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Short Report: Treatment

The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes

F. Corrado, R. D'Anna, G. Di Vieste*, D. Giordano, B. Pintaudi*, A. Santamaria and A. Di Benedetto*

Department of Obstetrics and Gynecology and *Department of Internal Medicine, University of Messina, Messina, Italy

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Abstract

Aim To test the hypothesis that myoinositol supplementation will improve insulin sensitivity as measured by markers of insulin resistance such as homeostasis model assessment of insulin resistance and adiponectin in women with gestational diabetes.

Methods The trial was carried out in diet-treated patients with gestational diabetes diagnosed in our department between April 2008 and September 2009. Subjects were randomly assigned to receive either myoinositol supplementation (4 g daily) plus folic acid (400 μg daily)—the study group—or folic acid only (400 μg daily)—the control group. Both groups received the same diet prescription. Homeostasis model assessment of insulin resistance and adiponectin were assayed while fasting at the time of the diagnostic oral glucose tolerance test and after 8 weeks of treatment.

Results There were 69 evaluable patients, 24 in the study group and 45 in the control group. Fasting glucose and insulin, and consequently homeostasis model assessment of insulin resistance, decreased in both groups (50% in the study group vs. 29% in the control group), but the decline in the study group was significantly greater than that in the control group ($P = 0.0001$). Adiponectin increased in the myoinositol group while it decreased in the control group ($P = 0.009$).

Conclusion Myoinositol improves insulin resistance in patients with gestational diabetes.

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Keywords adiponectin, gestational diabetes, homeostasis model assessment of insulin resistance, insulin resistance, myoinositol

Introduction

Gestational diabetes mellitus is characterized by an increase of physiological insulin resistance. The main clinical feature (fetal macrosomia) supports the central role of this metabolic impairment in the syndrome's pathogenesis.

The molecular mechanism underlying insulin resistance in gestational diabetes is not fully understood [1]. Inositol phosphoglycan is one of the intracellular mediators of the insulin signal and is correlated with insulin sensitivity in Type 2 diabetes [2,3]. Recently, increased urinary excretion of inositol phosphoglycan has been directly related to blood glucose levels in gestational diabetes [4]. Similarly, increased urinary excretion has been reported [5] for polycystic ovary syndrome, which is a medical condition characterized by insulin resistance, and which has been successfully treated with myoinositol and folic acid [6]. These findings are consistent with a defect in tissue availability or utilization of inositol phosphoglycan in polycystic ovary syndrome that may contribute to the insulin resistance of the syndrome, therefore the administration of inositol phosphoglycan would improve the intracellular action of insulin [7]. These observations suggest the possibility that insulin resistance in gestational diabetes, as in polycystic ovary syndrome, could be improved by inositol administration. The aim of our randomized, prospective, controlled study is to determine whether myoinositol supplementation will increase the action of endogenous insulin, measured by markers of insulin resistance such as homeostasis model assessment of insulin resistance and adiponectin.

Correspondence to: Prof. Rosario D'Anna, Department of Obstetrics and Gynecology, Policlinico Universitario 'G.Martino', Via Consolare Valeria 1, 98125 Messina, Italy. E-mail: rosariodanna@tin.it

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Patients and methods

All 93 consecutive patients diagnosed with gestational diabetes in our department from April 2008 until September 2009 were asked to participate in our study. Among them, 84 agreed to

participate and were randomly assigned, at a ratio of 1:2, to take myoinositol and folic acid plus diet (n = 28) or folic acid only plus diet (n = 56). Based on a previous report concerning on the effects of myoinositol on post-menopausal women to have an 80% power to detect a 20% reduction in homeostasis model assessment of insulin resistance calculations, we required at least 20 patients with gestational diabetes. Thus, we calculated that, in the study period, we could have approximately 70–75 patients with gestational diabetes who would possibly participate in the trial. Therefore, we chose a 1:2 randomization to have a larger control group because the primary outcome selected (homeostasis model assessment of insulin resistance) may have a high individual variability.

The diagnostic oral glucose tolerance test was performed between 24 and 28 weeks of gestation and the results evaluated according to criteria recommended by the American Diabetes Association [8]. The study was approved by the Institutional Review Committee (E347/2008) and each patient gave written informed consent.

With a computerized randomization, participants were assigned to receive either myoinositol plus folic acid (2 g plus 200 μg twice/day—Inofolic®; Loli Pharma, Rome, Italy) or folic acid only (400 μg/day), while all received the same diet treatment according to the American Diabetes Association recommendations [8].

