Clinics of Surgery

Research Article

ISSN: 2638-1451 | Volume 8

Role of Myoinositol in Reducing Insulin Resistance in PCOS Patients

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Received: 19 Oct 2022
Accepted: 26 Oct 2022
Published: 31 Oct 2022
J Short Name: COS

Citation:

Paswan A. Role of Myoinositol in Reducing Insulin Resistance in PCOS Patients. Clin Surg. 2022; 8(4): 1-4

1. Abstract

Despite affecting 5-10% of all reproductive age women PCOS is the most ill understood endocrinological disease. First recognized by Stein &Leventhal in 1935, PCOS is charcaterized by polycystic ovaries, menstrual irregularities and clinical/biochemical hyperandrogenism and infertility. It has been related to heredity, environmental factors, obesity at birth and insulin resistance. These patients are liable to go into metabolic syndrome cardiovascular disease and type II diabetes mellitus, in later life. Hence the study was done using myoinositol to treat obese and normal weight patients to see its effect on HOMA Index and Plasma Glucose/ Insulin ratio.A case control study of 50 PCOS 50 patients were given 2gms myoinositol plus 500mg folic acid. 50 patients were given only 500mg folic acid to see the effect of myoinositol on the HOMA index &gulocose/insulin ratio It was seen that the glucose/insulin ratio siginificantly improved in the patients receiving myoinositol. Hence it was seen to be a useful treatment incases of PCOS, to reduced the insulin resistance.

2. Introduction

Incidence – About 15% of the reproductive population

A good % of PCOS are obese, but lean PCOS patients are also seen

PCOS is seen most commonly in the reproductive age but it is now seen frequently in the adolescent also. Obesity is defined as BMI > 30 kg/m2 PCOS – is a symptom complex including oligomenorhoea, hyperandrogenism and polycystic ovaries, and infertility is usually associated.

3. Basic Eitiopathology

The basic eitiopathology of PCOS is Insulin resistance (I.R.) Hyperandrogenism (HA)

Older patients have abdominal obesity and certain metabolic disorders which is noted in 65-70% of PCOS patients, among whom 70-80% are obese

The LH / FSH ratio is raised. SHBG is low hence Free Testosterone is raised. Studies have shown altered IRM or abnormal insulin signal transduction leading to Insulin resistance, and abnormal ovarian steroidogenesis

Hence Insulin sensitizers improve androgen levels and restore ovulation. CYP 11 liyase activity is seen hyper insulinemia and hyperandrogenism. Elevated LH levels were seen in both insulin resistnace and hyper androgenism (BALEN 1999, DiamantiKandarakis 206, Legro 1998). Weight lost as indicated by the waste hip ratio improves endocrine profile menstrual cylcilicity and ovulation (Huber B1990 Kiday 1992, Pusqual 1989).

PCOS women with IR have a higher level of free testosteron and hirsutism (Legro 2006 a). Patients with irregular cycles have higher chances of anovlation and infertility than those with regular cycles (Robinson 1993). These patients showed Clomifene resistance. In later life 8% devloped Type II diabetes. Obese women have a BMI of>30 kg/m2, lean PCOS patients have a BMI <25kg/m2 Insulin resistance in PCOS

Insulin resistance is a key factor in the pathogenesis of anovulation and hyperandrogenism in PCOS. Indeed, hyperinsulinemia could produce hyperandrogenism in PCOS women via the following distinct and independent mechanisms:

By stimulating ovarian androgen production through its own receptor as well as IGF-I receptor.

By inhibiting hepatic synthesis of SHBG thus reducing its plasma levels.

By stimulating CYP17, an enzyme for androgen production.

The net result of these actions is an increase in circulating levels of free (active form) testosterone. In addition, topromoting hyperandrogenism, recent evidence indicates that hyperinsulinemia contributes to the anovulation of PCOS. Indeed, hyperinsulinemia could adversely affect folliculogenesis and impede ovulation by increasing intra ovarian androgen production, altering gonadotropin secretion, or directly affecting follicular development. Confirming the important role of hyperinsulinemic insulin resistance in the pathogenesis of PCOS, insulin reduction, whether achieved by inhibition of pancreatic insulin release (diazoxide or octreotide) or improvement in peripheral insulin sensitivity (metformin, myo-inostol, troglitazone), is associated with a reduction in circulating androgens, animprovement in ovulatory function, and enhanced fertilityin women with PCOS.

Altered insulin signaling and its relationship with insulin resistance and PCOS (Figure 1).

