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USE OF INSULIN SENSITIZERS IN THE TREATMENT OF ADOLESCENTS WITH POLYCYSTIC OVARIAN SYNDROME

Avani M.S, K. Krishnakumar, L. Panayappan, Lincy George*

Department of Pharmacy Practice, St. James College of Pharmaceutical Sciences, Chalakudy.
St.James Hospital Trust Pharmaceutical Research Centre (DSIR certified), Chalakudy, Kerala, India.

ABSTRACT

Polycystic ovarian syndrome is the most common endocrinopathy seen in women of reproductive age. Women with PCOS may present with menstrual irregularities, chronic anovulation, infertility, obesity and hyperandrogenism. PCOS is associated with insulin resistance and hyperinsulinemia in most of the patient. Besides its gynecological manifestations, PCOS is also associated with increased metabolic and cardiovascular risks. Hormonal contraceptives have been the main management of common PCOS symptoms, such as menstrual irregularity and clinical stigmata of androgen excess. Insulin sensitizers were one of the first metabolic modulators to be incorporated in the clinical management PCOS. Recognizing that insulin resistance is central to the pathophysiology of PCOS, newer agents, eg. Thiazolidinedione followed with almost comparable efficacy to metformin. This review article is mainly focused on use of insulin sensitizers in the treatment of adolescents with polycystic ovarian syndrome.

Key words: Polycystic ovarian syndrome, Insulin sensitizers.

INTRODUCTION

Polycystic ovarian syndrome is a common female endocrine disorder characterised by polycystic ovaries, excess androgen and irregular periods, emerges during or after puberty. Obesity, insulin resistance and hyperinsulinemia are highly prevalent co-morbidities of PCOS [1]. The most common methods of managing PCOS are drug therapy and life style modifications. Drug therapy includes the use of oral contraceptives, anti-androgens and insulin sensitizing agents. Insulin sensitizing agents have recently been proposed as a therapy for the treatment of PCOS. These agents improve insulin action by increasing insulin sensitivity, thereby decreasing hyperinsulinemia. Since almost all obese PCOS women and more than half of those with normal weight are insulin resistant and present with some degree of fasting or stimulated hyperinsulinemia,the use of insulin sensitizers could therefore be suggested in most patients with PCOS [2].

Life Style Modifications and Weight Loss

Unlike drug therapy, there are no ADR associated with life style modifications in the management of PCOS .life style modification should be the first line of treatment prescribed to women with PCOS. Life style modification includes weight loss, dietary treatments and exercise. Mild to moderate weight loss will highly reduces the symptoms of PCOS. Weight loss of only 2-7% of initial body weight leads to improved ovulation and a reduction in androgen levels [(1)].Hypo caloric diet can help to facilitate weight loss. A hypo caloric diet is not designed to be restrictive in any particular nutrient. The goal is simply to reduce the caloric intake.PCOS women on in this type of diet experience improvement in both reproductive and metabolic abnormalities including insulin resistance [3].

Studies of insulin sensitizers and insulin lowering drugs in adolescents with PCOS

Studies of insulin-sensitizing drugs in PCOS have used the drugs metformin, troglitazone and D-chiro-

Corresponding Author :- **Lincy George** Email:- stjamesdruginfo@gmail.com

inositol, with metformin as the most comprehensively evaluated drug. These all drugs are used for enhancing ovulation. None of the insulin sensitizing drugs has FDA approval for use in PCOS [4].

Metformin

Metformin is the only remaining member of the biguanide family that has been used for the treatment of DM for a long time .It is the most commonly used drug in type 2 DM. Metformin works by improving the sensitivity of peripheral tissues to insulin, which results in a reduction of circulating insulin levels .It is also inhibits hepatic gluconeogenesis and increase the glucose uptake by peripheral tissues and reduce fatty acid oxidation [5].

Androgen Lowering Effect of Metformin

Metformin is treatment of choice for the metabolic consequences seen in PCOS for its insulin sensitizing and androgen lowering properties. The MOA is unclear. The two targets for metformin regulating steroid and glucose metabolism are AMP activated protein kinase (AMPK) signalling and the complex 1 of the mitochondrial respiratory chain. Androgen biosynthesis requires steroid enzyme 17α-hydroxylase and 3 β-hydroxysteroid dehydrogenase type-2, which are over expressed in ovarian cells of PCOS women. At last metformin inhibit androgen production by mechanism targeting HSD3B2 and CYP 17-lyase.this regulation involves inhibition of mitochondrial complex 1 but appears to be independent of AMPK signalling [6].

