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A comparative study between myo-inositol and metformin in the treatment of insulin-resistant women

K. NAS, L. TŰŰ

MensMentis HealthCenter, Budapest, Hungary

Abstract. – OBJECTIVE: Insulin resistance (IR) is af common disorder, which can impair female fertility and is characterized by phenotypic heterogeneity. Life-style treatment and insulin sensitizers are commonly used in the management of women with IR and consequent hyperinsulinemia, in order to restore the normal endocrinological and clinical parameters. Metformin (MET) is considered one of the first approaches to this pathology but new evidences are showing promising results using myo-inositol (MYO) in the management of this pathology.

The aim of this retrospective data analysis was to evaluate the therapeutic efficacy of MYO (4 g myo-inositol plus 400 mcg folic acid/day) *versus* MET (on average 1225 mg/day) treatment in a heterogeneous group of IR patients. The focus was on progesterone and prolactin levels, menstrual cycle disorders, pregnancy rates, serum fasting glucose and insulin levels.

PATIENTS AND METHODS: Records about 6 months treatment (MYO or MET or both insulin sensitizers) at 237 women in reproductive age were analyzed retrospectively. The patients showed symptoms of IR without diabetes or pre diabetes.

RESULTS: All the groups showed a significant improvement ($p<0.05$) in prolactin and progesterone level after the treatment. Furthermore, the treated groups reported a significant improvement in the menstrual cycle disorders, while the only life-style group showed an increase but not statistically significant ($p>0.05$).

CONCLUSIONS: MYO and MET, associated with life-style, had both significant beneficial effects on serum progesterone and prolactin levels, menstrual cycle disorders and pregnancy rates in patients without severe carbohydrate metabolism malfunctions. Nevertheless, no significant differences were found between the MET and the MYO groups. Significant results in hormone levels and symptoms were reached with the combination of both treatments, whereas fasting serum insulin levels were slightly improved. Furthermore, the body mass index (BMI) was moderately but not significantly higher in MET and MET+MYO group.

Key Words:

Myo-inositol, Metformin, Menstrual alteration, Progesterone, Prolactin, HOMA, Insulin resistance, Pregnancy.

Introduction

Insulin resistance is characterized by alterations in its intracellular signaling[1], affecting several metabolic abnormalities with or without body mass index (BMI) alterations[2-4]. IR with consequential hyperinsulinemia[5] is the key factor in the pathogenesis of anovulation[6] and hyperandrogenism[7], possibly resulting in a major metabolic disease[8] and gonadal dysfunction[7]. Patients in reproductive age with IR are often affected by infertility, ovarian dysfunction and menstrual irregularity[9,10]. Compensatory hyperinsulinemia and beta-cell function correlating with IR[11] are easily assessed in everyday clinical practice by the equation of homeostasis model assessment for insulin resistance (HOMA-IR) developed by Matthews et al[12]. This state is determined by genetic and environmental factors and plays an important role in different pathologies such as Polycystic Ovary Syndrome (PCOS), which today is one of the most common endocrinopathies in women in reproductive age[13]. PCOS shows a relevant incidence in the population with an estimated prevalence of 5-10%[14-16].

In the treatment of IR and PCOS life-style, changes are strongly recommended, showing outstanding results combined with complex tailored treatment[17].

Insulin sensitizers are commonly used in the management of women with IR and consequent hyperinsulinemia. These treatments are also used for IR related diseases such as PCOS, in order to restore the normal endocrinological and clinical parameters by lowering insulin secretion[18].

Corresponding Author: Katalin Nas, MD; e-mail: naskatalin@gmail.com

Metformin (MET), a biguanide, is one of the most studied and usually prescribed to these patients. MET reduces glucose absorption from the gastrointestinal tract, suppresses gluconeogenesis and enhances peripheral insulin sensitivity[19].

Some investigations[20-24] suggest that the inositol phosphoglycan (IPP) second messengers cascade could be impaired in PCOS leading to an insulin resistance. Myo-inositol (MYO) is an isomer of a C6 sugar alcohol and it is an insulin-sensitizing agent, previously classified as belonging to the vitamin B complex[25]. Recent studies demonstrated that MYO has a role in the activation of the glucose metabolism controlling enzymes[26,28], and MYO deficiency was found in PCOS women with IR[26]. The administration of MYO was found to enhance ovulation, to decrease testosterone and insulin levels in serum, therefore, restoring the metabolic and hormonal profile of PCOS women with IR[27,26].

The primary outcome of our retrospective trial was to evaluate the efficacy of MYO treatment compared to MET treatment on progesterone, prolactin and menstrual cycle disorders of women with IR. As secondary outcomes, BMI, pregnancy rates, serum fasting glucose and insulin levels in women of childbearing age with IR were checked.

Patients and Methods

A heterogeneous group of women with insulin resistance was selected using our records between October 2013 and February 2016. In this study, 237 patients out of 411 with IR were enrolled using the following inclusion criteria:

- Diagnosed with IR characterized by HOMA-IR>2[28,29];
- Diagnosed menstrual alterations;
- Ages between 25-45 years;
- Regular check-ups with time intervals not longer than 6 months.