Evidence suggests that women with PCOS have a markedly reduced level of circulating inositol and an increased 24-hour urinary clearance of inositol compared to women with normal insulin sensitivity and this deficiency of inositol contributes to insulin resistance in PCOS individuals.

Since inositol is a precursor of PI-3 Kinase, deficiency of inositol decreases PI-3 Kinase activity.

- Reduced activity of PI-3 Kinase reduces translocation of GLUT 4 thereby causing hyperglycrmia. This brings about altered insulin signalling that causes hyperinsulinemia and thus insulin resistance in PCOS.

Hence inositol deficiency is considered a basic pathophysiology of hyperinsulinemia in patients of PCOS and inositol supplementation in the form of myo-inosito can be used for improving insulin sensitivity and hormonal parameters in these patients.

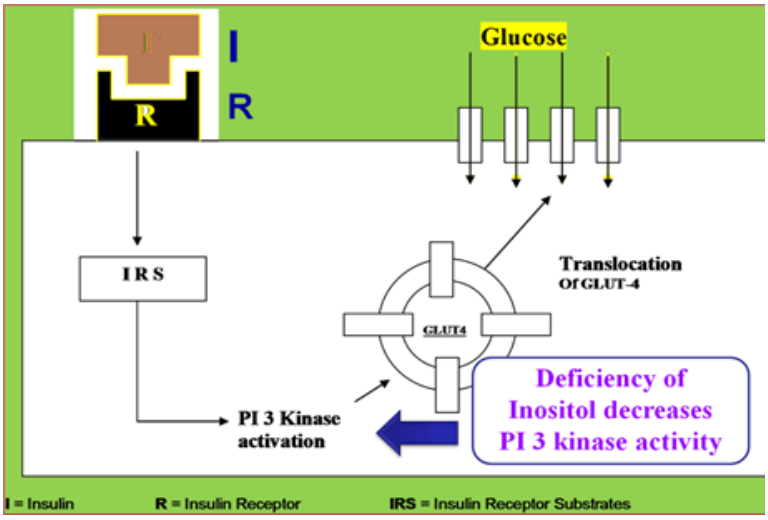


Figure 1:

4. Material and Methods

Study Design: A case control study was done in the dept of Obst and Gyn DMCH

Study Period: 1 year – 31st October 2014 31st October 2015.

Sample Size: 50 study patients & 50 controls

Sample Collection: Patients coming to Darbhanga Medical College Hospital Laheriasarai, were from Darbhanga District, and the neighbouring Districts of Samastipur, Madhubani and Sitamardhi.

50 Obese and non-obese PCOS patients between 20-40 yrs were selected and given 2gm Myoinositol with 500 µgm Folic acid. 50 control cases were given only 500 µgm Folic acid.

Control cases matched in age, parity and BMI with the study group

4.1. Exclusion Criteria

Diabetics, cases of hyperandrogenism due to CAH, adr. Tumors, Cushings syndrome.

4.2. Inclusion Criteria

PCOS patients with criteria established by ESHRE (European Society for Human Reproduction & Embryology. i.e., hyperandrogenism and presence of 12 or more follicles in each ovary measuring 2-9 mm and/or increased ovarian volume (>10ml), and history of oligomenorhoea.

4.3. Data collection

The fasting insulin levels glucouse to insulin ratio and the HOMA index baseline were estimated to find out the insulin sensitivity, after 12weeks of treatment.

50 Obese and non-obese PCOS patients between 20-40 yrs were selected and given 2gm Myoinositol with 500 µgm Folic acid. 50 control cases were given only 500 µgm Folic acid.

Consent was taken from all patients for participation in the study.

Clearance was taken from the ethical society.

4.4. Statistical Analysis

Data were reported as mean values ± standard deviation (SD). We tested data for significant differences after 12 weeks of treatment in both groups.

HOMA index was computed as (basal glucose) x (basal insulin) ÷ 405.

Insulin sensitivity was computed as glucose to insulin ratio

To compare the two groups unpaired t test (Parametric distribution) was used.

To compare the pre and post treatment values within the group paired t test was used. The p values less than 0.05 were considered statistically significant.

5. Discussion

Inositol is an Insulin sensitizer as IPG plays a key role in the cellular processes that control glucose metabolism, second messenger in Insulin signal and calcium oscillations involved in meosis.

Inositol is the precursor of phosphatidyl inositol 3 kinese (key enzyme in the transduction path way of insulin), which is deficient in PCOS patients. Myoinsitol is a cyclitol found in animal and plants acting as secondary messengers specially as IP3 IP6 Inositol glycans it is involved in insulin sensitivity

Baillargeon JP et al found the plasma concentration of DCI Inositol to be much lower (0.19ml mol/L) than normal subjects.

