

## **Efficacy of herbal formulation (HYPONIDD) in the management of anovulatory PCOS women: A comparison with metformin**

Antidiabetic herbal medicines *Gymnema Sylvestre* and *Pterocarpus marsupium* in Hyponidd can be used as effectively as metformin for lowering insulin resistance and hyperandrogenemia in anovulatory women with PCOS without any side effects of metformin

Herbal formulation (Hyponidd) as insulin sensitizing drug

### **Authors**

**Dr. Mrs. Meena Chimote** M.D.; DNB. (Obstetrics-Gynecology)

Medical Director  
Vaunshdhara Assisted Conception Centre  
9, Dr. Munje Marg, Congress Nagar.  
Nagpur. INDIA. 440012.

**Dr. Nirmalendu Nath** PhD.

Ex. Head of the Department – Biochemistry.  
University of Nagpur.  
8, East high Court Road, New Ramdaspath.  
Nagpur. India. 440010.

**Dr. Natachandra Manohar Chimote** PhD

Scientific Director  
Vaunshdhara Assisted Conception Centre  
9, Dr. Munje Marg, Congress Nagar.  
Nagpur. INDIA. 440012.

**Place of study:** Vaunshdhara Clinic & Assisted Conception Centre  
9, Dr. Munje Marg, Congress Nagar, Nagpur. India. 440012.

**E Mail:** vaunsh\_ngp@sancharnet.in

**Abstract**

## **Efficacy of herbal formulation (HYPONIDD) in the management of anovulatory PCOS women with insulin resistance: A comparison with metformin**

**Objective:** To compare efficacy of antidiabetic herbal medicine Hyponidd as insulin resistance reducing agent with metformin in anovulatory PCOS.

**Subjects:** PCOS anovulatory women (n = 147) having insulin resistance were treated with Hyponidd (n = 75) and metformin (n = 72) for three months. The BMI, WHR, day three serum fasting insulin, glucose, LH, FSH, E2, testosterone and SHBG levels were measured before and after treatment in each group. Post treatment ovulation induction was done with CC 100 mg and Day 21 serum progesterone was measured.

**Results:** Significant post treatment reduction in FG: FI ratio, LH: FSH ratio, serum SHBG, Free testosterone index and free Estradiol index was found in both Hyponidd and metformin groups as compared to their baseline values. Post treatment BMI and WHR in Hyponidd group was found to be reduced significantly as compared to no change in metformin group. Percentage ovulation in both groups improved significantly. Hyponidd group showed no side effects as compared to metformin group.

**Conclusion:** Herbal medicine Hyponidd is as effective as metformin in reducing insulin resistance, hyperandrogenemia and in increasing ovulation rate in anovulatory PCOS women with added advantage of almost no side effect of gastric disorders as found in metformin.

**Key words:** Herbal medicine (HYPONIDD), PCOS, Insulin resistance and metformin

### **Introduction**

Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder characterized by menstrual irregularities, clinical and / or biochemical hyperandrogenism and hyperinsulinemia secondary to reduced insulin sensitivity<sup>1</sup> and is the most common endocrinopathy in women, affecting 5–10% of the population. In recent years it has been widely recognized that most women with PCOS have some degree of insulin resistance<sup>2</sup>. Insulin resistance has been defined as a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal response<sup>3</sup>. Therefore, abnormality of insulin secretion and action has been implicated in the pathophysiology of PCOS. It has been reported that in clinical practice, women with PCOS showed menstrual irregularity (dysfunctional bleeding, 29%; amenorrhea, 51%), hyperandrogenism (69%), virilization (21%) and infertility (mean incidence, 74%)<sup>4,5</sup>.

For the last two decades many authors have shown that insulin resistance and the consequent hyperinsulinemia is the driving factor for increased androgen production in obese as well as non-obese PCOS subjects<sup>2,6-10</sup>. This has been used as a rationale for using insulin sensitizers such as metformin<sup>11-16</sup>, troglitazone, rosiglitazone, pioglitazone<sup>17</sup>, D-chiro-inositol<sup>18,19</sup> and  $\alpha$ -glucosidase inhibitors (acarbose)<sup>20</sup> in the management of PCOS. Metformin is the most thoroughly investigated drug studied to reverse the hyperinsulinaemia of PCOS and its clinical and metabolic expressions. However, nausea, vomiting, and other gut disturbances were noted as major adverse effects<sup>21,22</sup>. The unpleasant gastrointestinal side effects of metformin preclude its use and as a result there are drop outs. Administration of D-chiro-inositol to obese PCOS patients for 6–8 wk was reported to reduce the insulin curve after OGTT<sup>18</sup>. In this study, PCOS women showed a significant reduction in plasma testosterone and ovulated during therapy. No side effects have yet been reported.

