A Local Study on the Effect of Glipizide and Metformin as Combination Drugs in the Treatment of Polycystic Ovary Syndrome in El-beida, Libya

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Abstract
This current research study was designed to investigate the effect of using the combination of metformin and glipizide over using every drug alone in the treatment of women with polycystic ovary syndrome (PCOS). Thirty (30) women with PCOS were divided into three groups, group I received glipizide (5mg/day) for three months, group II received metformin (500mg/day) for three months, and group III received glipizide (5mg/day) and metformin (1000mg/day) as combination drugs for a similar amount of treatment. The blood samples were drawn before treatment and after three months of treatment. The fasting plasma glucose, insulin, testosterone, and leutinizing hormone (LH) were measured before and after treatment. The reduction of insulin, glucose, LH, and testosterone levels were greater within the group received the mix of glipizide and metformin than those taken everyone alone. Testosterone levels decreased considerably (P<0.05) from baseline level 1.00±0.43ng/ml to 0.52±0.31ng/ml once treatment with combination. The speed of ovulation was 30.0%, 50.0%, and 70.0% in glipizide, metformin, and combination of each, respectively. The combination of glipizide with metformin has a great impact on the ovulation rate.

1 Introduction
Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. PCOS is the most common endocrine abnormality among women of reproductive age. PCOS is a heterogenous disorder of unsure etiology. It is characterized by chronic anovulation and hyperandrogenism affecting about 5-10% of adult women. The association between insulin-resistant hyperinsulinism and PCOS is well recognized and will play a very important pathogenic role in development of PCOS. Obese and lean women with PCOS manifest insulin resistance independent on weight, though obesity is an additive issue that aggravates insulin resistance. There is some knowledge to counsel that insulin enhances the result of gonadotropic hormone on preovulatory ovarian cyst arrest. It is possible that hyperinsulinemia because of insulin resistance drives the gonadotropic hormone have an effect on female internal reproductive organ theca cells to cause androgen excess that are as such programmed to provide additional androgens. Excess androgens are best-known to interfere with the process of cyst maturation, thus inhibiting ovulation and manufacturing of additional arrested follicles. It is been postulated that in PCOS ovaries there is an increased resistance to all insulin functions, apart from steroidogenic result and therefore the final result's excess androgen production even with normal insulin level. Metformin is a biguanide hypoglycemic agent that is approved for the management of type II polygenic disease. Its main mechanism of action is reduction of hepatic glucose production (inhibition of gluconeogenesis). It additionally will increase insulin mediate glucose utilization in peripheral tissue and reduce enteral absorption of glucose. Some authors have incontestable the extra edges of exploitation metformin like these related to cycle regulation and induction of ovulation, protection from maternity losses, and improvement of cardiovascular risk factors. Moreover, metformin markedly will increase each spontaneous ovulation rate and clomiphene-
induced ovulation rate for obese girls with PCOS. Several studies have shown improvements in ovulatory function, development of normal flow, and restoring of fertility. In spite of these benefits, several employees reported that metformin result could also be to some extent transient and a few cellular adaptations might occur during additional prolonged therapy. Glipizide sensitizes the beta cells of pancreatic islets of Langerhans insulin response and that means that a lot of insulin are free in response to glucose than would be without glipizide intake. Glipizide acts by partially blocking K+ channels among beta cells of pancreatic islets of Langerhans. By obstruction K+ channels, the cell depolarizes, which results in the gap of voltage-gated Ca2+ channels. The resulting calcium influx encourages insulin release from beta cells. Therefore, this present study was designed to point out whether combination of glipizide and metformin has benefits over using each drug alone within the treatment of women with PCOS.

2 Methods and Materials

This study was conducted at Al Salam Hospital in El-beida, Libya from August 2019 to October 2019. The study groups included 50 Libyan women, 30 case with PCOS aged 18-35 years with a mean age 28.30±4.07 years, and 20 normal control subjects aged 18-35 years with a mean age 28.10±7.00 years. The patients included during this study were diagnosed with PCOS, non-diabetic, non-hypertensive, and non-pregnant. The patients were under gynecologist supervision throughout amount of treatment. The diagnosing of PCOS was created by gynecologist depending on ultrasound examination, clinical options, and laboratory tests (hormonal assay). The patients concerned during this study were on traditional diet. They were divided randomly into three groups. Group I included 10 patients (BMI 28.80±3.90 Kg/m²), aged 29.70±6.40 years. The patients received glipizide 5mg daily in two divided doses (2.5mg in the morning and 2.5mg in the evening before meals) for three months. Group II included 10 patients (BMI 34.20±6.00 Kg/m²), aged 26.50±4.00 years. The patients received metformin 500mg in the evening with meals) for three months. Group III enclosed 10 patients (BMI 30.10±5.20Kg/m²), aged 24.90±4.60 years. The patients received metformin 1000mg daily in two divided doses (500mg in the morning and 500mg in the evening with meals) for three months. Group III enclosed 10 patients (BMI 34.20±6.00 Kg/m²), aged 26.50±4.00 years. The patients received a combination of the two drugs (glipizide5mg/day and metformin1000mg/day) for three months. Control group enclosed 20 normal women (BMI 30.00±4.80 Kg/m²), aged 27.10±6.00 years.