This heterogeneous group of patients included also a small number of PCOS women. The exclusion criteria were:

- Patients with amenorrhea;
- Patients with premature ovarian failure;
- Patients with IDDM, NIDDM or any type of pre diabetes (IFG or IGT).

The tailored treatment consisted of diet, physical exercises based on BMI and body constitution (evaluated with InBody R20), medical treatment with metformin (750-2550 mg/day), myo-inositol (4 g myo-inositol plus 400 μg folic acid/day) or both. Life-style changes were emphasized and closely followed with controls and reeducations if needed. Data' extraction were incorporated on average 6 months of treatment per patient. Patients were divided in four groups according to the applied tailored treatments: Group 1: life-style treatment only (41 patients). Group 2: life-style and myo-inositol treatment (62 patients). Group 3: life-style and metformin treatment (81 patients). Group 4: life-style, myo-inositol and metformin treatment (53 patients).

Fasting glucose and fasting insulin levels independent from the menstrual cycle, progesterone and prolactin levels measured in the luteal phase of the menstrual cycle were collected. HOMA-IR index was calculated as (basal glucose) x (basal insulin)/22.5[12]. Data on length of menstrual cycles were extracted; normal length of a menstrual cycle was determined in 25-35 days[29]. We were also seeking data on conception difficulties and occurred pregnancies during the examined period.

Statistical Analysis

Data analysis and statistics were performed with R 3.2.3 program. Data were introduced with confidence limits at 95% (p-value<0.05 was considered statistically significant). Distribution of pregnancy rates between the groups was determined with pairwise comparisons of proportions (p-value adjustment method: Bonferroni). Menstrual cycle disorders were investigated with Fisher's exact test; possible differences between the groups were evaluated with McNemar-test. Progesterone, prolactin, and fasting glucose level changes were compared with paired t-test, whereas Mann-Whitney test was used for serum fasting insulin and HOMA-IR values.

Results

Progesterone levels significantly increased after 6 months of treatment during the luteal phase of the menstruation cycle in each group, but there were no differences among the 4 groups (Table I).

Similar results were obtained for prolactin (Table II) with a significant decrease in all the groups and this was particularly evident in the combination group. No significant differences among the groups were retrieved.

Menstrual cycle disorders were significantly improved in the treated groups while a not stati-

Table I. Changes in serum progesterone levels comparing levels at baseline (T0) and after 6 months (T6) of treatment. Statistically significant results are considered with $p<0.05$ (*).

Progesterone levels (nmol/l)	T0	SD	T6	SD	p
Group 1	33.6	± 7.64	51.7 *	± 5.09	0.033
Group 2	35.3	± 5.66	47.3 *	± 2.69	0.039
Group 3	32.1	± 8.91	56.4 *	± 8.49	0.034
Group 4	28.6	± 7.35	41.8 *	± 6.65	0.048

Table II. Changes in serum prolactin levels comparing levels at baseline (T0) and after 6 months (T6) of treatment. Statistically significant results are considered with $p<0.05$ (*).

Prolactin levels (mIU/l)	T0	SD	T6	SD	p
Group 1	410.28	± 67,81	325.96*	± 26,91	0.036
Group 2	381.15	± 68,52	254.80*	± 28,85	0.023
Group 3	494.73	± 85,98	382.3*	± 39,46	0.048
Group 4	479.3	± 101,12	271,1*	± 48,22	0.017

stically significant improvement was retrieved in the life-style group: Group 1 (p=0.094), Group 2 (p=0.027), Group 3 (p=0.039) and Group 4 (p=0.025) (Figure 1). Out of 237 patients, 168 (71%) suffered from conception difficulties. No statistically significant differences were found in the proportions of infertile women among the groups. Out of 168 patients desiring pregnancy 71 (42.26%) conceived in the observed period. Similarly, no differences were detected among the groups regarding this parameter, as well as for serum fasting glucose levels, during all the treatment.

At the beginning, serum fasting insulin levels were higher in the MET and the MET+MYO group, showing recognizable, but not significant changes after 6 months of complex tailored treatment.

HOMA-IR index values were under 2.5 in Group 1 and Group 2 at the beginning of treatment. HOMA-IR index values showed decreasing tendencies mainly in the groups treated with MET (value at the beginning of treatment: 2.95; value after 6 months treatment: 2.41) and MET+MYO (value at the beginning of treatment: 3.4; value after 6 months treatment: 3.05), without statistical significance within and among the groups at the end of 6 months.