Age old Indian Ayurvedic medicines such as *Gymnema sylvestre* (Gudmar: a source of acarbose) and *Pterocarpus marsupium* (a source of D- chiro inositol) are known to have antidiabetic activity<sup>23,24</sup>. These observations implied the probable use of therapeutic application of the combined use of these two herbal medicines as insulin sensitizing drug in anovulatory PCOS women with insulin resistance. Therefore we carried out a comparative study of efficacy of Indian herbal drug- Hyponidd<sup>®</sup> (marketed by Charak Pharmaceuticals (I) Pvt. Ltd. India) prepared from extracts of plants and herbs and metformin (Glyciphage: marketed by Franco – Indian Pharmaceuticals Pvt Ltd. Mumbai, India) in anovulatory PCOS women.

## **Material and Methods**

### **Subjects**

#### ***Patient selection***

172 PCOS patients participated in this study. All women were in good health and none had taken any medication known to affect carbohydrate metabolism or gonadal function for at least 6 months before the study. Spontaneous onset of puberty and normal sexual development were reported in all the patients. Since puberty, all PCOS patients had been affected by hirsutism / acne, oligomenorrhoea or secondary amenorrhoea.

The following inclusion criteria were established for PCOS patients as per Rotterdam revised consensus on diagnosis criteria<sup>25</sup> for PCOS: (i) menstrual abnormalities (<6 menstrual periods in the last year); (ii) clinical manifestations of hyperandrogenism, such as excessive hair growth /

hirsutism and raised incidence of acne; (iii) elevated serum concentrations of total testosterone (>80 ng/dl) (iv) normal serum prolactin (PRL) and a normal thyroid function test. By transvaginal ultrasonography, all PCOS patients showed > 10 subcapsular follicles of 3–8 mm diameter in one plane in one ovary and increased ovarian volume.

Clinical manifestations of hyperandrogenism, such as raised acne scores and excessive hair growth, (modified Ferriman-Gallwey score, Ferriman and Gallwey; 1961) by a single observer was used to assess the degree of hirsutism. A score of at least 8 of a total of 36 was taken as significant. Elevated serum concentrations of total testosterone (>80 ng/dl), fasting glucose: fasting insulin ratio (FG: FI ratio) < 4.5 was observed in most of the PCOS women with normal serum prolactin (PRL) and a normal thyroid function test.

### ***Study design and procedures***

The Ethical Committee of our Reproductive Endocrine department approved the study and written informed consent was obtained from each PCOS woman. For each woman, the body mass index (BMI) was calculated using the following formula:  $BMI = \text{weight (kg)} / [\text{height (m)}^2]$ . Waist: Hip ratio was calculated as waist (cm) / hip (cm). In all patients, basal fasting serum concentrations of LH, FSH, estradiol, testosterone, PRL, insulin, fasting blood sugar and SHBG were determined on day 2 or day 3 of the follicular phase of a spontaneous or progestin-induced cycle. Ultrasound ovarian volume was calculated during the follicular phase, according to the formula  $(4/3) \times (D1/2) \times (D2/2) \times (D3/2)$  where D1 is the length, D2 the width and D3 the depth of the ovary.

Out of 172 PCOS women who consented to undergo treatment with either metformin (500 mg one t.i.d. for three months) or Hyponidd (2 b.i.d. for three months), 12 women withdrew just before starting the treatment. Remaining 160 PCOS women were randomly divided into two equal groups i.e. Hyponidd group (n = 80) and Metformin group (n = 80). Each woman was instructed to take the drug half an hour before food intake. At the end of the treatment, each patient underwent the same clinical, endocrine evaluations as prior to the treatment.