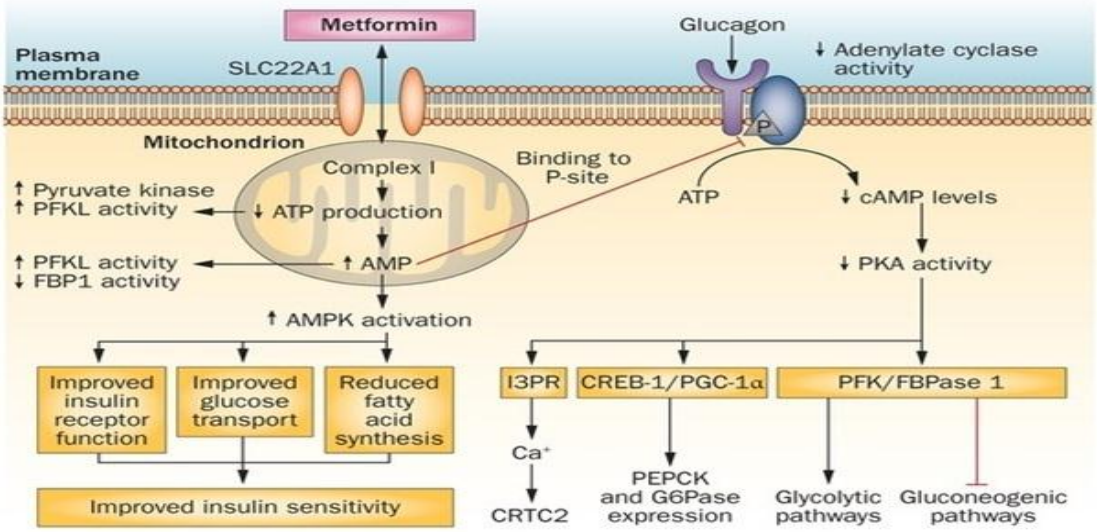
Metformin Monotherapy

A dose of 1.5 – 2g per day is necessary for getting clinical effect of metformin is used alone.One of the studies shows that the effect of therapy with metformin alone (n=14) versus metformin with estrogen progesterone combination pills (EP)(n=13)on HbA1C and lipid parameters over 10-14 months in 27 over weight girls, drawn from a clinic population of adolscents with PCOS.After 10 month metformin only group compared with the metformin and EP group had a decrease in total cholesterol and triglycerides and similar changes in BMI and HbA1C [6].

Metformin in combination with estrogen –progestin Combination pills or antiandrogens

Women with PCOS have both abnormally elevated luteinizing hormone (LH) secretion and hyperinsulinemia as a result of insulin resistance. The combination of hypersecretion of LH and insulin causes ovarian androgen over production. It may leads to hirsutism and prevents normal ovarian follicle growth and regular ovulation.PCOS can be treated by lowering LH hypersecretion or by reversing the hyperinsulinemia caused by insulin resistance. So the use of oral contraceptives plus metformin in combination to simultaneously attack the two principle causes of PCOS: hyper secretion of LH and insulin [7].

Fig 1. Metformin: Insulin Sensitizers



Thiazolidinediones (TZD)

The insulin sensitizing thiazolidinediones are selective ligands of the nuclear transcription factorperoxisome-proliferator activated receptor γ(PPARγ),which is more seen in adipose tissue and also seen in pancreatic beta cells, vascular endothelium and macrophages. The two available PPARγ agonist are rosiglitazone and pioglitazone. The mechanism of action of thiazolinediones are: directly by the so called 'fatty acid steal hypothesis' and indirectly by increasing the expression of a diponectin, Anadipocytokine with an insulin sensitivity effect, and probably by decreasing the

expression of 11 β-hydroxy steroid dehydroxygenase type 1,an enzyme which catalyzes the conversion of inactive cortisol to active cortisol. According to the 'fatty acid steal' hypothesis, thiazolidinedione promote fatty acid uptake and storage in adipose tissues. In this way they increase adipose tissue mass and spare other insulin sensitive tissues from the harmful metabolic effects of high concentrations of free fatty acids [8-9].

D-Chiro-Inositol

D-Chiro-inositol is a new insulin sensitizing drug; it is not yet commercially available. It has been demonstrated in a randomized, double-blinded and placebo-controlled trial to increase the frequency of ovulation in obese women with PCOS .A preliminary study reported a threefold increase in the frequency of ovulation in lean women treated with D-chiro-inositol for 6-8 weeks with PCOS treated with D-*chiro*-inositol for 6–8 weeks [10-11].

CONCLUSION

Polycystic ovarian syndrome is one of the most common female endocrine disorders in the reproductive age. The development of PCOS has been linked to hereditary and environmental factors including genetics, insulin resistance, obesity and birth weight. Insulin resistance play a key role in the development of PCOS. Insulin sensitizing agents are the drug therapy used. Common forms of insulin sensitizing drugs include metformin and rosiglitazone. These drugs are intended to be used in combination with diet and exercise. They are commonly prescribed to people with type 11 diabetes mellitus. These drugs work by inhibiting hepatic glucose production and increasing insulin sensitivity in the peripheral tissues.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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