The positive effect of Myoinsitol could be due to the pivotal role of inositol p3 in the regulation of calcium release during oocyte development which conditions the acquisition of meotic competence and drives oocytes to the final stages of maturation

Previous studies have demonstrated that Myo-Inositol supplementation can restore spontaneous ovarian activity (spontaneous ovulation, menstrual cyclicity), and consequently fertility in most women with PCOS. A significant improvement of typical hormonal parameters was observed in PCOS patients after myo-inositol treatment: decreased LH,FSH, and testosterone circulating levels, and increase SHBG,estrogens and progesterone circulating levels. Hyperinsulinism and Insulin peripheral sensitivity was improved as evidenced by reduction in Homeostatic model assessment (HOMA) index for insulin resistance and/or reduction of the area under the curve (AUC) of glucose and insulin during an oral glucose tolerance test (GTT). Markers of cardiovascular risk was also improved with a decrement in systolic and diastolic blood pressure, a decrease in LDL and total cholesterol concentrations. In some studies, anthropometric measurements showed a significant decrease in the Body Mass Index (BMI) and a decrease in circulating leptin concentration in myo-inositol group after at least 16 weeks of treatment (Figure 2 and 3).

All obese and 50% normal weight PCOS are IR presenting with hyperinsulinaemia IR -> altered LH/FSH ratio -> prevention of dominant follicle

Insulin stimulates sensitivity of follicles to LH -> increased production of androgens by stimulation cytochrome P450C 17a (Figure 4-10)

In our study the mean S.Insulin in the untreated group was 21.49 compared to 16.28 in the treated group.

The mean Pl.Glucose in the untreated group was 149.7 compared to 142.81 in the treated group

The mean of the Pl.Glucose/S.Insulin in the untreated group was 6.90 versus 8.96 in the treated group, a difference of 28.3%

The mean differences in the HOMA index was 8.56 in untreated to 6.25 in the post treatment, a difference of 27%.

All the differences were significant at $p < 0.001$

Our findings were similar to those of P.G.Artini et al

In the study of Genazzani et al. gm of myoinositol were given to 20 PCOS patients. The LH /FSH ratio and insulin levels significantly reduced, the HOMA index reduced and the glucose/insulin ratio was decreased Post treatment.

Unfer et al. analyzed six RCTs and found that 12weeks post treatment with 2gm myoinositol, there was a positive reduction in hyperinsuliminemia, restoring ovulation and oocyte quality.

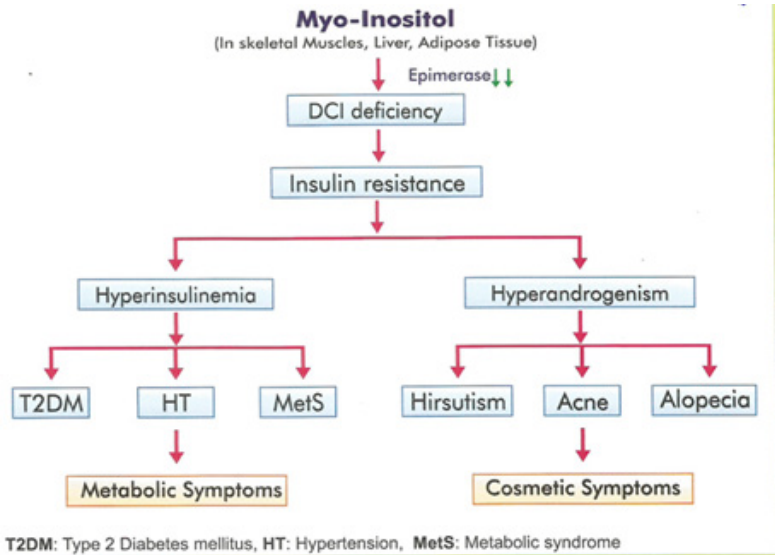
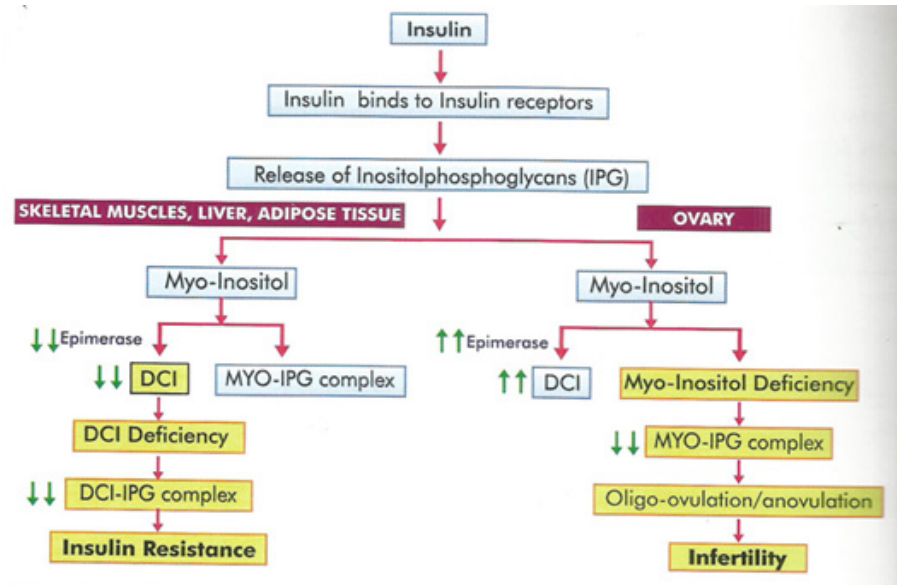