### **Hormone measurements**

Blood samples were withdrawn through an indwelling catheter placed in the antecubital vein, after an overnight fast. The blood samples were centrifuged, and the sera were collected and stored at  $-20^{\circ}\text{C}$ , until insulin, estradiol, LH, FSH, testosterone, PRL, and SHBG serum

concentrations were measured. Serum glucose concentrations were determined immediately by the glucose oxidase method. Insulin was measured by a commercially available radioimmunoassay kit (Diagnostic System Laboratory Pvt. Ltd. – DSL, Texas, USA.), for which the intra and interassay coefficients of variation (CVs) were 4.8 and 8.2% respectively. Estradiol, LH, FSH, testosterone, SHBG and PRL were measured using commercially available immunoradiometric kits (DSL kits). All samples were assayed in duplicate. The intra-assay CVs of LH and FSH were 4.2 and 6.9% respectively, and the inter-assay CVs were 9.9 and 10.8% respectively. The intra-assay and inter-assay CVs for each steroid were 7.9 and 10.1% for testosterone, 8.0 and 10.8% for estradiol respectively. The intra-assay and inter-assay CVs for PRL were 6.2 and 4.9% respectively. The intra-assay and inter-assay CVs for SHBG were 4.2 and 4.9%.

### **Statistical analysis**

Each group was evaluated for the changes in the weight, BMI, WHR and hormone parameters after the treatment. Unpaired *t*-test was used for analyzing the data for intercomparison of pretreatment and post treatment groups whereas, one way ANOVA unpaired '*t*' test was used for intracomparison of post treatment Hyponidd and metformin groups and *P* values were calculated. *P* value less than 0.05 was considered significant. Graph Pad Prism for Windows 6.2 performed the statistical analysis of data.

## **Results**

### ***Pre-treatment values***

Table 1 summarized the baseline distribution of various diagnostic criteria of PCOS as observed in the two groups.

During three months of therapy, eight women from metformin group left treatment in between due to nausea or hypoglycemia or gastric upset. Whereas two women from Hyponidd group gave up treatment due to reasons other than side effects and we lost track of three women soon after the treatment. Thus seventy- two (72) women from metformin group and seventy-five (75) women from Hyponidd group completed three months treatment.

### ***Anthropometric parameters***

The results of changes in anthropometrical parameters are given in Table 2.

A significant reduction in anthropometrical parameters - BMI, waist girth and waist: hip ratio was observed in Hyponidd group after three months treatment while no change was observed in these parameters in metformin group. Intercomparison between Hyponidd and metformin groups after treatment showed that Hyponidd treatment was more effective in reducing waist girth, WHR and BMI than metformin. However, reduction in clinical hyperandrogenism was quite evident and similar in both the groups.

### ***Metabolic parameters***

Most importantly, hyperinsulinemia, fasting glucose: fasting insulin ratio (FG: FI) and indicators of insulin resistance such as homeostasis model assessment of insulin resistance and  $\beta$  cell function index in Hyponidd group showed very significant and parallel improvement like metformin group as demonstrated in table 3.

Figure 1 depicted significant post treatment increase in fasting glucose: fasting insulin ratio demarcating a very significant decrease in insulin resistance in both the groups. Figure 2 represented improvement in HOMA – IR in both groups after treatment.

### ***Hormone parameters***

As shown in table 4, a decline in LH: FSH ratio was significant in both the groups after treatment. Due to rise in SHBG level and lowering of estradiol and testosterone, free estradiol index (FEI) and free testosterone index (FTI) in these groups reduced significantly indicating diminution in hyperandrogenemia in both the groups after treatment. Post-treatment intercomparison showed almost similar degree of improvement in these hormonal parameters. But interestingly reduction in baseline post-treatment estradiol level in Hyponidd group was significant as compared to metformin group.

Comparative results in table 5 established that Hyponidd treatment was not only as effective as metformin in reducing insulin resistance and improving ovulation rate but also helped in reducing obesity, LH: FSH ratio and hyperandrogenemia significantly as compared to metformin.

### Side effects

Seventy-two of eighty subjects completed three months metformin treatment. Eight subjects in metformin group on account of gastrointestinal disturbances such as nausea, vomiting, abdominal pain and diarrhea gave up treatment in between whereas; seventy-five out of eighty subject in Hyponidd group completed the treatment without any such complaint. Five subjects in Hyponidd group left the treatment due to their personal problems.

### Discussion

It has been evidenced for the first time in the present study that, administration of antidiabetic herbal medicine Hyponidd to anovulatory PCOS women lowered insulin resistance and hyperandrogenemia. It also improved incidence of ovulation. Thus, It may be stated that Hyponidd is as effective as metformin.

