The effect of therapy with myo-inositol on insulin resistance of patients with polycystic ovary syndrome followed up for 3 months.

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Introduction.

Inositol is an isomer of glucose, also referred to as sugar alcohol, six-fold alcohol of cyclohexane, and also as Vitamin B8. Epimerisation of six hydroxyl groups causes that inositol occurs in nine isomeric forms, including biologically active ones: myo-inositol (MI) and D-(+)-chiro-inositol (DCI). Other biologically important isomers of inositol are: L-(-)-chiro-inositol, muco-inositol, allo-inositol and neo-inositol[1].

The main source of myo-inositol is diet, as the compound is found in a broad selection of food products, including whole grain, seeds and fruit. Citrus fruit, wholegrain products, nuts, wheat germ, legumes and yeast are particularly rich sources of MI. Daily human diet supplies approx. 1 g of inositol, mostly in the MI form, and that satisfies the daily demand for the substance[2]. MI may be also synthesised from glucose, via fructose-6-phosphate – its direct precursor, transformed into myo-inositol by enzyme cyclase[1,3,4]. Myo-inositol is a precursor of the phosphatydylinositol cycle and a component of phospholipids. MI is a component of cellular membranes and plays an important role in cellular morpho- and cytogenesis, as well as in lipid synthesis. MI is a precursor in synthesis of secondary hormone mediators, e.g. gonadotropin-releasing hormone (GnRH), TSH and insulin. In humans, epimerase is able to convert myo- inositol into L- or D-chiro-inositol[5].

Attributing MI the name of a vitamin is not entirely precise, as the substance is synthesized by human organism. MI presence was demonstrated in the brain, liver and kidneys. It is also present in circulating blood, from where it is up-taken by cells that do not synthesize it. Exogenous MI is absorbed in intestine, and then deposited in the brain, cells of the myocardium and of skeletal muscles, as well as in bones and gonads. Myo-inositol is also produced by saprophytic bacteria[1].

Inositol was first discovered over one hundred years ago, in urine of diabetic patients. However, its importance was not recognised at that time. Only in 1941 Gavin and McHenry

discovered important metabolic roles of the compound.

Inositol secretion was altered in patients with type 2 diabetes, which suggested an association between a reduced inositol clearance and insulin resistance. Hence inositol was defined as a substance influencing insulin susceptibility[6].

Inositol has been lately included in the clinical practice of infertility treatment[7-9]. As the preferred therapy in polycystic ovary syndrome (PCOS), constituting one of causes of ovulation disorders, is the use of substances increasing tissue susceptibility to insulin, the therapy with inositol is currently recommended for chronic PCOS therapy[7-15].

Reports published recently suggest applicability of inositol in prevention of folic acid-resistant neural tube defects[1617].

In the clinical practice, the biologically active isomer of inositol - myo-inositol is most commonly combined with folic acid. A daily dose is 2 g of MI and 200 µg of folic acid.

Study description.

This study was aimed at the assessment of a 3-month therapy with myo-inositol on insulin resistance in patients diagnosed with polycystic ovary syndrome with coexisting insulin resistance. The diagnosis of PCOS was based on criteria suggested by the Androgen Excess Society (AES), and insulin resistance was determined by calculation of the mathematical model for insulin resistance assessment HOMA (HOmeostatic Model Assessment)[18-20]. In physiological conditions the index is 1.0. Higher values suggest peripheral insulin resistance or insulin resistance of hepatic origin. The HOMA-IR index is closely correlated (r = 0.88) with the insulin susceptibility index determined based on the standard euglycemic clamp[18-20].

Thirty one (31) patients aged between 20 and 33 years were enrolled. The following were performed during the first visit (Visit 0):

- body weight measurement and determination of body mass index (BMI);
- arterial blood pressure measurement and calculation of the mean arterial pressure (MAP);
- pulse assessment;
- transvaginal ultrasound for determination of presence of a dominant follicle or a corpus luteum;
- determination of blood level of luteinizing hormone (LH) and follicle stimulating hormone (FSH), with calculation of the LH/FSH ratio;
- oral glucose tolerance test (OGTT) with 75 g of glucose; glycemia, and insulin level determined on empty stomach and in 1 and 2 hours after the test, and HOMA-IR index calculated.

At enrolment the study group was stratified in respect to the value of the HOMA-IR index:

- Patients with **low insulin resistance** (HOMA-IR 1.0 - 1.99), U = 15;
- Patients with **medium insulin resistance** (HOMA-IR 2.0 - 3.0), U = 9;
- Patients with **high insulin resistance** (HOMA-IR >3.0), U = 7;

After determination of the level of insulin resistance, patients were qualified for the therapy with a preparation containing 2 g of MI and 200 µg of folic acid (Inofem, Establo Pharma). Maltodextrin in amount of 37 mg or less per sachet was used as a carrier substance for active ingredients in the applied formula.

