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Mini Review

Effect of Metformin Treatment on the Serum Levels of Vitamin B12 and Folic Acid in Patients with Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome is a common endocrinological disorder of women characterised by menstrual abnormalities, hirsutism, anovulatory infertility with the presence of immature follicles in the enlarged ovaries. Metformin, a commonly used hypoglycemic agent, is employed in the treatment of PCOS since insulin resistance has been recognised as one of the contributing factors in the development of PCOS. Metformin also helps in maintaining proper ovulation by regulating the levels of LSH and FH. Use of Metformin in PCOS is associated with significant reduction in the serum levels of Vitamin B12 and Folic acid. Monitoring the levels of Serum Vitamin B12 and Folic acid in PCOS patients with metformin therapy and providing them with proper Vitamin B supplementation will prevent the occurrence of these conditions.

Keywords: *Metformin; PCOS; Vitamin B12; Folic Acid*

Introduction

PCOS (Polycystic Ovarian Syndrome) is the most common endocrinological disorder affecting approximately 2 in 10 women population globally in their reproductive age [1]. It is characterized by the presence of menstrual abnormalities such as oligomenorrhea or amenorrhea, hyperandrogenism, anovulatory infertility, hirsutism along with the enlargement of ovaries which consist of numerous immature follicles [8]. It is greatly associated with the risk of developing metabolic disorders like Type-2 Diabetes Mellitus, hypertension and dyslipidemia [1]. Though the etiology of PCOS is unknown, there are certain factors like obesity, hyperlipidemia which can contribute to the development of PCOS [3]. These factors also increase the risk of developing cardiovascular diseases and stroke. Homocysteine levels are also found to be profoundly increasing in the blood in women with PCOS, which is one of the predisposing factor for CVD [1]. Metformin, a primary hypoglycemic agent which is an insulin sensitizer, is being used in the treatment of PCOS. Though Metformin therapy is found to be effective for PCOS, it has a moderate impact in the serum levels of Vitamin B12, folic acid, Follicle stimulating hormone, Luteinizing hormone and prolactin [6].

Contributing factors of PCOS

The exact etiopathogenesis of PCOS is complex and not yet clearly understood. Most of the evidence suggest that the important factors which contribute to the development of PCOS include: Insulin resistance, hyperinsulinemia and hyperandrogenism [4].

Insulin resistance can be termed as the decreased or null response of the cell to the normal levels of circulating insulin. Insulin resistance can lead to the improper functioning of hypothalamic-pituitary-ovaries axis [3] and this condition is compensated by the body by increasing the production of insulin resulting in Hyperinsulinemia. This condition can further lead to increased release of insulin like growth factor-1 (IGF-1) from the liver, resulting in the elevation in the levels of male sex hormone (Androgen) leading to Hyperandrogenism. This could be resulted from Hyperinsulinemia by decreasing the levels of sex hormone binding globulin (SHBG) in the circulation [7]. However, it should be noted that obese women are more prone to PCOS as obesity possesses the risk of developing Hyperinsulinemia. Incidence rate which shows that approximately 8 in 10 women who have PCOS are obese [7], certainly supports that there is an interrelationship between obesity, hyperinsulinemia and PCOS. It has been observed that the patients with PCOS also have alteration in the Intima-media thickness (IMT) in the common carotid arteries with the alternation in the structure and function of endothelium, which is indicated by the alternation of biochemical marker called Endothelin-1 in the plasma [5]:

1. Hyperhomocysteinemia is also observed in most of the cases of women with PCOS.

2. Homocysteine provides its action in the body by undergoing remethylation or trans-sulphuration to methionine or cysteine and cystathionine with the help of the vitamins like Vitamin B6, Vitamin B12 and folic acid.

3. Though homocysteine is an essential amino acid which is helpful in growth of body cells and tissue [1], higher levels of homocysteine in the blood can predispose to CVD.

Metformin: A boon to treat PCOS

Metformin, an oral hypoglycemic agent and a primary insulin sensitizer is being used in the treatment of PCOS. This is because insulin resistance is linked to impaired development of follicle, impair local steroidogenesis through IGF imbalance. It also has an effect on intra-ovarian protease inhibitor and plasminogen activator inhibitor-1 [4]. Though the mechanism of metformin in treating PCOS is unclear, it is found to be decreasing the hepatic glucose production, increasing the sensitivity of insulin in the uterine cells and thereby reduces insulin resistance [9].

It lowers the insulin production which further leads to decrease in the production of androgen and thereby regulates ovulation. This can further reduce the risk of developing long term complications like T2DM, HTN, and CVD by significantly restoring the parameters of normal endothelial structure and function. Certain studies suggest that the use of metformin regains the normal ovarian steroidogenesis and PAI-1 [4]. Lowering the levels of luteinizing hormone (LH) in the serum is also achieved, which enhances ovulation.

Combined effects associated with metformin

Metformin which is being used to induce ovulation in PCOS patients, is normally prescribed at a dose of 500 mg thrice daily for a period of 6 months [4]. Side effects which are most commonly associated with metformin therapy includes: myalgia, anorexia, gastrointestinal disturbances like nausea, vomiting, diarrhea. Approximately 1 in 4 PCOS women who receives metformin therapy experience malaise [6]. Some serious adverse effects like lactic acidosis and renal impairment can also occur rarely in some patients [4]. Though the use of metformin in PCOS becomes significant, there are some other effects which being associated with long term use of metformin, it includes: Vitamin B12 deficiency as well as reduction in serum folic acid levels [1]. Mechanisms which are commonly linked to Vitamin B12 deficiency after metformin therapy include: alteration in the gut motility along with the depression in the secretion of intrinsic factor which leads to decrease in calcium dependent absorption of vitamin B12 in the terminal ileum and also competitive inhibition of vitamin B12 absorption. Besides this, there are some other effects associated with metformin therapy which found to be beneficial in PCOS include: reduction in the levels of FSH, LH which thereby promotes the proper maintenance of ovulation [3,10-30].

Conclusion

PCOS on long term which can contribute highly for developing CVD, can be treated with Metformin therapy but it is often being associated with the alteration in the serum levels of Vitamin B12 and Folic Acid. Thus, by monitoring the levels of these in the serum frequently and also by providing Vitamin B supplementation, this effect can also be well prevented.

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