Figure 2:



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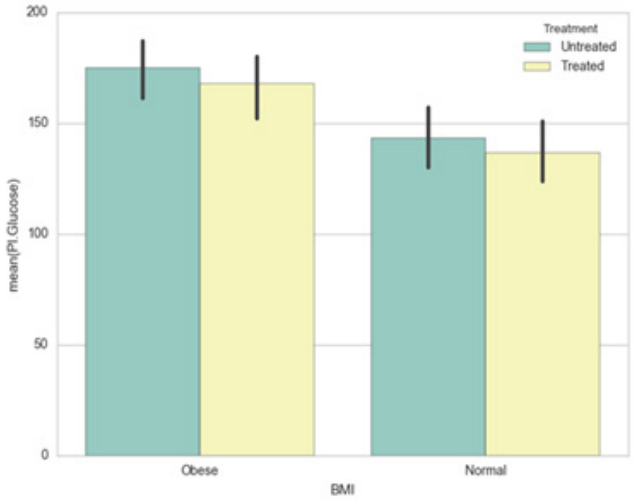

Figure 4: Observation Results

The HOMA index reduced, glucose/insulin ratio significantly increased, furthermore, after glucose load, both insulin response and the area under the curve (AUC) were significantly reduced.

Observations were done 12weeks after giving 2gm myoinositol daily to both obese and normal patients

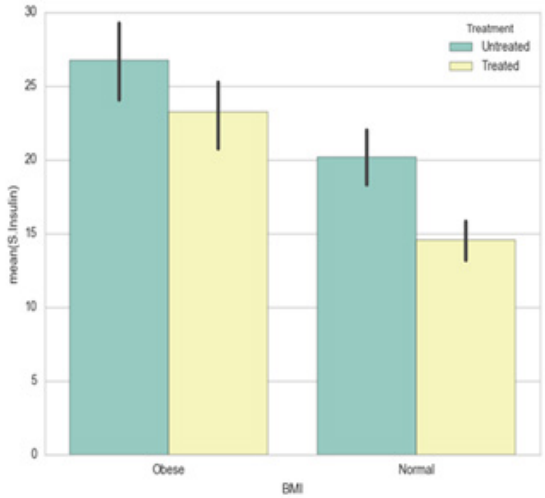

Figure 5: Chart showing marked reduction in the serum insulin level in the normal BMI PCOS pts. as compared to the obese PCOS pts. after treatment with 2gm Myoinositol for 12 weeks.

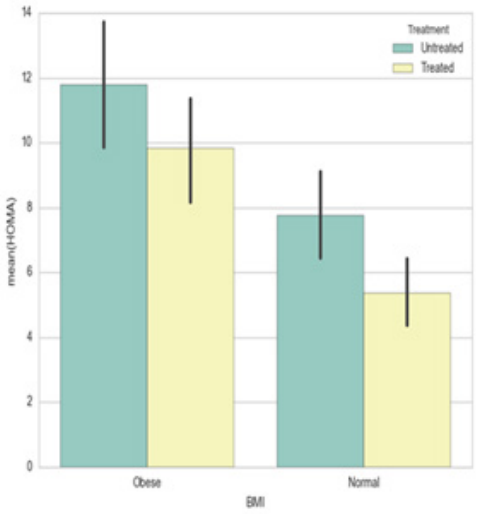

Figure 6: Chart showing the reduction in HOMA index in obese and normal BMI PCOS pts. after treatment with 2gm Myoinositol