There is a large data documenting the clinical efficacy of metformin in the treatment of PCOS-associated insulin resistance. It also has been established that administration of insulin sensitizing drugs, such as metformin, *D-chiro*-inositol and acarbose<sup>26</sup> to both obese and lean women with the PCOS increase the frequency of ovulation and decreases circulating androgens. In the present study, administration of herbal medicine Hyponidd to anovulatory PCOS women also witnessed similar results. However, it was observed in those studies that the use of metformin caused such gastrointestinal side effects as nausea, vomiting, and diarrhea. Coinciding with these already established side effects of metformin, the present study showed a drop out rate of 10% in metformin group as against no drop out in Hyponidd group on account of nausea, vomiting, diarrhea or hypoglycemia. This finding has truly established a better tolerance with Hyponidd as compared to metformin.

It may be noted that Hyponidd is a formulation of various herbs along with two major antidiabetic herbal components *Gymnema sylvestre* and *Pterocarpus marsupium*. It was also found that *Gymnema sylvestre* may be a source of disaccharide – acarbose. Acarbose, an inhibitor of the enzyme  $\alpha$ -glycosidase, is a drug in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) with few side effects and high clinical efficiency as an anti-hyperglycaemic agent<sup>27</sup>. Acarbose reversibly inhibits  $\alpha$ -glucosidase activity of intestinal villi and therefore it slows digestion of complex carbohydrates and the more readily absorbed mono- and disaccharides. Inhibition of this enzyme causes a reduction in glucose absorption and therefore a decrease in postprandial hyperglycemia<sup>28,29</sup>. In addition to acarbose like activity in *Gymnema sylvestre*, the

finding of its leaves extract appeared to enhance endogenous insulin, possibly by regeneration / revitalization of the residual beta cells in insulin-dependent diabetes mellitus<sup>23</sup> also improved its role as a insulin sensitizing drug. We therefore may state that *Gymnema sylvestre* in Hyponidd along with other herbs lowered hyperinsulinemia without much side effects due to its holistic physiological pathway.

It has been also reported that three important phenolic constituents of *Pterocarpus marsupium* heartwood namely marsupsin , pterosupin and pterostilbene significantly lowered the blood glucose level of hyperglycemic rats, and the effect was comparable to that of 1,1-dimethylbiguanide i.e. metformin<sup>24</sup>. Most recently, gas chromatography of extract of *Pterocarpus marsupium* has indicated the presence of D-chiro inositol (DCI). It is established that metformin enhanced<sup>30</sup> the action of insulin in PCOS in part by improving insulin-mediated release of the DCI-IPG (inositolphosphoglycan). Therefore it may also be stated that *Pterocarpus marsupium* in Hyponidd, due to presence of DCI in it may be in part, fulfill the deficit of phospholipid containing DCI in PCOS women to reduce insulin resistance.

The findings of the present study also point towards an added advantage of *Gymnema sylvestre* in Hyponidd as a weight reducing agent over metformin, which did not show any change in waist girth and WHR. Hence, it may be postulated that this additional characteristic of Hyponidd may contribute in reduction of centroid obesity and peripheral aromatization of androgens to estrogens, which may be responsible for hyperandronaemia<sup>31</sup>. It is therefore suggested that further study should be carried out to evaluate the role of *Gymnema sylvestre*, which may be acting like acarbose in reducing hyperandrogenemia.

The present study suggests that herbal medicine- Hyponidd containing *Gymnema Sylvestre* and *Pterocarpus marsupium* effectively reduced insulin resistance, hyperandrogenemia equally like metformin. However, the reduction in BMI and waist girth as well as decrease in the incidence of LH: FSH ratio with Hyponidd treatment was more perceptible as compared to metformin. To explain these results, particularly effect of reduced centroid obesity in the form of reduced WHR and BMI; further studies are warranted to support the efficacy of this herbal medicine.

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**Table 1.** Baseline distribution of various diagnostic criteria of PCOS as observed in the two groups

Diagnostic criteria	Hyponidd group (n = 75) No. (%)	Metformin group (n = 72) No. (%)
Menstrual irregularity	66 (88)	71(88.7)
BMI > 25	62 (82.7)	58 (80.6)
Hyperandronaemia (sr. testosterone > 80 ng/dl)	57 (76)	58 (77.5)
LH: FSH ratio > 2.0	71 (95)	68 (95)
Hirsutism / Acne (F-G score > 10)	44 (58.7)	49 (68)
Insulin resistance (FG: FI ratio)	69 (92)	66 (92)

