A short-term evaluation of a new insulin-sensitizing product in women with polycystic ovary syndrome

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SUMMARY: A short-term evaluation of a new insulin-sensitizing product in women with polycystic ovary syndrome.

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Polycystic ovary syndrome (PCOS) is a disease affecting 5-10% of women of childbearing age and is manifested by oligo/amenorrhoea, anovulatory cycles, hirsutism, micro-polycystic ovaries. Insulin resistance is a feature of patients with PCOS, most pronounced in obese patients. Insulin resistance and consequent hyperinsulinaemia are related to many aspects of the syndrome such as hyperandrogenism, reproductive disorders, acne and hirsutism. In the long term there may be cardiovascular, lipidic and pressure problems. Modifying lifestyle and diet can partially improve these symptoms. New insulin-sensitizing molecules, such as inositol, have been recently marketed, able to exert a similar effect to metformin, but without side effects.

Methods. Patients (n = 20) have been treated (n = 20) by an association (Mioxin®) with: • 2000 mg of myo-inositol; • 48 mg of banaba [Lagerstroemia speciosa (L.) Pers., Leaves] titrated 1% in corosolic acid; • 400 UI of vitamin D3 • 400 µg of folic acid • 40 µg of chromium in the dose of a sachet a day for 3 months.

Prior to administration and after one month, a glucose loading curve (OGTT) was performed with glucose and insulinemia determination and after 3 months a clinical evaluation of BMI and menstrual cycle was performed.

Conclusions. The results have demonstrated the efficacy of this new product even in the short term, by reducing the insulin resistance observed at OGTT which translates from a clinical point of view into a reduction in body weight and an improvement in cyclicity menstrual.

KEY WORDS: PCOS - Insulin resistance - Banaba - Inositol.
Insulin action on the ovaries is in fact mediated by inositol-glycan mediators and is thus distinguished from the insulin-mediated tyrosine phosphorylation cascade that improves the use of glucose in other body districts. This indicates that insulin signal induction pathways are different in the ovaries and that insulin action on steroidogenesis is maintained even in insulin resistance cases. Hyperinsulinemia may increase the production of androgens in the PCOS by directly stimulating the ovary, either indirectly through stimulation of LH secretion and inhibition of IGF binding protein (IGFBP) and SHBG synthesis. The human ovary has insulin-specific receptors, which suggests a role of this substance in the regulation of ovarian function (12).

Even banaba has great hypoglycemic properties, it’s called “phyto-insulin” or “green insulin” for its ability to modulate insulin and glucose levels, having a synergic but not additive treatment with insulin (13, 14). The hypoglycemic action is due to the phytocomplex of banaba, although the active principle with a therapeutic action has been identified in corosolic acid (15). Its hypoglycemic activity is made up by the suppression of gluconeogenesis and by the oxidation of glucose through the pathway of pentose-phosphates. Corosolic acid is also able to inhibit the differentiation of adipocytes, making it useful in the treatment of overweight and obesity. It seems also that banaba can lower blood glucose levels, also acts on fat in the liver by reducing the accumulation of triglycerides, which would also have a positive effect on cholesterol (16).

Chromium is an essential mineral in human nutrition and plays a key role in carbohydrate metabolism. It’s poorly absorbed with diet, while organic sources (Cr picolinate) are better absorbed. Chromium, binding to the chromodulin oligopeptide, acts in glycemic metabolism, amplifying the insulin signal and thereby contributing in reducing insulin resistance (17, 18).

Vitamin D has an important role in the pathogenesis of PCOS. Several studies have shown correlation between low levels of Vitamin D with PCOS and obesity, which is an important factor in the development of insulin resistance. Altered concentrations in 25-hydroxyvitamin D (25OHD) serum are correlated with SHBG synthesis. The human ovary has insulin-specific receptors, which suggests a role of this substance in the regulation of ovarian function (12).

Materials and methods

Twenty patients with PCOS, 23 to 36 years of age, insulin-resistant (glycogen-insulinemic curve) were enrolled.

Informed consent was obtained from all patients before attending the study and the study was approved by the Clinical Research Committee. All patients met the PCOS diagnostic criteria, defined by the recent ESHRE / ASRM (2) consensus, with the exclusion of other endocrinopathies.

At the time of enrolment, all patients underwent basic work-up: medical and gynaecological history (length of the menstrual cycle) and complete physical examination including body mass index (BMI) (kg/m²). Furthermore patients have been evaluated on the FSH hormone profile (mUI /ml); LH (mUI / ml); Estradiol (E2) (pg/ml); Prolactin (PRL) (uUI /ml); Total testosterone (T) (ng/ml); Androstenedione (A) (ng/ml) and glucid metabolism by performing the glycemic curve and insulinemic curve in six, 0, 30, 60, 90, 120 and 180 min.