During the diagnostic oral glucose tolerance test, blood samples were collected while fasting to determine baseline glucose and insulin and then repeated after 8 weeks of treatment: homeostasis model assessment of insulin resistance was then calculated according to the formula of Matthews *et al.* [9]. Adiponectin was assayed in the fasting blood sample. For each patient, maternal age, parity, pre-pregnancy BMI and gestational age at diagnosis were recorded.

Serum glucose (reference concentrations 4.8–13.8 mmol/l; intra- and interassay coefficients of variation 0.9–1.2 and 1.9–2.7%, respectively) was measured using an appropriate commercial kit (Biosystem Reagent and Instruments, Barcelona, Spain), while serum insulin (reference concentrations 17.4–66.8 μIU/ml; intra- and interassay coefficients of variation 1.8–2.5 and 2.8–5.9%, respectively) was measured with ELISA (DRG Diagnostics, Marburg, Germany). Adiponectin was measured by ELISA, using a commercially available adiponectin ELISA kit (Linco Research Inc., St Charles, MO, USA). The lower limit of the sensitivity of the assay was 0.8 ng/ml. In our laboratory, at a level of 30 ng/ml, the intra- and interassay coefficients of variation were 1.9 and 7.5%, respectively.

Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) computer software was used for the statistical analysis.

The variables were expressed as means ± SD or n (%). After testing data for normality, Student's t-test, paired Student's t-test or the Wilcoxon signed-rank test were used to compare values between baseline and the end of the study. Furthermore, we calculated a delta (Δ) value, which is a relative change calculated by subtracting the later value from the earlier value, for both homeostasis model assessment of insulin resistance and adiponectin. $P < 0.05$ was considered significant for all the data analysed.

Results

There were three women in the study group and nine in the control group who required insulin treatment because glycaemic goals [8] were not reached with diet alone; these individuals were excluded from the study. Furthermore, one woman in the study group and two women in the control group were excluded because they delivered prematurely before 35 weeks of gestation. The final data analyses included 24 women treated with myoinositol and folic acid and 45 treated with folic acid only.

The baseline characteristics (age, pre-pregnancy BMI, parity, gestational age at diagnosis) of the 69 evaluable patients in the two groups were similar (Table 1). No difference was present for the weight gain in pregnancy prior to the oral glucose tolerance test, or for fasting glucose or insulin at the time of the oral glucose tolerance test; consequently, the homeostasis model assessment of insulin resistance index showed no basal difference between the groups at the initiation of the study. Adiponectin levels did not differ at baseline (Table 1).

After 8 weeks of treatment, the weight increase was similar between the two groups (Table 1). The fasting glucose level decreased significantly in both groups. Similarly, the fasting plasma insulin concentration and homeostasis model assessment of insulin resistance decreased in both groups. The administration of myoinositol was associated with an increase in circulating adiponectin, while no significant change was found in the mean plasma adiponectin concentrations of the control group. The delta decrease (Fig. 1) revealed that the myoinositol group experienced significantly greater changes than did the control group (homeostasis model assessment of insulin resistance P = 0.0001; adiponectin P = 0.009).

Discussion

There was a significant greater decrease in markers for insulin resistance among women with dietary-treated gestational diabetes randomly assigned to take myoinositol plus folic acid as compared with those taking folic acid alone. Starting from similar baseline measures, homeostasis model assessment decreased by 50%, while adiponectin increased by 28%. This adipocytokine, with insulin sensitizing, anti-inflammatory and anti-atherogenetic effects, was chosen because it has been reported to be negatively correlated to glucose and insulin concentrations in pregnancy with gestational diabetes [10,11]. It is the only adipocyte-derived hormone to be downregulated in the insulin-resistant state, so the pregnancy-mediated changes in adiponectin were strongly correlated with basal insulin levels and insulin sensitivity [12].

Table 1 Characteristics of patients who received myoinositol plus diet or diet alone, at baseline and after 8 weeks from diagnostic oral glucose tolerance test (OGTT)

	Inositol group (n = 24)		Control group (n = 45)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Age (years)	28.7 ± 3.5		28.4 ± 3.7	
Pre-pregnancy BMI (kg/m^2)	25.1 ± 4.7		24.2 ± 4.1	
Parity ≥ 1 (N)	10		15	
Gestational age at OGTT (weeks)	26.0 ± 0.6		26.3 ± 0.8	
Weight increase in pregnancy (kg)	7.5 ± 3.6	10.2 ± 5.1	8.4 ± 4.4	10.7 ± 6.3
Fasting glucose (mmol/l)	5.5 ± 0.3	4.6 ± 0.3*	5.4 ± 0.2	5.1 ± 0.3*
Fasting insulin (μIU/ml)	31.2 ± 7.1	19.0 ± 5.8*	33.9 ± 5.3	26.0 ± 6.8*
HOMA-IR (units)	6.9 ± 1.7	3.5 ± 1.1*	7.4 ± 1.1	5.3 ± 1.4*
Adiponectin (μg/ml)	12.8 ± 5.1	16.1 ± 6.6	12.2 ± 4.6	11.3 ± 4.8

All continuous variables are expressed as mean ± SD.
*Statistical significance (P < 0.05), obtained from paired Student's t-test, of the post-treatment with respect to the pre-treatment value.
HOMA-IR, homestasis model assessment of insulin resistance.