**TABLE 2.** Anthropometrical and clinical characteristics of the PCOS subjects

Parameter	Metformin group (n = 72)			Hyponidd group (n = 75)			Difference in groups <i>P</i>
	Before t/t	After t/t	<i>P</i>	Before t/t	After t/t	<i>P</i>	
Age (yrs)		28.7 ± 0.7			29.0 ± 0.7		NS
Waist girth (cm)	79.8 ± 2.3	79.4 ± 1.8	NS	81.1 ± 1.8	76.1 ± 1.0	< 0.05	< 0.05
BMI (kg/m <sup>2</sup> )	24.0 ± 0.5	23.9 ± 0.7	NS	23.9 ± 0.85	22.1 ± 0.4	< 0.05	< 0.05
W/H ratio	0.856 ± 0.004	0.855 ± 0.001	NS	0.858 ± 0.009	0.836 ± 0.005	< 0.005	<0.005
Clinical hyperandrogenism	10.7 ± 0.35	9.6 ± 0.2	< 0.006	10.5 ± 0.37	9.5 ± 0.2	< 0.05	NS

**TABLE 3.** Metabolic parameters of the PCOS subjects before and after treatment

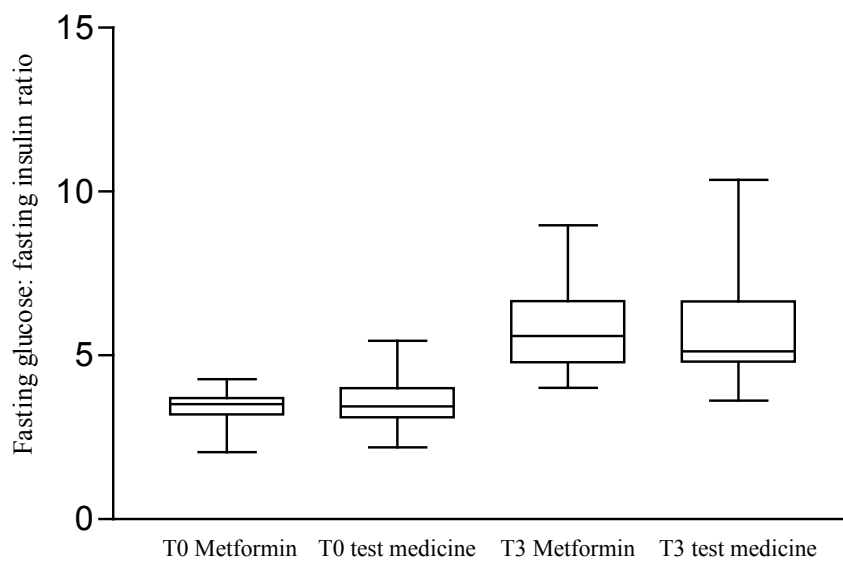
Parameters	Metformin group			Hyponidd group			Difference in groups <i>P</i>
	Before t/t	After t/t	<i>P</i>	Before t/t	After t/t	<i>P</i>	
Fasting insulin (µU/ml)	25.6 ± 0.74	15.8 ± 0.6	< 0.0001	25.5 ± 0.5	16.4 ± 0.6	< 0.0001	NS
Fasting Glucose (mg/dl)	86.0 ± 1.2	86.3 ± 1.1	NS	89.7 ± 2.6	89.5 ± 2.1	NS	NS
Fasting glucose: insulin ratio	3.4 ± 0.07	5.8 ± 0.19 <sup>a</sup>	< 0.0001	3.55 ± 0.1	5.7 ± 0.2 <sup>a</sup>	< 0.0001	NS
HOMA - IR	5.4 ± 0.2	3.5 ± 0.3 <sup>a</sup>	< 0.0001	5.7 ± 0.2	3.7 ± 0.2 <sup>a</sup>	< 0.0001	NS
B- cell function index	457.5 ± 30.9	219.6 ± 11.9	< 0.0001	462.4 ± 63.7	202.4 ± 15.1	0.0002	NS

