

## **Magnesium supplementation and insulin resistance in patients with rheumatoid arthritis**

Mohsen Norouzi (1), Boshra Rezvankhah (2), Mohammad Reza Haeri (3), Hosein Heydari (4), Javad Tafaraji (4), Navid Shafigh (5), Jamshid Ordoni Avval (6), Alireza Rahat Dahmardeh (6), Niyooosha Masoumzadeh (7,8), Mohammad Gharehbeblou (5,6)

(1) *Department of Internal Medicine, School of Medicine, Qom Branch, Islamic Azad University, Qom, Iran;* (2) *Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Science, Tehran, Iran;* (3) *Department of Biochemistry, School of Medicine, Qom University of Medical Science, Qom, Iran;* (4) *Department of Pediatrics, School of Medicine, Qom University of Medical Science, Qom, Iran;* (5) *Department of Anesthesiology and critical Care Medicine, School of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran;* (6) *Department of Anesthesiology and Critical Care Medicine, School of Medicine, Zahedan University of Medical Science, Zahedan, Iran;* (7) *Department of Infectious Disease and Tropical Medicine, School of Medicine, Zahedan University of Medical Science, Zahedan, Iran;* (8) *Department of Infectious Disease and Tropical Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Science, Tehran, Iran.*

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### **Abstract**

Rheumatoid arthritis (RA) is a multifactorial disease affecting the immune system and many tissues in the body. This study aimed to evaluate the effect of magnesium supplementation on insulin resistance and fasting blood sugar (FBS) of patients with RA. In this prospective uncontrolled before-after study, RA patients referring to Rheumatology clinics of Qom City from January 2020 to January 2021 were evaluated. First, the patients received the routine rheumatoid arthritis treatment including 5 mg Prednisolone and 200mg Hydroxychloroquine daily for 6 months and FBS and insulin levels were measured after. Then, they received the routine arthritis rheumatoid treatment in addition to 300 mg/day oral Magnesium sulfate for 6 months and then, FBS and insulin levels were measured. The Homeostasis Model Assessment of insulin resistance (HOMA-IR) was used for determining insulin resistance. Thirty five patients with RA and the mean age of  $49.83 \pm 2.58$  years were enrolled. Twenty eight cases (80%) were female and 7 cases (20%) were male. The mean HOMA-IR before and after consumption of oral magnesium were  $3.04 \pm 0.29$  and  $2.43 \pm 0.19$ , respectively. Statistically significant differences were found between FBS, insulin and HOMA-IR before and after consumption of oral magnesium ( $p < 0.05$ ). Our data suggested that magnesium supplementation reduces FBS, insulin and HOMA-IR in patients with rheumatoid arthritis. Thus, magnesium supplements may be an alternative method for prevention of type 2 diabetes in RA patients.

**Key Words:** Magnesium; insulin resistance; rheumatoid arthritis.

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**R**heumatoid arthritis (RA) is a multifactorial chronic inflammatory autoimmune disease with unknown etiology, progressing to synovial inflammation, pain and stiffness of numerous joints.<sup>1</sup> No pathognomonic test exists for RA diagnosis, but a combination of clinical, laboratory and imaging features is helpful. The annual incidence rate of RA is 0.5-1% as it is the most common chronic inflammatory disease in India with prevalence

of 0.75%.<sup>2,3</sup> Its prevalence in females is almost three times higher than males.<sup>4</sup> Several studies have shown the association between RA and cardiovascular diseases and it increases the risk of cardiovascular death up to 50%.<sup>5</sup> Recent studies have shown that insulin resistance (IR) and type 2 diabetes are more prevalent in RA patients than normal population.<sup>6</sup> Del Rincón et al. reported a significant correlation between type 2 diabetes and carotid atherosclerotic plaque in RA

patients.<sup>7</sup> One reason for this correlation is high inflammatory factor level like tumor necrosis factor (TNF), interleukin (IL)-6, IL-1 and IL-8 but the exact cause of this correlation is unclear.<sup>8</sup> As type 2 diabetes is a traditional risk factor for cardiovascular diseases, prevention and control of IR and type 2 diabetes in patient with RA is so important.<sup>9</sup> The overall mechanism of the insulin resistance pathogenesis is still unknown. Magnesium (Mg), a predominant intracellular ion, is a crucial metallic co-factor of many enzymatic reactions involved in post-receptor signaling and is critically involved in energy metabolism, fatty acid synthesis and glucose utilization.<sup>9</sup> It is believed that its deficiency can contribute to insulin resistance and epidemiological studies have described an inverse association between the intake levels of Mg rich foods and MS.<sup>10,11</sup> Recent evidences suggest that magnesium deficiency plays an important role in decreasing insulin resistance and some others believe that its deficiency is associated with insulin resistance.<sup>12-14</sup> Lopez-Ridaura et al. showed that magnesium deficiency is common in patients with diabetes as well as in a cohort study has shown that the risk of diabetes in people with high magnesium levels were significantly lower.<sup>15</sup> Guerrero-Romero et al. reported that oral magnesium in non-diabetic patients with low magnesium improves insulin sensitivity.<sup>16</sup> In chronic inflammatory diseases like RA Magnesium decreases and its reduction is one of the diagnostic criteria for of RA.<sup>17</sup> Although there is evidence to suggest that magnesium supplementation may help improve insulin sensitivity in type 2 diabetes patients and that it may be useful as an adjuvant therapy, the benefits of magnesium supplementation in RA patients has not yet been established.