Patients have been treated (n = 20) by an association (Mioxin®) with: • 2000 mg of myo-inositol; • 48 mg of banaba [Lagerstroemia speciosa (L.) Pers., Leaves] titrated 1% in corosolic acid; • 400 UI of vitamin D3 • 400 µg of folic acid • 40 µg of chromium in the dose of a sachet a day for 3 months.

After 1 month of treatment, the loading curve was repeated and after 3 months a clinical evaluation of all patients with baseline hormone repetition was performed.

Statistical analysis

Statistical analysis was performed using SPSS statistical software version 17 (SPSS I Chicago, IL, USA). Results have been presented as Media (M) ± Standard Deviation (DS). The data were considered statistically significant for values of p < 0.05.
Results

All the patients completed the study protocol and no particular side effects have been referred. Table 1 shows values for insulin and blood glucose uptake before and after one month treatment with Mioxin®; Table 2 shows the characteristics of the cycle, BMI values and hormone doses before and after three months of treatment with Mioxin®.

The results showed a significant reduction in insulin levels after OGTT at one-month treatment with Mioxin® at all times between 0' and 120' (Figure 1). With regard to the glycemic curve after one month of treatment, patients showed a significant reduction in blood glucose levels, although these results were significant only in the time 0', 30', 120' (Figure 2). After three months of treatment with Mioxin®, all women showed a significant reduction in menstrual cycle duration and in BMI value, as well as an improvement in hormonal values compared to evaluation before treatment. In particular, the menstrual cycle duration ranged from an average of 58,95 ± 17,12 days to 36,3 ± 5,99 (p <0,005) (Figure 3); BMI varied from 29,06 ± 2,99 kg/m² to 26,42 ± 1,72 kg/m² (p <0,005) after 3 months of therapy (Figure 4). There is also a significant reduction in LH values ranging from 12,14 ± 4,71 mUI /ml to 9,2 ± 1,4 mUI /ml (p <0,05) which leads to a correction of the LH/FSH value. Among the hormone values the most relevant ones are androstenedione (A) and testosterone (T), which have showed a significant reduction; androstenedione increased from 2,57 ± 0,67 ng/ml to 1,84 ± 0,28 ng/ml (p <0,01); testosterone ranged from 0,72 ± 0,14 ng/ml to 0,6 ± 0,13 ng/ml (p <0,01).

Discussion

Our data prove the efficacy of this new nutraceutical containing insulin-sensitizing substances and confirm the central role of insulin resistance in PCOS etiopathogenesis.

In particular, the action of myo-inositol is due to a sensitization of peripheral tissues to insulin action. In addition, the synergy of action with other components, and in particular with banaba, is important and results in a significant improvement in serum levels of blood glucose and insulinenia already since the first month. This positive action on the various factors most involved in causing the syndrome continues in the following months, and at a distance of 3 months, there is a clinical improvement of the menstrual cycle and a reduction in the BMI value. Normalization of basal levels and glucose and insulin ratio is observed both in overweight patients and

Table 1 - Glyco-Insulinemic Curve Data Before and After One Month of Treatment with Mioxin®. Values are expressed as Mean (M) and Standard Deviation (SD).

<table>
<thead>
<tr>
<th></th>
<th>BASAL</th>
<th>Time 0'</th>
<th>Time 30'</th>
<th>Time 60'</th>
<th>Time 90'</th>
<th>Time 120'</th>
<th>Time 180'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (mU/l)</td>
<td>12,91 ± 8,47</td>
<td>90,99 ±48,68</td>
<td>88,85 ± 41,93</td>
<td>82,92 ± 57,04</td>
<td>74,51 ± 62,04</td>
<td>32,79 ±33,35</td>
<td></td>
</tr>
<tr>
<td>1 MONTH</td>
<td>Time 0'</td>
<td>Time 30'</td>
<td>Time 60'</td>
<td>Time 90'</td>
<td>Time 120'</td>
<td>Time 180'</td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>8,66 ± 3,08</td>
<td>63,46 ±33</td>
<td>61,83 ±30,52</td>
<td>53,16 ±34,08</td>
<td>39,86 ±31</td>
<td>22,59 ±20,21</td>
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<tr>
<td>BASAL</td>
<td>Time 0'</td>
<td>Time 30'</td>
<td>Time 60'</td>
<td>Time 90'</td>
<td>Time 120'</td>
<td>Time 180'</td>
<td></td>
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<tr>
<td>Glycemia (mg/dl)</td>
<td>95,3± 9,99</td>
<td>151,75 ±30,86</td>
<td>142,05 ±44,84</td>
<td>120,5 ±44,75</td>
<td>108,65 ±30,39</td>
<td>83,3 ± 26,08</td>
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<tr>
<td>1 MONTH</td>
<td>Time 0'</td>
<td>Time 30'</td>
<td>Time 60'</td>
<td>Time 90'</td>
<td>Time 120'</td>
<td>Time 180'</td>
<td></td>
</tr>
<tr>
<td>Glycemia (mg/dl)</td>
<td>88,05 ±6,58</td>
<td>134,3 ± 15,46</td>
<td>122,95 ±29,19</td>
<td>104,75 ±23,03</td>
<td>92,55 ±15,82</td>
<td>76,5 ±10,46</td>
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</table>
in patients with normal BMI. These data confirm the importance of inositol activity in PCOS patients (28).

