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ORIGINAL ARTICLE

The effects of magnesium supplements on adiponectin level and insulin sensitivity in first-degree relatives of subjects with type 2 diabetes

AREZOO AFKHAMI-ARDEKANI, BABAK MAJIDI, SAEEDEH JAM ASHKEZARI, MOHAMMAD HOSAIN AFRAND, SEID MOHAMMAD MOHAMMADI, MOHAMMAD AFKHAMI-ARDEKANI*

For author affiliations, see end of text.

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ABSTRACT

The interaction between intracellular magnesium level, adiponectin production and insulin sensitivity has been recently suggested in both diabetic patients and their first-degree relatives. The present study aimed to investigate whether magnesium supplements are able to increase plasma adiponectin and affect insulin sensitivity in first-degree relatives of subjects with type 2 diabetes. Seventy subjects who were first-degree relatives of diabetic patients were randomly allocated to either Mg hydroxide supplementation plus lifestyle (case group, n = 35) or mere lifestyle change and placebo (control group, n=35). The subjects were seen at 16-weeks intervals for at least 24 months. There was no difference in baseline level of adiponectin between intervention and control group (p = 0.612), but significantly increased in intervention group (mean change of 6.51 ± 4.33 mg/dl, p ≤ 0.001) and significantly reduced in control group (0.70 ± 0.52 mg/dl, p ≤0.001) after 16-week intervention protocol. No difference was revealed in initial insulin resistance between the two study groups (p = 0.527), but it was revealed lower in intervention group after completing treatment (p ≤ 0.001). On the other hand, after 16 week of initial interventions, insulin resistance index reduced as 0.56 ± 0.85 units (p ≤ 0.001), while increased in control group as 0.68 ± 0.78 units (p ≤0.001). The increase in adiponectin production as well as decrease in insulin resistance is expected by administrating magnesium supplements in first-degree relatives of the patients with diabetes mellitus.

Keywords: *Magnesium, Adiponectin, First-degree Relatives, Type 2 diabetic patients*

Diabetes mellitus is now a growing health burden whole of the world and also has been a public problem with endemic feature in most countries. Along with some genetic tendencies in appearing diabetes mellitus and insulin resistance, some acquired factors such as dietary habits have a major role as a trigger for diabetes [1-2]. In this regard, dietary magnesium has a viral role as a main cofactor in production and regulation of some metabolic enzymes involved in glucose metabolism [3-6]. In fact, dietary magnesium can effectively improve insulin sensitivity especially in those patients with or susceptible to diabetes [7-8].The association of magnesium deficiency and insulin resistance in patients with diabetes mellitus has been well demonstrated in both children and adults [9-10]. On the other hand, because of the essential role of insulin to mediate intracellular magnesium balancing [11], magnesium deficiency can stimulate insulin resistance pathways leading diabetes controlling disturbance. Magnesium has a central role in pathogenesis of insulin resistance that improvement of diabetes control especially in obese individuals using administration of magnesium supplements has been recently presented as a hypothesis [12-13]. Beside of the role of magnesium in metabolism of insulin as well as

regulation of insulin sensitivity, adiponectin as an adipokine expressed on adipose tissues can sensitize body tissues to insulin and thus its defects can result in insulin resistance, uncontrolled diabetes and even metabolic syndrome [14-15]. Soheilykhah et al. (2009) showed thatserum adiponectin level was significantly lower in gestational diabetes in comparison with healthy pregnant women [16]. In fact, adiponectin act on insulin metabolism can be mediated by its specific receptors (AdipoR1 and AdipoR2) that may be down-regulated in those with insulin resistance [17]. Therefore, adiponectin and its specific receptors can be therapeutic targets for novel drugs affecting insulin resistance [18-19]. The production and metabolism of adiponectin can be affected by both genetic and environmental factors [17, 20].

Although some interactions between gene polymorphisms as the genetic arm and some obesity-related factors such as specific dietary regimens as the environmental arm has been suggested to be involved in adiponectin changes in diabetic patients, various aspects of these factors have not been cleared. Moreover, due to certain role of both magnesium and adiponectin in regulation of insulin sensitivity, the interaction between these two agents has remained uncertain. Because of the importance of these interactions in both diabetic patients and their first-degree relatives, we aimed for the first time to investigate whether magnesium supplements are able to increase plasma adiponectin and affect glucose homeostasis and insulin sensitivity in first-degree relatives of subjects with type 2 diabetes.

MATERIALS AND METHODS

Trial design

This study was a randomized clinical trial that was conducted from January 25, 2012 to December 25, 2014. The trial was registered at the Iranian Registry of Clinical Trials (http://www.irct.ir) with the IRCT ID: 201105036296N2.