The average BMI of the groups did not differ significantly, but slightly higher BMIs could be detected in Group 3 and Group 4. The average

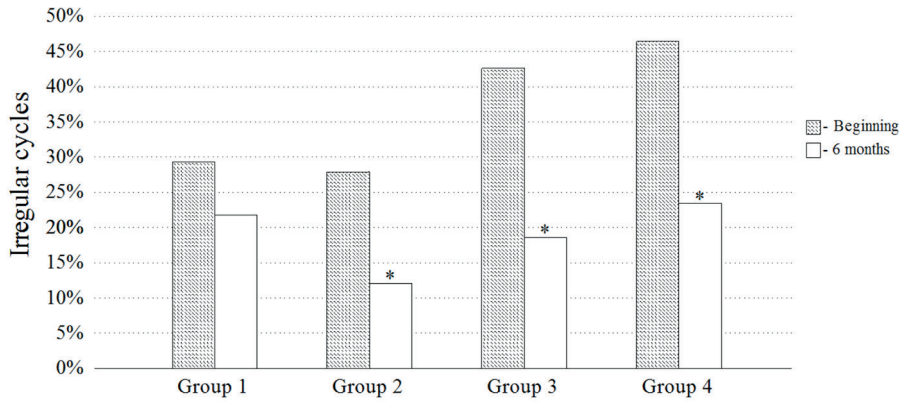

Figure 1. Rate of irregular cycles at beginning and after 6 months of treatment. Statistically significant results are considered with $p<0.05$ (*).

BMI was 22.94 in Group 1, 22.1 in Group 2, 24.61 in Group 3 and 25.3 in Group 4.

Discussion

Insulin resistance (IR) is a common disorder, which can impair women fertility and is characterized by phenotypic heterogeneity[2]. For example, polycystic ovary syndrome (PCOS) is the most common endocrine disease affecting women fertility[4] and IR seems to be one of the crucial pathways at the base of menstrual irregularity, anovulation, and infertility[7].

Today, MET is considered as one of the most common treatments for type 2 diabetes mellitus, due to its great efficacy in reducing insulin levels[30]. MET is also commonly used in pathologies characterized by insulin disorders such as IR and PCOS[14]. Nevertheless, its adverse effects are well described in the literature, reason why metformin use is not always recommended[30]. Recent studies reported a relevant evidence on MYO as alternative insulin-sensitizing agent for PCOS. In particular, interesting results of MYO have been found in several studies where this treatment was able to improve menstrual alterations, hyperandrogenism and metabolic and hormonal alterations. In relation to these findings, we wanted to investigate whether MYO could represent an alternative approach in the management of patients with IR and related menstrual alterations. Both MYO and MET treatments, associated with life-style changes, significantly improved menstrual cycle disorders. This evidence seems to be strongly related to the effect of this treatment in increasing progesterone levels and, on the other side, decreasing prolactin levels.

Myo-inositol treatment of patients with IR has a beneficial effect on conception outcome. Our retrospective trial suggests that both MYO and MET therapies can achieve significant changes without significant differences between MYO and MET therapy. This is probably due to the short time frame of evaluation. Our former investigations confirmed better pregnancy outcomes (71%) with complex tailored treatment at longer-term observations[17].

As patients with normal fasting glucose levels without any type of diabetes or pre diabetes were investigated, we didn't expect major changes at glucose values. Protracted hypoglycemia due to MYO or MET was not reported.

Serum fasting glucose and insulin levels, along with HOMA-IR changes, did not show any statistical significance. These results confirmed our expectations, because the patients with diagnosis of diabetes or pre-diabetes were not enrolled in the study. In consequence, we could speculate, they did not show strong alterations in the HOMA-IR and for this reason, we could not find significant modifications in the target groups. However, HOMA-IR might achieve significant changes during a complex tailored treatment by increasing the number of cases and the length of the observation period. Therefore, considering the lower average HOMA-IR retrieved in the group 1 and the group 2, MYO associated with life-style changes could represent the first approach for the treatment of hormonal and menstrual cycle alterations. Besides its comparable efficacy in the management of IR and related symptomatology, we could speculate that MYO could have a beneficial effect in maintaining physiological insulin parameters in those patients who do not show severe IR.

Minor differences in average BMI among the groups suggest that clinicians might prefer MYO to MET in cases where weight loss is not desired or might even lead to harmful changes in the patient's condition.

The aim of authors was to provide the best treatment according to their knowledge and not to fit classical study criteria. For this reason, authors decided to divide patients in order to follow a tailored treatment, and so the number of patients per group was different. Raising and equalizing the numbers of cases in the groups and a longer observation period might lead to more definite differences, possibly reaching the significance among the groups, especially at decreasing serum insulin levels which influences the pregnancy outcome.

Conclusions

We found that MYO could represent a possible alternative in the treatment of IR patients without diabetes or pre diabetes in all those cases where metformin cannot be used. Indeed, in this clinical study, MYO and MET showed the same efficacy in the treatment of menstrual cycle disorders related to IR. Anyway, while MET side effects are widely reported in the literature[30], no side effects of MYO have been reported so far. Further studies have to evaluate whether it is possible to enhance the therapeutic efficiency of medical treatment through the combination of MET and MYO.

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Conflict of interest
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