid profile in women with PCOS.

The present results demonstrate that metformin treatment improves the lipid profile in women with PCOS where there is significant decrease in serum level of cholesterol, triglyceride, low density lipoprotein and very low density lipoprotein in patient with PCOS after treatment with metformin if compared with the result before treatment, while high density lipoprotein increase significantly after treatment. The concentration of serum free fatty acid (FFA) primarily depends on the lipolysis of adipose triacylglycerols that releases FFA and glycerol from adipocytes. Catecholamines are the most important hormones that govern lipolysis through elevating cellular cyclic adenine mono phosphate (cAMP) production and

activating cAMP-dependent protein kinase (23,24), so the catecholamines leads to more FFA efflux to the portal venous system and directly provides a substrate for hepatic lipoprotein metabolism or production. The reduction of the catecholamine-induced lipolytic rate by metformin may prevent the ectopic lipid accumulation (25). The defective ability of insulin to inhibit lipolysis in adipose tissue also leads to an increased FFA release (26). Studies suggest that promotion of insulin sensitivity by metformin is associated with an overall reduction in plasma FFA levels (27). Insulin resistance cause increasing hepatic gluconeogenesis and inhibiting glucose uptake and oxidation in skeletal muscle (28), glucose in the liver converted to free fatty acids and cholesterol (29). Metformin could reduce hepatic glucose production and fatty acid levels through genetic mechanism. Indeed, it decreases expression of genes for regulatory proteins of fatty acid oxidation and gluconeogenesis (30). Metformin has been suggested to reduce lipid uptake or synthesis in the intestine and in the hepatocytes (31). It enhances insulin sensitivity in both the liver, where it inhibits hepatic glucose production, and the peripheral tissue, where it increases glucose uptake and utilization into muscle tissue (32), the reduced FFA level is associated with increased glucose disposal. Therefore, the FFA-lowering effect could be essential to mediate the enhanced insulin action of metformin (25).

Lovejoy et al. observed that administration of exogenous androgen to women led to increased visceral fat accumulation and decreased serum HDL (33). Thus, androgens may affect lipid metabolism and fat deposition .PCOS characterized by high androgen level, hyperandrogenism has been associated with increased hepatic lipase (HL) activity. This enzyme, which has a role in the catabolism of HDL particles (34), Metformin may reduce androgen levels by reducing pituitary gonadotrophin secretion, ovarian and adrenal androgen secretion, and by increasing the plasma levels of SHBG (35,36,37). High baseline SHBG level has been identified as one of the predictors of a greater elevated of HDL level (38). Furthermore, there are reports directly linking low SHBG levels to a high risk of cardiovascular disease (39,40). This explains increase of HDL and reduced fat after metformin treatment.

The present study confirms the presence of a more atherogenic lipid profile in women with PCOS (41) including increase level of lipoprotein and decreased HDL, These are considered to be risk factors for CVD (35, 42). metformin, by way of its beneficial effects on lipids, could be

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