Participants

The study was performed in strict accordance with the ethical guidelines of the Helsinki Declaration. The study's protocol was approved by the Medical Ethics Committee of Shahid Sadoughi University of Yazd, Iran. Written informed consent forms were obtained from all participants. The study was a single-center, double-blind, randomized, placebo-controlled trial. All of the studies were performed at the Yazd Diabetes Research Center of Shahid Sadoughi University Hospitals after a 10- to 12-hour fast. Seventy subjects who were first-degree relatives of diabetic patients included after providing written informed consent if they fulfilled the following inclusion criteria: (i) body mass index (BMI) ≥ 25 kg/m2; (ii) age more than 25 years old and (iii) serum glucose 2 h after an oral glucose load of ≤200 (Table 1).

Table 1: Inclusion criteria of the study

Fasting blood Sugar	<126 mg/dl
Two hour post prandial sugar	< 200 mg/dl
Body mass index	<25 kg/ m2
Age	>25 years old

Selection criteria

In this study, Patients who were eligible and had FBS≤126 and 2hpp≤200 mg/dl randomly allocated to either Mg hydroxide supplementation plus lifestyle (case group, n = 35) or mere lifestyle change and placebo (control group, n=35). All of participants were first degree relative of type 2 diabetes. Exclusion criteria was being a known diabetic case and using vitamin D, magnesium or other supplements during past 3 months as well as receiving metformin or any other drugs affecting insulin resistance.

Interventions

Subjects were randomized to receive magnesium (Mg) hydroxide (500 mg)/day or placebo [Microcrystalline cellulose (C6H10O5) is refined wood pulp. It is a white, free-flowing powder. Chemically, it is an inert substance] for 16 weeks. After 4 months, the patients were invited to reassess serum biomarkers. Informed consent was taken from all the participants. Lifestyle modification rationale was described and applied to both groups. They were informed about being at risk for diabetes mellitus and recommended to regular exercise (fast walking for 30 minutes daily or swimming), diet including consumption of fresh fruits and vegetables and low fat dairy as well as avoiding use of excessive carbohydrates and high-fat diet. The case arm of study was recommended to use one Mg Hydroxide tablet 500mg daily. Insulin sensitivity indices (ISIs) according to homeostatic model assessment (HOMA) were calculated from the oral glucose tolerance test (OGTT) as recently described and served as study endpoints. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula 1 (HOMA-IR (milliunits per liter × milligrams per deciliter) = [(fasting IR × fasting glucose)/405]. Body height, body weight, and waist circumference (WC) were measured in standing position and body mass index (BMI) was calculated by the formula 2 (BMI (kg/m2) = weight (kg)/height (m) 2) . WC at the umbilical level was measured with a non-stretchable tape in late expiration in standing position. Systolic and diastolic blood pressures were measured with a standard mercury sphygmomanometer on the left or right arm in sitting position after taking a rest for 10 min. Venous blood samples were collected in the morning after overnight fast to measure serum creatinine, lipids, glucose, HbA1c and IR. The value of HbA1c (%) was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%), calculated by the formula 3 (HbA1c (%) = HbA1c (%) + 0.4%). Low-density lipoprotein-cholesterol (LDL-C) was calculated using the