Patients were taking MI at the dose recommended by the Polish Gynaecological Society for the therapy of PCOS, that is 4 g a day[15]. Control visits were planned after 1 month (Visit 1) and after 3 months (Visit 2) of the therapy. In case of patients who had menstruation during the treatment with MI, tests were performed on day 10 of the cycle. The same tests as those performed during enrolment were repeated during each control visit.

Considering absence of the normal distribution of the HOMA-IR index value in the study group, HOMA-IR was reported as a median. The statistical analysis was completed using the Wilcoxon-signed rank test for sequences, comparing the following pairs Visit 0/Visit 1 and Visit 0/Visit 2 (Statistica, ver. 10, Statsoft, Tulsa, OK, USA).

Results.

In the group of patients with low insulin resistance (HOMA-IR 1.0-1.99) a statistically significant reduction of the mean blood pressure and pulse was observed both after 1 (Visit 1) and after 3 (Visit 2) months of the study. Moreover, a statistically significant reduction of the LH/FSH ratio and of the HOMA-IR index was observed at the second control visit (Visit 2) (Table 1).

Table 1. Values of studied parameters in the group of patients with low insulin resistance.

Parameter	Visit 0	Visit 1	Visit 2	p (Visit 0/1)	p (Visit 0/2)
BMI	20.39	20.02	19.83	p > 0.05	p > 0.05
MAP	94	93	92	**p < 0.05**	**p < 0.05**
Pulse	78	72	66	**p < 0.05**	**p < 0.05**
LH/FSH	1.51	1.22	0.93	p > 0.05	**p < 0.05**
HOMA IR	1.65	1.66	1.56	p > 0.05	**p < 0.05**

Moreover, in 11 (of 15) patients the occurrence of ovulation within the 3-month follow-up period was confirmed, and occurrence of spontaneous menstruation was observed in that group of patients.

In the group of patients with medium insulin resistance (HOMA-IR 2.0 – 3.0) a statistically significant reduction of the HOMA-IR index value was observed after 3 months of therapy with the myo-inositol formula (Visit 2).

Detailed data are presented in the Table 2.

Table 2. Values of studied parameters in the group of patients with medium insulin resistance.

Parameter	Visit 0	Visit 1	Visit 2	p (Visit 0/1)	p (Visit 0/2)
BMI	20.82	20.69	20.01	p > 0.05	p > 0.05
MAP	93	88	91	p > 0.05	p > 0.05
Pulse	73	70	74	p > 0.05	p > 0.05
LH/FSH	0.94	0.97	1.00	p > 0.05	p > 0.05
HOMA IR	2.41	1.75	1.96	p > 0.05	**p < 0.05**

Occurrence of ovulation during the 3-month therapy was confirmed in 9 (100%) patients, and the group of patients confirmed occurrence of spontaneous menstruation during that period. No statistically significant differences of studied parameters both at the Visit 1 and the Visit 2 were observed in women with high insulin resistance (HOMA-IR > 3.0) (Table 3).

Table 3. Values of studied parameters in the group of patients with high insulin resistance.

Parameter	Visit 0	Visit 1	Visit 2	p (Visit 0/1)	p (Visit 0/2)
BMI	27.26	29.07	27.72	p > 0.05	p > 0.05
MAP	106	102	102	p > 0.05	p > 0.05
Pulse	85	84	85	p > 0.05	p > 0.05
LH/FSH	2.41	1.85	1.42	p > 0.05	p > 0.05
HOMA IR	3.73	3.34	3.37	p > 0.05	p > 0.05

In 5 (of 7) patients the occurrence of ovulation within the 3-month follow-up period was confirmed, and occurrence of spontaneous menstruation was observed in that group of patients.

Discussion.

Polycystic ovary syndrome is one of the most common causes of menstruation disorders in reproductive women. Insulin resistance occurs in 80% of patients with obesity and PCOS and in 30 to 40% of non-obese patients with PCOS[21]. Hyperinsulinemia resulting from insulin resistance stimulates production of androgens in ovarian theca cells. The stimulation occurs via the insulin receptor (IR) and the insulin-like growth factor receptor (IGFR). Increased ovarian production of androgens leads to symptoms of hyperandrogenism (hirsutism, dermatological problems with seborrohea, acne and male type alopecia) on one hand, and on the other hand results in premature atresia of ovarian follicles, causing anovulation and reduced production of sex hormone binding globulin (SHBG)[22-25].