Parameters	Metformin group			Hyponidd group			Difference in groups
	Before t/t	After t/t	<i>P</i>	Before t/t	After t/t	<i>P</i>	<i>P</i>
LH (mIU/ml)	8.6 ± 0.7	7.0 ± 0.4	< 0.05	8.7 ± 0.5	6.97 ± 0.3	<0.005	NS
FSH (mIU/ml)	3.96 ± 0.3	4.4 ± 0.2	NS	3.8 ± 0.2	4.1 ± 0.2	NS	NS
LH: FSH ratio	2.45 ± 0.2	1.66 ± 0.1	< 0.005	2.46 ± 0.2	1.75 ± 0.04	0.0006	NS
SHBG (nmol/Lit)	15.3 ± 0.8	45.1 ± 1.2	< 0.0001	15.3 ± 1.2	42.97 ± 1.2	< 0.0001	NS
FEI	18.85 ± 1.7	4.66 ± 0.3	< 0.0001	18.6 ± 2.2	4.4 ± 0.2	< 0.0001	NS
FTI	20.46 ± 2.2	3.88 ± 0.2	< 0.0001	21.97 ± 2.7	4.2 ± 0.2	< 0.0001	NS
Serum Estradiol (pg/ml)	68.6 ± 5.4	54.6 ± 3.8	< 0.05	62.4 ± 6.6	43.4 ± 2.1	< 0.005	< 0.05
Serum testosterone (ng/dl)	79.8 ± 6.8	48.2 ± 2.1	< 0.0001	79.4 ± 5.1	51.0 ± 1.4	< 0.0001	NS

Parameters	Metformin group (n = 72)		Hyponidd group (n=75)		Difference in groups <i>P</i> value
	Pretreatment	post treatment	Pretreatment	Post treatment	
Obesity (BMI >25 kg/m <sup>2</sup> )	25 / 72 (34.7 %)	25 / 72 (34.7 %)	26 / 75 (34.6 %)	20 / 75 (26.6%)	< 0.05
Insulin resistance (FG: FI < 4.5)	71 / 72 (98.6 %)	10 / 72 (14 %)	72 / 75 (96 %)	9 / 75 (12 %)	NS
LH: FSH ratio	55 / 72 (76.4 %)	14 / 72 (19.4 %)	66 / 75 (88%)	6 / 75 (8.0 %)	< 0.05
Percentage ovulation D 21 sr. P > 9.0 ng/ml	15 / 72 (20.8%)	64 / 72 (88.8%)	11 / 75 (14.7%)	64 / 75 (85%)	NS

**Figures:**

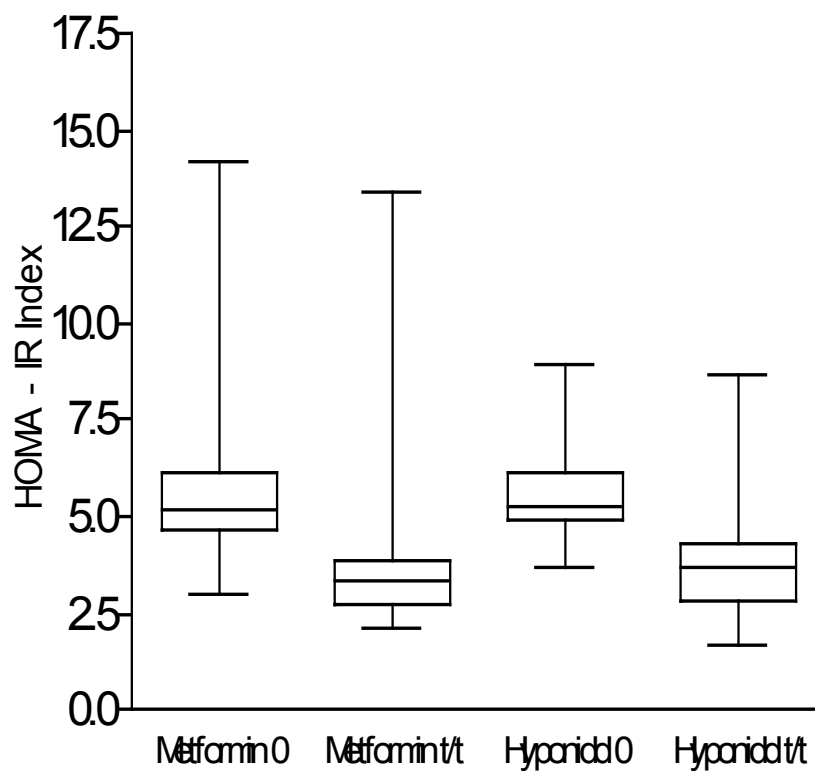
Figure 1: Comparison of pre and post treatment fasting glucose: insulin ratio in Metformin & test medicine groups



*To: Pretreatment and T3: Post treatment, Test medicine: Hyponidd*

Figure 2.

## Comparison of pre and post treatment HOMA-IR in Metformin &amp; Hyponidd groups



*Metformin0: Pretreatment metformin group, Metformin t/t: Post treatment metformin group, Hyponidd0: pretreatment Hyponidd group and Hyponidd t/t: post treatment Hyponidd group.*