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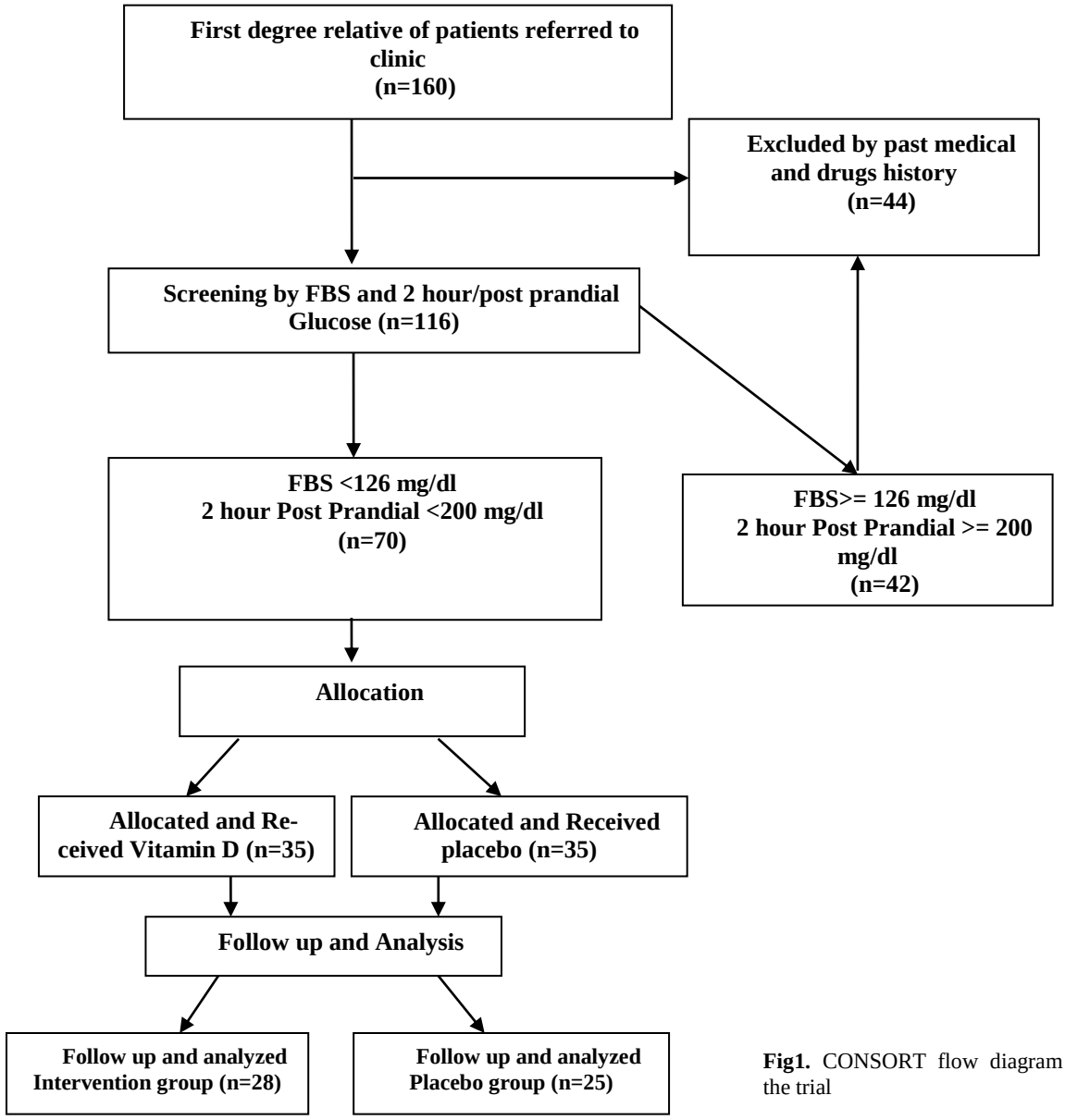

Fig1. CONSORT flow diagram of the trial

Friedewald formula. For the purpose of the present study serum samples were immediately stored at –20°C after blood collection. All frozen samples were thawed on ice and subjected to me- asurements for adiponectin (Adiponectin ELISA Kit, Ani Biotech Oy Co., AviBion Human Adiponectin Eli A kit (Acro30). The subjects were randomly selected to receive Mg or placebo (PLA).

Outcomes

In this study, before beginning the intervention, demographic parameters, age, and gender of patients were recorded. Before and 16 weeks (four month) after the initiation of the intervention, we recorded fasting blood sugar (FBS), HbA1c, two-hour Post Prandial (2hpp) glucose, serum levels of TG, cholesterol, HDL, LDL, Mg, adiponectin and fasting insulin level.

Sample size

According to relevant studies and by using of the sample size formula, $n = \sigma 2\ (Z\alpha+Z\beta)2/d2$, assuming an alpha error of 5% and a study power of 80%, the sample size was determined to be 35 subjects for each group. Fig. 1 shows the consort flow diagram of the trial.

Randomization and blinding

This randomization was blinded to the investigator. A 16-weeks supply of the medication was dispensed, and the subjects were asked to return all unused pills and pill container at their next study visit. During the 16-weeks period of study, patients were followed by phone call or via SMS bi-weekly to remind the instructions to them. The subjects were seen at 16-weeks intervals for at least 2 week. During each visit, weight, blood pressure, and skinfold measurement were performed.