The pathomechanism of insulin resistance in PCOS has not been fully understood yet. In the light of currently available data, the role of inositolphosphoglycans (IPG) is notable. IPGs are mediators of intracellular insulin action and of intracellular signal transduction[3,4,23,26]. IPGs are referred to as secondary transducers of the insulin signal inside cells. Two intracellular transducers associated with IPG have been described, depending on the type of inositol isomer: myo-inositol phosphoglycans (MI-IPG), and chiro-inositol phosphoglycans (DCI-IPG). Disrupted signalling into cells by the insulin receptor leads to decreased IPG transport into cells, and causes a secondary reduction of the cellular level of the substance[4]. No reduced insulin susceptibility is found in an ovary, despite the peripheral insulin resistance. Hyperinsulinemia leads to an increased production of androgens and increased release of IPG, simultaneously leading to an increased epimerization of MI into DCI. The increased channel transport of DCI-IPG leads to imbalance of the compound content in relation to MI-IPG (with prevalence of DCI-IPG) and – along with the signal originating directly from IR - additionally stimulates ovarian theca cells for intensified production of ovarian androgens[3,4,23,26].

The fact of development of insulin resistance in women with polycystic ovary syndrome makes substances improving insulin susceptibility of cells applicable in treatment of the syndrome. Metformin is currently recommended. Used chronically the drug reduces hyperinsulinemia and hyperandrogenemia, which results in restoration of ovulation and regular menstruation in patients with PCOS[27].

Reduced availability or altered metabolism of inositol or IPG, as well as imbalance of DCI and MI for the favour of the first one, lead to development of insulin resistance and occurrence of symptoms of PCOS[21-28].

There are many publications focusing on efficacy of MI in reduction of PCOS symptoms, both in relation to laboratory and clinical parameters, in the available literature. A significant reduction of serum LH and prolactin levels, as well as a reduced LH/FSH ratio were confirmed

in the group of patients taking MI. Moreover, parameters directly associated with insulin resistance, including glycemia value in OGTT and indexes: HOMA and insulin susceptibility index (ISI) also were significantly improved. Restoration of regular menstrual cycles, much more frequent ovulations (69.5%), reduced volume of ovaries, increased progesterone level during the luteal phase, and reduced testosterone and DHEA levels were also observed[3,12,29,30].

Similar results were obtained in the group of obese patients treated with MI. An interesting correlation was found: the higher baseline insulin resistance was, the better therapeutic effect of the therapy with MI were observed. However, no body mass index (BMI) reduction was observed after the MYO therapy[29,30].

Also combined with an oral contraception (OC) pill used in women with PCOS, significantly superior therapeutic results were achieved, compared to OC alone. The assessment involved the reduction of hyperandrogenism-associated hirsutism (a symptom very often present in women with PCOS), measured using the Ferriman-Gallway scale. Also levels of androgens and insulin resistance values were lower in women using OC combined with MI. A significant improvement of the lipid metabolism was also observed in that group, compared to the group receiving OC alone[31].

Restoration of normal ovulation following the introduction of MI is associated with improved fertility of women suffering from PCOS. Clomifene citrate is often used in those patients for induction of ovulation. There are reports regarding the use of MI in patients with PCOS resistant to induction with clomifene citrate, but conclusions drawn from those publications were ambiguous. The problem requires further randomized studies[8,32].

The available literature of the subject analysed the effect of MI on the controlled gonadotrophin hyperstimulation in patients with PCOS. Patients receiving additionally MI required a significantly lower total dose of gonadotrophins for stimulation. As a result they had a lower level of oestradiol on the last day of stimulation, which accounted for reduced risk of ovarian hyperstimulation syndrome (OHSS).

In PCOS patients prepared for extracorporeal fertilization and receiving MI and DCI, a higher quality of oocytes and a higher number of post-transfer pregnancies were found in women using MI. Similar conclusions were drawn for non-PCOS gonadotrophin stimulated patients[8,32,33].

Results of studies allow drawing a conclusion that the level of insulin resistance influences effects of treatment with myo-inositol formulas in PCOS patients. While the clinical effect (spontaneous ovulation and menstruation) was observed in each study group in just 3 months

of the therapy, improvement of laboratory parameters was observed only in case of patients with low or medium insulin resistance. In women with low insulin resistance participating in the study, a statistically significant reduction of not only HOMA-IR index, but also of the LH/FSH ratio and functional cardiovascular parameters were achieved in just 3 months of treatment.

Only a significant reduction of HOMA-IR index was observed in patients with medium insulin resistance. As regards the group of women with PCOS and coexisting high insulin resistance, occurrence of clinical signs of efficacy of the therapy with myo-inositol suggests that reduced insulin resistance could be achieved in that group following a longer period of MI monotherapy or combined therapy. The confirmation of that hypothesis requires further investigations.

Conclusion.

Myo-inositol seems to be an effective and safe therapeutic alternative for patients with PCOS, particularly those with low and medium insulin resistance.

LITERATURE

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