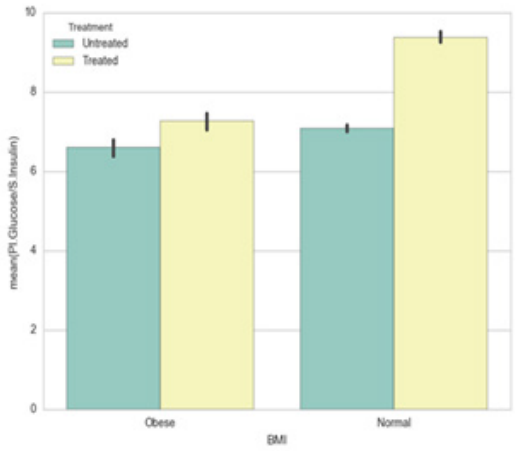

Figure 7: Pl.Glucose / S.Insulin

The pl.glucose/s.insulin ratio in the obese patients went up by 10.2% in the obese PCOS group & in the normal BMI, PCOS patients it went up by 32.5% after treatment with Myoinositol

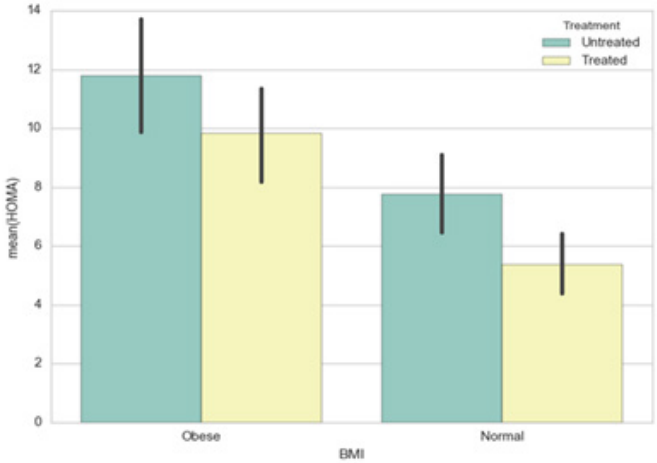

Figure 8: HOMA

The mean HOMA in obese PCOS pts. Went down by 16.7% in the treated group (by Myoinositol), whereas in the normal BMI pts. HOMA went down by 30.9%

	Untreated		Treated		
	Mean	SD	Mean	SD	% change
S.Insulin	21.49	6.18	16.28	5.60	-24.28%
Pl.Glucose	149.70	42.40	142.81	41.54	-4.60%
Pl.Glucose/S.Insulin	6.98	0.35	8.96	0.95	28.28%
HOMA	8.56	4.49	6.25	3.62	-26.96%

Figure 9:

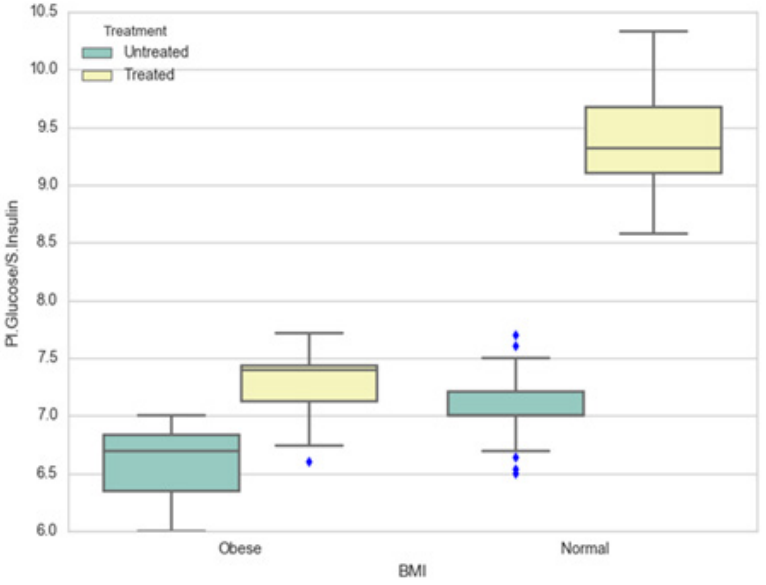

Figure 10:

6. Conclusion

Myoinositol is a useful drug in reducing insulin resistance and therefore hyperandrogenism in PCOS patients, thereby the androgenic mileu is reduced enhancing ovulation hence, correcting infertility. In the long run PCOS patients are liable to go into metabolic syndrome (dyslipidemia + CVS problems, namely hypertension and type II diabetes mellitus – Legro 2006). Hence it is of utmost importance that PCOS patients be treated early

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