Table 2: The levels of study parameters before and after interventions

Index	Group	Before intervention mean ±SD	After intervention mean ±SD	p-value
BMI	Intervention group	29.1 ± 3.5	28.9 ± 3.0	0.144
	Control group	29.0 ± 3.6	29.0 ± 3.5	0.788
	P-value	0.927	0.879	
Magnesium	Intervention group	1.97 ± 0.19	2.06 ± 0.43	0.146
	Control group	1.97 ± 0.16	1.97 ± 0.33	0.999
	P-value	0.891	0.370	
FBS	Intervention group	96.1 ± 9.6	91.3 ± 9.3	0.001
	Control group	97.6 ± 11.1	103.9 ± 12.3	≤ 0.001
	P-value	0.542	≤ 0.001	
2HPP	Intervention group	119.4 ± 21.4	111.0 ± 19.9	0.073
	Control group	114.7 ± 23.5	108.8 ± 18.3	0.069
	P-value	0.391	0.641	
Insulin level	Intervention group	12.23 ± 4.64	10.47 ± 3.26	0.005
	Control group	11.56 ± 4.6	13.37 ± 6.17	0.001
	P-value	0.556	0.016	-
HbA1c	Intervention group	4.92 ± 0.92	5.03 ± 0.93	0.546
	Control group	4.91 ± 0.74	5.04 ± 0.74	0.346
	P-value	0.921	0.968	-
Cholesterol	Intervention group	183.0 ± 31.9	181.1 ± 28.8	0.505
	Control group	193.6 ± 31.4	197.8 ± 38.8	0.315
	P-value	0.165	0.018	
Triglyceride	Intervention group	157.9 ± 64.3	168.9 ± 63.0	0.394
	Control group	162.3 ± 56.4	157.3 ± 36.0	0.627
	P-value	0.766	0.521	
HDL	Intervention group	35.5 ± 6.0	37.2 ± 10.7	0.353
	Control group	36.9 ± 3.7	36.7 ± 50.8	0.832
	P-value	0.227	0.872	
LDL	Intervention group	115.8 ± 23.0	112.6 ± 20.0	0.362
	Control group	119.3 ± 23.6	130.3 ± 18.1	0.027
	P-value	0.530	≤ 0.001	

The unused pills were counted and recorded. If there was a discrepancy in the number of pill left, this was

Statistical methods

The data are presented as mean ± standard deviation (SD). The unpaired t-test was used to examine the differences in the two genders. Statistical significance was assessed using ANOVA. All statistical analyses were performed using SPSS software (version 17; SPSS, Chicago, IL, USA). All statistical tests were two-sided, and differences with probability values ≤ 0.05 were considered to be statistically significant.

Research ethics

The proposal for this thesis research was presented to the Ethics Committee of Shahid Sadoughi University of Medical Sciences and approved by the Internal Medicine Department. The Ethics Committee approved the study with the number P/17/1/50970 on December 23, 2010. This study also was registered in the Iranian Registry of Clinical Trials (irct.ir) with the IRCT ID: 201105036296N2. The patients were informed about the objective and nature of the study, and each participant provided written consent in her native language prior to the study.

RESULTS

The two intervention group and control group were matched for average age (40.1 ± 7.3 years versus 39.1 ± 7.8 years, p = 0.233) and male gender (54.3% in both groups).

Regarding the levels of biomarkers after completion of treatment protocols, no difference was revealed in serum levels of some markers including body mass index, serum magnesium level, 2HPP, HbA1c, triglyceride, or high density lipoprotein (HDL) between intervention and control groups, however intervention protocol could significantly reduce serum levels of fasting blood sugar, insulin level, total cholesterol and low density lipoprotein (LDL), but not observed in control group (Table2).

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Table 3: The levels of adiponectin and insulin resistance before and after interventions

Index	Group	Before Intervention mean ±SD	After intervention mean ±SD	p-value
Adiponectin	Intervention group	5.16 ±2.63	11.67 ± 4.45	≤ 0.001
	Control group	4.87 ± 2.06	4.16 ± 2.00	≤ 0.001
	P-value	0.612	≤ 0.001	
Insulin resistance	Intervention group	2.92 ± 1.18	2.36 ± 0.77	≤ 0.001
	Control group	2.75 ± 1.12	3.43 ± 1.55	≤ 0.001
	P-value	0.527	≤ 0.001	

Although the changes in some biomarkers including body mass index, serum magnesium level, 2HPP, HbA1c, total cholesterol, triglyceride, and HDL were not significant after both treatment regimens compared with those of before, however both fasting blood glucose and insulin levels significantly reduced in intervention group and increased in control group. Also, the serum level of LDL remained unchanged in intervention groups, while increased in control group (Table2).

There was no difference in baseline level of adiponectin between intervention and control group ($p = 0.612$), but significantly increased in intervention group (mean change of 6.51 ± 4.33 mg/dl, $p \leq 0.001$) and significantly reduced in control group (0.70 ± 0.52 mg/dl, $p < 0.001$) after 16-week intervention protocol (Table2).