The originality of this clinical trial is related to the speed of action of the product used, which has led to a significant reduction of basal and whole blood glucose and insulin curves. This type of action is attributed to a synergistic mechanism among the various substances that, acting on different factors responsible for insulin resistance, normalize insulin levels after just thirty days of treatment.

What it is observed on BMI and menstrual cycle confirms the efficacy of these substances in restoring menstrual regularity, resulting in ovulation recovery. The reduction of insulin resistance together with a significant weight loss represent the key through which the effectiveness of this type of product is realized.

In addition, phosphate inositols, and in particular myo-inositol, have been acknowledged some important antioxidant effects. They can act as anti-inflammatory

| TABLE 2 - DATA ON LENGTH OF THE MENSTRUAL CYCLE (DAYS), BMI, AND HORMONE DOSES OF THE PATIENTS IN THE STUDY BEFORE AND AFTER THREE MONTHS OF TREATMENT WITH MIOXIN®. THE VALUES ARE EXPRESSED AS MEAN (M) AND STANDARD DEVIATION (SD). P VALUE: *P< 0,05; **P< 0,01; ***P< 0,005. |
|---------------------------------|---------------------------------|---------------------------------|
|                                | BASAL                           | AFTER 3 MONTHS                  |
| Cicle (days)                   | 58,95 ± 17,12                   | 36,3 ± 5,99**                   |
| BMI (kg/m²)                    | 29,06 ± 2,99                    | 26,42 ± 1,72**                  |
| FSH (mUI/ml)                   | 5,81 ± 1,55                     | 5,42 ± 0,74                     |
| LH (mUI/ml)                    | 12,14 ± 4,71                    | 9,2 ± 1,4*                      |
| E2 (pg/ml)                     | 39,02 ± 15,49                   | 32,1 ± 5,6*                     |
| PRL (uUI/ml)                   | 13,26 ± 2,12                    | 12,31 ± 2,32                    |
| T (ng/ml)                      | 0,72 ± 0,14                     | 0,6 ± 0,13*                     |
| A (ng/ml)                      | 2,57 ± 0,67                     | 1,84 ± 0,28**                   |

Figure 1 - Results of the insulin-like curve after administration of 75 mg glucose in six times (0', 30', 60', 90', 120', 180') in patients in the study before and after one month of treatment with Mioxin®. Values are expressed as mean (M) and standard deviation (SD). p value: *p< 0,05.

Figure 2 - Results of the glycemic curve after administration of 75 mg glucose in six times (0', 30', 60', 90', 120', 180') in patients in the study before and after one month of treatment with Mioxin®. Values are expressed as mean (M) and standard deviation (SD). p value: *p< 0,05.
agents, not blocking the oxidation chain directly, but increasing the activity of the major antioxidants (29, 30).

By reducing LH, prolactin and testosterone levels, myo-inositol can lead to a regularization of menstrual cycles in terms of rhythm and proper ovulation process (31).

Our study showed not only the correction of the LH/FSH ratio needed for a correct ovulation, but also a reduction in androgenic hormones concentration, responsible for the clinical signs of hyperandrogenism.

The useful effects of banaba and corosolic acid on glucid and lipid metabolism seem to involve many mechanisms including increased cellular glucose absorption, altered sucrose and starch hydrolysis, decreased gluconeogenesis, and regulation of lipid metabolism. These effects may be useful to avoid the symptoms associated with metabolic syndrome, as well as improve women’s health benefits.

Our data confirm that the use of chromium supplementation can play an important role in reducing the inflammation of PCOS caused by hyperglycaemia through free radicals of oxygen (ROS) (32, 33). Chromium, through binding to the chromoduline oligopeptide, intervenes in glycaemic metabolism, amplifying the insulin signal and thereby so reducing insulin resistance.

The role of Vitamin D in PCOS is now demonstrated by several clinical studies that correlate low levels of Vitamin D3 with the onset of PCOS. Vitamin D contrasts insulin resistance directly and indirectly. Vitamin D can also counteract hyperandrogenism and has been shown to play an important role in the fertilization and implantation process, increasing the probability of pregnancy (34). In conclusion we can say that this new association carries a similar, and almost superimposable, insulin-sensitizing action to the one performed by metformin. The peculiarity behind the results obtained is the result of the synergistic effect of using 2 gr of myo-inositol, with banaba acting as “phyto-insulin” in combination with chromium and vitamin D.

**References**

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