2.1 Sample collection

10ml of blood samples utilized in this study were drawn from PCOS patients. The first sample was collected before treatment as a baseline level. Fasting blood samples were used for the measurement of glucose, insulin, and hormones (LH and testosterone). Blood samples were left at room temperature for 30 minutes for action, centrifuged so serum was separated and picked up in small aliquots (0.5ml) and kept at (-20°C) till biochemical and hormonal analyses were performed. The bodily fluid was used for measure of fasting plasma glucose, insulin, testosterone, and LH levels.

2.2 Biochemical and hormonal assays

Fasting insulin levels were determined by radioimmunoassay (RIA) method. Blood serum testosterone levels were determined also by RIA method. Blood serum LH was determined by immunoradiometric assay (IRMA) method. Fasting plasma glucose was measured by enzymatic method.

2.3 Diagnosis of infertility

It depends on the inability of any couple to conceive a child among a 12 months period of unprotected sexual intercourse.

2.4 Statistical analysis

The results were expressed as means±SD. Student T-test was used to examine the difference in the mean of parameters tested. P value of less than 0.05 was considered significant.

3 Results

As shown in table 1, the most patients in this study were infertile (30.00%) and oligomenorrhea (26.66%). The hirsutism was obvious symptom in (20.00%) of the patients. The combination of metformin and glipizide reduced the levels of serum insulin, glucose, LH, and testosterone which were more than that produced by metformin or glipizide alone as presented in tables 2, 3 and 4. The testosterone level was significantly decreased (P<0.05) only after treatment with combination compared to the baseline levels.

As shown in table 5, the ovulation rates were 30.0%, 50.0%, and 70.0% in glipizide, metformin and combination of both, respectively.

Table 1: Data of thirty (30) patients with PCOS

<table>
<thead>
<tr>
<th>Character</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsutism</td>
<td>6 (20.00%)</td>
</tr>
<tr>
<td>Regular cycle</td>
<td>3 (10.00%)</td>
</tr>
<tr>
<td>Infertility</td>
<td>9 (30.00%)</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>8 (26.66%)</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>4 (13.33%)</td>
</tr>
</tbody>
</table>

4 Discussions

In this study, the administration of insulin sensitizing agents glipizide and metformin alone or together for three months showed non-significant reduction (P>0.05) in blood serum glucose levels and blood serum insulin levels. The efficacy and percentage of improvement were seen to be more obvious in combination group than with either drug alone (Tables 2, 3 and 4).
4). Glipizide showed additional improvement than metformin. However, in the present study, glipizide and metformin treatment improved insulin resistance as a result of there was an improvement in fasting insulin and fasting glucose levels, similar results were reported by other studies27, 28.

Table 2: Effect of treatment of glipizide (5 mg/day) on levels of testosterone, LH, insulin, and glucose in group I

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control levels (n=20)</th>
<th>Baseline levels (before treatment) (n=30)</th>
<th>After treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.34±0.01</td>
<td>0.94±0.44*</td>
<td>0.71±0.43* (24.40)</td>
</tr>
<tr>
<td>LH (μU/ml)</td>
<td>4.50±0.15</td>
<td>11.60±3.40*</td>
<td>10.60±3.10* (8.60)</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>8.40±1.70</td>
<td>15.60±5.50*</td>
<td>10.40±3.60* (33.50)</td>
</tr>
<tr>
<td>Glucose (mg/100ml)</td>
<td>82.00±4.90</td>
<td>89.80±7.00</td>
<td>84.00±5.80 (6.40)</td>
</tr>
</tbody>
</table>

Values are means±SD, n= No. of women. % = percentage of change compared with baseline levels. *P < 0.05 for comparison with control group.

Table 3: Effect of treatment of metformin (1000 mg/day) on levels of testosterone, LH, insulin, and glucose in group II

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control levels (n=20)</th>
<th>Baseline levels (before treatment) (n=30)</th>
<th>After treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.34±0.01</td>
<td>0.81±0.41*</td>
<td>1.00±0.43* (24.40)</td>
</tr>
<tr>
<td>LH (μU/ml)</td>
<td>4.50±0.15</td>
<td>10.50±3.40*</td>
<td>10.90±1.80* (14.20)</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>8.40±1.70</td>
<td>13.50±5.40*</td>
<td>21.20±5.90* (42.00)</td>
</tr>
<tr>
<td>Glucose (mg/100ml)</td>
<td>82.00±4.90</td>
<td>89.20±8.20</td>
<td>82.10±6.20 (6.70)</td>
</tr>
</tbody>
</table>

Values are means±SD, n= No. of women. % = percentage of change compared with baseline levels. *P < 0.05 for comparison with control group. **P < 0.05 for comparison with baseline alone.