No difference was revealed in initial insulin resistance between the two study groups ($p = 0.527$), but it was revealed lower in intervention group after completing treatment ($p \leq 0.001$). On the other hand, after 16 week of initial interventions, insulin resistance index reduced as 0.56 ± 0.85 units ($p \leq 0.001$), while increased in control group as 0.68 ± 0.78 units ($p \leq 0.001$) (Table3).

Assessing effects of magnesium supplement on both adiponectin and insulin resistance was similarly observed in both genders and also in both age subgroups of 25 to 39 years and 40 to 59 years and thus gender and age indices did not interact effects of magnesium on adiponectin and insulin resistance index.

Association between two indices of adiponectin level and insulin resistance index and other baseline parameters were assessed using the multivariate linear regression models. In this regard, only significant linear association between insulin resistance index and insulin level was found with the following linear equation: insulin resistance index = 0.238insulin + 0.01 ($R2 = 0.98$, $p \leq 0.001$).

DISCUSSION

Our study could demonstrate increase in adiponectin level as well as decrease in insulin resistance following use of magnesium supplement, while these effects were not revealed in placebo group. Regarding regulatory effects of adiponectin on glucose metabolism, it has been well demonstrated its anti-diabetic effects and thus is now expected as a novel therapeutic tool for diabetes. Thus, a decrease in the circulating levels of adiponectin contributes to the development of diabetes and its related metabolic disturbances [21].

The role of adiponectin is mainly related to the modulation of some metabolic processes including glucose regulation and fatty acid metabolism by exerting anti-diabetic and anti-inflammatory effects [22].

In this regard, some metabolic disturbances such as impaired glucose tolerance, obesity, dyslipidemia, diabetes are triggered by disturbing adiponectin multimerization caused by either gene mutations or environmental factors. With respect to the effects of adiponectin on diabetes and insulin sensitivity, it has been shown that adiponectin can directly or indirectly regulate insulin sensitivity by insulin signaling and the molecules involved in glucose and lipid metabolism [14, 23]. Besides, in parallel with our results with regard to lowering effects of magnesium deficiency on adiponectin defect, intracellular magnesium deficiency can lead to tyrosine kinase activity within insulin signaling and glucose-induced insulin secretion, leading to impaired insulin sensitivity in adipocytes [24-27]. Therefore, increase in insulin resistance can be caused by intracellular magnesium impairment and thus administrating magnesium supplement can reduce insulin resistance in diabetic patients and also in first-degree relatives as shown in our observation. In fact, it can be concluded that the changes in three indicators of adiponectin in adipose tissues, intracellular magnesium level, and insulin sensitivity can be occurred in parallel with each other. On the other hand, it can be expected simultaneous occurrence of magnesium deficiency, adiponectin production defect, and increase in insulin resistance index. Soheilykhah et al. (2012) showed that Zinc significantly increases the level of adiponectin in first degree relatives of diabetic patients [28]. The level of insulin and homeostasis model assessment (HOMA) index after zinc supplementation decreased but this reduction was not significant.

Our study could show increase in adiponectin production as well as decrease in insulin resistance by administrating magnesium supplements in first-degree relatives of the patients with diabetes mellitus. We focused on first-degree relatives of diabetic patients, because there is no evidence in association of intracellular magnesium concentration with adiponectin level as a cofactor for regulation of insulin sensitivity in these

individuals. In fact, this association not only may be revealed in diabetic patients, but also in their first-degree relatives. This finding can be important because first-degree relatives of diabetic patients are at risk for diabetes mellitus and thus by using magnesium supplements, regulating adiponectin production and also increasing insulin sensitivity to glucose changes can be achieved in these at risk individuals.

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CURRENT AUTHOR ADDRESSES

AREZOO AFKHAMI-ARDEKANI, Medical student of Tehran University of Medical Sciences. Faculty of Medicine, Tehran, Iran.

BABAK MAJIDI, Department of Internal Medicine, Internist, Shahid Sadoughi University of medical sciences, Yazd, Iran.

SAEEDEH JAM ASHKEZARI, Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

MOHAMMAD HOSAIN AFRAND, Ali-Ebne-Abitaleb Faculty of Medicine, Islamic Azad University, Yazd Branch, Yazd, Iran.

SEID MOHAMMAD MOHAMMADI, 5- Department of Internal Medicine, Endocrinology, Shahid Sadoughi University of medical sciences, Yazd, Iran.

MOHAMMAD AFKHAMI-ARDEKANI, Department of Internal Medicine, Endocrinology, Shahid Sadoughi University of medical sciences, Yazd, Iran. E-mail: Afkhamiam@yahoo.com (Corresponding author)

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