The aim of this study was to evaluate the effect of 300 mg/day magnesium supplementation on insulin resistance and fasting blood sugar (FBS) of patients with rheumatoid arthritis.

## Materials and Methods

### Study participant

In this prospective uncontrolled before-after study, patients referring to Rheumatology clinics of Qom City from January 2020 to January 2021 were evaluated. The RA was diagnosed according to American College of

Rheumatology's criteria which was revised in 1978.<sup>18</sup> Patients with type 2 diabetes mellitus, treated with prednisolone at a dose higher than 7.5 mg/day, candidate for drug therapy and patients with liver and kidney diseases, ischemic heart failure, Lupus, and pregnant women were excluded from the study. All patients completed a questionnaire and demographic characteristics were recorded.

The study protocol was approved by medical ethics committee of Islamic Azad University of Qom medical branch (medical Ethics Committee Approve number: Q78-18537) and it was performed in accordance with the principles of the Declaration of Helsinki in medical ethics. Also, written informed consent was obtained from all participants prior to enrollment in the study.

### Study protocol and measurement

First, the patients received the routine rheumatoid arthritis treatment including 5 mg Prednisolone and 200 mg Hydroxychloroquine daily for 6 months and FBS and insulin levels were measured after 12 hours overnight fasting. Then, they received the routine arthritis rheumatoid treatment in addition to 300 mg/day oral Magnesium sulfate capsule manufactured by Nature Co, Canada for 6 months and FBS and insulin levels were measured after 12 hours overnight fasting and were compared with baseline indexes. Blood insulin was measured by Elisa method. The Homeostasis Model Assessment of insulin resistance (HOMA IR) was used for determining insulin resistance. HOMA IR is widely used as a noninvasive surrogate marker of insulin resistance, which is calculated by multiplying fasting insulin [ $\mu\text{IU/mL}$ ]  $\times$  fasting glucose [ $\text{mg/dL}$ ]/405.<sup>19, 20</sup> Insulin resistance was considered when HOMA-IR was higher than 2.7.<sup>21</sup>

### Statistical analysis

Continuous quantitative data are expressed as mean $\pm$ standard deviation (SD). Two-tailed parametric tests were used for comparison of normally distributed variables, and nonparametric tests to compare variables when the assumption of normal distribution was not met. Student's paired t-tests or Wilcoxon tests were performed before and after treatment for comparison, and independent t-tests or Mann-Whitney tests were

**Table 1.** Analyzed parameters before and after consumption of oral magnesium

Characteristics	Before Mg intake (n=35)	After Mg intake (n=35)
FBS (mg/dL)	102.31 $\pm$ 2.04	95.60 $\pm$ 1.46
Insulin ( $\mu\text{IU/mL}$ )	11.93 $\pm$ 1.10	10.34 $\pm$ 0.81
HOMA-IR	3.04 $\pm$ 0.29	2.43 $\pm$ 0.19

**Table 2.** Comparison of the means before and after consumption of oral magnesium

Paired Differences	Mean	p-value
Pair 1 FBS 1 - FBS 2	6.71±12.18 (mg/dL)	<0.05
Pair 2 Insulin 1 - Insulin 2	1.58±4.52 (mg/dL)	<0.05
Pair 3 HOMA-IR 1 - HOMA-IR 2	0.61±1.20	<0.05

used for non-paired comparison. In addition, categorical variables were compared by Chi-squared or Fisher exact tests. A p value less than 0.05 was considered being statistically significant. Data analysis was performed using the “Statistical Package for the Social Science” (SPSS, Inc., Chicago, IL, USA) version 16.0.

**Results**

Thirty five patients with rheumatoid arthritis and the mean age of 49.83±2.58 years were enrolled. Twenty eight cases (80%) were female and 7 cases (20%) were male. The mean glucose, insulin and insulin resistance before and after oral magnesium consumption are shown in table 1.