Table 4: Effect of treatment of combination glipizide (5mg/day) and metformin (1000mg/day) on levels of testosterone, LH, insulin, and glucose in group III

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control levels (n=20)</th>
<th>Baseline levels (before treatment) (n=30)</th>
<th>After treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.34±0.01</td>
<td>1.00±0.43*</td>
<td>0.52±0.31* (27.00)</td>
</tr>
<tr>
<td>LH (μU/ml)</td>
<td>4.50±0.15</td>
<td>10.90±1.80*</td>
<td>5.80±2.40* (14.20)</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>8.40±1.70</td>
<td>21.20±5.90*</td>
<td>11.50±4.50* (42.00)</td>
</tr>
<tr>
<td>Glucose (mg/100ml)</td>
<td>82.00±4.90</td>
<td>89.20±8.20</td>
<td>82.10±6.20 (6.70)</td>
</tr>
</tbody>
</table>

Values are means±SD, n= No. of women. % = percentage of change compared with baseline levels. *P < 0.05 for comparison with control group. **P < 0.05 for comparison with baseline alone.

All groups of patients who received glipizide and metformin alone or together showed a small (non-significant) decline in LH levels when compared with baseline levels. Lack of change in LH levels also reported by several researchers28, 29. The effect of glipizide and metformin combination for three months was associated with vital decline in testosterone levels (P<0.05) (Table 4).

Table 5: Ovulation rates in PCOS patients for treatment with insulin sensitizing agents

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=10)</th>
<th>Group II (n=10)</th>
<th>Group III (n=10)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ovulation</td>
<td>7 (70.0%)</td>
<td>5 (50.0%)</td>
<td>3 (30.0%)</td>
<td>15</td>
</tr>
<tr>
<td>Ovulation</td>
<td>3 (30.0%)</td>
<td>5 (50.0%)</td>
<td>7 (70.0%)</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

The study also showed a larger decrease in insulin resulting in a lot of decrease in testosterone level. These results are in agreement with studies showed a reduction in body fluid androgen levels once the reduction of insulin levels by insulin sensitizing agents, and these results were independent in weight24-30. In general, the favorable result of hormone sensitizing agents on hyperandrogenemia in polycystic ovary syndrome is also due to reduced pituitary secretion of luteinizing hormone, reduced ovarian androgen secretion, and augmented levels of endocrine binding simple protein (SHBG)31. The administration of glipizide or metformin alone or each of them for three months demonstrated an improvement in the ovulation rate assessed by measurement of mid-luteal phase progesterone level in group III over group I and II (Table 5). This may result to the synergistic effect of two medications that
cause decrease the testosterone considerably ($P<0.05$). The percentages of ovulation rates were 70.0%, 50.0%, and 30.0% in groups III, II and I respectively. Many studies investigated impact of metformin on menstrual cyclicity, and a significant improvement within the frequency of menstrual cycles has been reported with associate increase in the share of ovulatory cycles as assessed by mid-luteal phase progesterone. KJ Meenanakumaari et al., 2004 found a significant negative correlation between insulin and progesterone, and between progesterone and luteinizing hormone concentration in PCOS women treated with metformin and suggested that insulin resistance/hyperinsulinemia is also responsible for low progesterone levels throughout the phase in PCOS. The luteal progesterone is also increased in PCOS by decreasing insulin levels with metformin. R Azziz et al., 2004 studied the impact of glipizide on menstrual cyclicity and ovulation in PCOS women. Azziz reported a rise within the mean rate of ovulation in dose-related fusion and he expected an improvement in the menstrual cycle when the improvement in ovulation.

5 Conclusion

It is preferred to use a combination of glipizide and metformin in infertile polycystic ovary syndrome women because it has more potent impact in the improvement of ovulation rate. The combination is also more useful to alleviate the hyperandrogenemia in women with polycystic ovary syndrome.

6 Acknowledgment

We would like to thank Dr. Reem Emhareb, gynecologist at Al Salam Hospital in El-beida, Libya for her help in preparing and diagnosing of patients. We are also grateful to Dr. Dareen Salem, lab technician at Al-nour Lab in El-beida, Libya for her expertise in laboratory work.

7 Conflicts of Interest

We hereby declare that there are no conflicts of interest regarding the publication of this research study.

8 Ethics

All participants provided written permission and consent before collecting data to conduct this research study.

9 Author’s Contributions

This work was carried out in collaboration between all authors. Author YSEM designed the study, wrote the protocol, and performed all the statistical analyses. Author NAMI collected the data, wrote the manuscript, and managed the literature searches. All authors reviewed and approved the final manuscript.

10 References