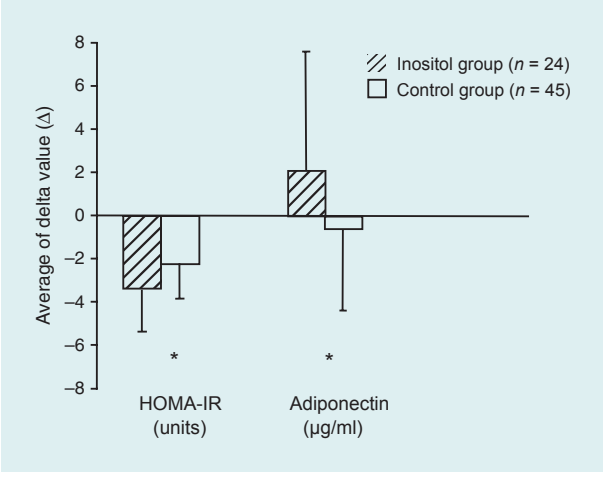

FIGURE 1 Delta changes in homeostasis model assessment of insulin resistance (HOMA-IR) and adiponectin concentration after 8 weeks of supplementation in myoinositol plus folic acid (treatment) vs. folic acid only (control) groups in patients with gestational diabetes. *Indicates statistical significance (P < 0.05) and the error bars refer to the standard deviation.

There was also a decrease in homeostasis model assessment in the group treated with folic acid and diet (29%), which may suggest that dietary therapy is an effective strategy for the achievement of acceptable glycaemic control in some women with gestational diabetes, although no significant difference was reported for adiponectin. The greater decrease in homeostasis model assessment among subjects receiving myoinositol supports a potential role for inositol to decrease insulin resistance in patients with gestational diabetes.

The present results are consistent with other studies in patients with polycystic ovary syndrome in which myoinositol supplementation decreased insulin resistance and restored spontaneous ovulation and menstrual cycles. Myoinositol induced spontaneous ovarian activity and reduced insulin levels in the study of Nestler *et al.* [7] (−38% after 6–8 weeks) and in the study of Gennazzani *et al.* [13] (−48% after 12 weeks), while no information was reported about adiponectin.

When metformin treatment was initiated for 39 patients with polycystic ovary syndrome, there was a significant 46% reduction in homeostasis model assessment of insulin resistance prior to conception that was maintained throughout pregnancy, apparently reducing the prevalence of gestational diabetes in this high-risk group [14]. This reduction was similar to that observed in our treated patients.

A weakness of this trial is that the myoinositol treatment was open label. Another limitation concerns the generalizability of the results. All subjects were Caucasian women from Sicily and no other ethnic groups were represented so it remains unclear whether the results found are applicable to patients from other countries. In a study of polycystic ovary syndrome, Nestler *et al.* [7] first reported positive results with Venezuelan women that were not confirmed in a later study [15] of Caucasian women from the USA. Insulin resistance is not determined by a single post-receptor enzymatic impairment, but by a polygenic mechanism with a number of enzymatic steps involved. The results reported in the present report may suggest a high prevalence of specific traits in our population, which are modifiable by myoinositol supplementation. Indeed, the biochemical mechanism for reported benefits of myoinositol oral administration on metabolic derangement in patients with gestational diabetes and other states of insulin resistance (e.g. polycystic ovary syndrome) are still unknown. It is possible that myoinositol exerts its intracellular effect directly on the activation of acetil CoA carboxylase-stimulating lipogenesis or as a precursor of D-chiro-inositol containing inositol phosphoglycan (DCI-IPG), which is bound to the extracellular matrix of the cells. It has been suggested that the binding of insulin to specific receptors stimulates D-chiro-inositol containing inositol phosphoglycan transport intracellularly [16] and explains its role as a mediator in the insulin signalling cascade [17].

In conclusion, apart from the speculation concerning the role of inositol as a second messenger in the intracellular enzymatic chain reactions of insulin, oral myoinositol seems to be an insulin-sensitizing factor, reducing plasma glucose levels without increasing endogenous insulin production but, on the contrary, reducing serum insulin levels. If these results can be confirmed with a larger multi-ethnic sample, myoinositol supplementation may be considered a simple and safe step in the treatment of gestational diabetes.

Competing interests

Nothing to declare.

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