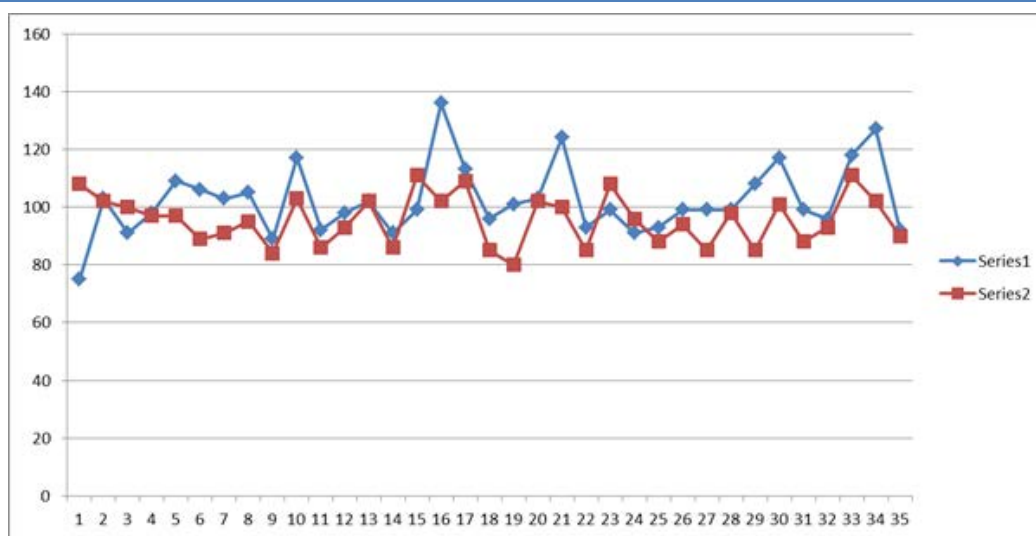
The mean HOMA-IR before and after consumption of oral magnesium were 3.04±0.29 and 2.43±0.19, respectively. Before consumption of oral magnesium, 5.71% (2/35) of the patients had FBS ≥126 mg/dL and 45.71% (16/35) had FBS ≥99 mg/dL. But after consumption of oral magnesium, FBS ≥ 126 mg/dL was not detected and FBS ≥99 mg/dL was only observed in

40% (14/35) of the patients. Also, insulin resistance was found in 71.42% (25/35) of the patients (Table 2).

Statistically significant differences were found between FBS, insulin and HOMA-IR before and after consumption of oral magnesium (p<0.05) (Figure 1 and Figure 2). Comparison of the mean FBS, insulin, and HOMA-IR before and after consumption of oral magnesium with %95 CI had statistically significant differences (p<0.05).

**Discussion**

The present study aimed to determine the effect of magnesium supplementation on FBS, insulin level and HOMA-IR in RA patients. Rheumatoid arthritis is a systemic autoimmune disease which initially presents as chronic synovial inflammation of multiple joints.<sup>1</sup> Patients with chronic inflammatory diseases such as RA are at increased risk of developing type 2 diabetes as a result of impaired glucose metabolism.<sup>22</sup> Magnesium is an essential nutrient and fourth most abundant mineral



**Fig 1.** Comparative values for FBS.

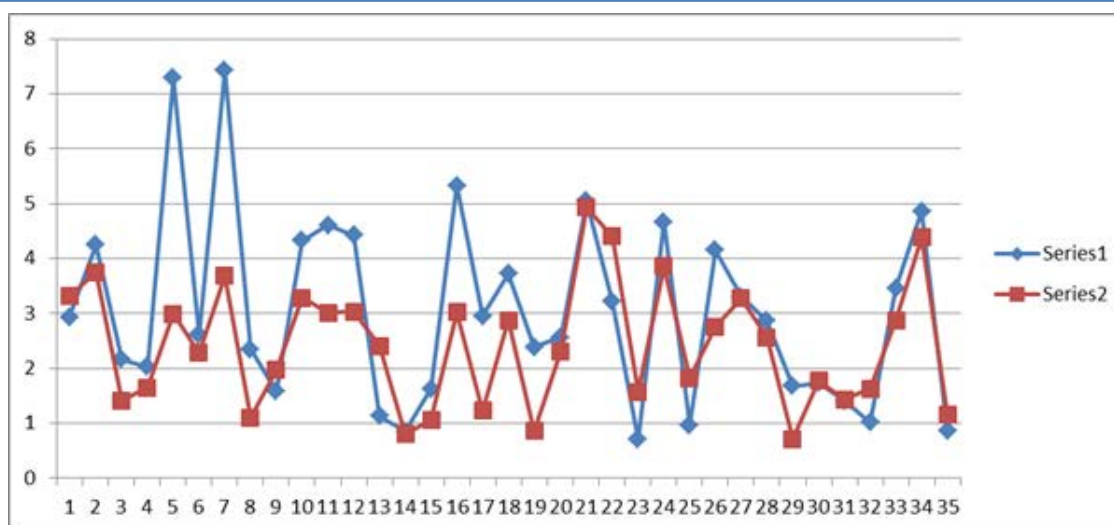


Fig 2. Comparative values for HOMA-IR.

found in the body.<sup>17</sup> It plays an important role in the regulation of glucose metabolism as a cofactor in enzymatic reactions and insulin activity.<sup>9-11</sup> Its levels changes in chronic inflammations and low Mg level have been suggested to be reasonable marker of RA.<sup>17</sup> In this study, the mean HOMA-IR reduced after 6 months Mg consumption. Hadjistavri et al., 2009 suggested that using a high dosage of Mg pidolate (600mg), in hypertensive patient, showed a benefic effect in insulin resistance after 3 months' supplementation.<sup>23</sup> The results of Cahill et al.'s study indicated that higher dietary magnesium intake is strongly associated with the attenuation of insulin resistance. They also found a strong inverse association between dietary magnesium with IR.<sup>24</sup> Several studies have correlated low serum magnesium with increased insulin resistance.<sup>13,14,25</sup> Contrary to us, in a study by Lima de Souza-Silva Mde et al., 2014 showed that 12 weeks of taking chelated Mg (400 mg/day) or placebo, did not show significant variation in fasting glucose, insulin, and HOMA-IR.<sup>26</sup> Furthermore, Lee et al., 2009 revealed that with 300 mg daily elemental magnesium or placebo for 12 weeks, no significant differences were found between HOMA-IR in intervention and control groups.<sup>27</sup> Magnesium has received considerable interest for its potential in improving insulin sensitivity and preventing diabetes.<sup>28</sup> The association between RA and diabetes is not straightforward. Patients with rheumatoid arthritis tend to be more inactive because of joint pain and fatigue.<sup>29</sup> In addition, compared with non RA controls, rheumatoid arthritis patients tend to have decreased lean muscle mass and central adiposity which

are considered as diabetes risk factors.<sup>30</sup> Some of these differences may result from differences in the duration or design of the study, type and dose of magnesium, or ethnic background of the subjects.<sup>15,31,32</sup> Mg is essential for the phosphorylation of tyrosine kinase on the insulin receptor, as well as for other protein kinases involved in post-receptor insulin signaling.<sup>33</sup> For these reasons, Mg replacement may contribute to reducing insulin levels and fasting glucose levels.<sup>26</sup> Magnesium supplementation is considered a food supplement, not a drug, and it is available in many countries.

In this study, statistically significant differences were found between FBS, insulin and HOMA-IR before and after magnesium supplementation. A study by Guerrero-Romero and Rodriguez-Moran (2005) reported a beneficial effect of magnesium supplementation on fasting and postprandial glucose levels and insulin sensitivity in type 2 diabetics with a low total serum magnesium level.<sup>32</sup> Most of epidemiologic studies have shown an inverse association between magnesium intake and fasting insulin concentration or the incidence of type 2 diabetes.<sup>9,15,31</sup>

In this study we were not able to adjust for significant risk factors associated with risk for diabetes. For example, BMI, age, family history, gestational diabetes and sedentary lifestyle were not available in this study. Also, exposure to corticosteroids did not allow for adequate control of the contribution of corticosteroids to development of diabetes. Since magnesium intake is highly associated with other healthy lifestyle and dietary factors, such as cereal fiber and calcium intakes, excluding the effect of magnesium intake on diabetes

risk from other factors are difficult. So, the potential influences of these factors deserve consideration.<sup>34</sup>

In conclusion, this study showed that magnesium supplementation reduces FBS, insulin and HOMA-IR in patients with rheumatoid arthritis. Thus magnesium supplements could be an alternative method for the prevention of type 2 diabetes in RA patients.

## List of acronyms

FBS - fasting blood sugar

HOMA-IR - Homeostasis Model Assessment of insulin resistance

IL-1 – interleukin 1

IL-6 – interleukin 6

IL-8 – interleukin 8

IR - insulin resistance

RA - Rheumatoid arthritis

TNF - tumor necrosis factor

## Contributions of Authors

All authors have substantially contributed to the study and have read and approved the final edited paper.

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## Conflict of Interest

The authors declare no conflict of interest.

## Ethical Publication Statements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Corresponding Author

Mohammad Gharehbeglou, Department of Anesthesiology and critical Care Medicine, School of Medicine, Zahedan University of Medical Science, Zahedan, Iran and Department of Anesthesiology and critical Care Medicine, School of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran.

ORCID iD: 0000-0002-6925-7934

E-mail: [m.gharehbeglou@zaums.ac.ir](mailto:m.gharehbeglou@zaums.ac.ir)

*E-mails and ORCID iD of co-authors*

Mohsen Norouzi: [mohsennorouzi@gmail.com](mailto:mohsennorouzi@gmail.com)

ORCID iD: 0000-0003-3066-218X

Boshra Rezvankhah: [b.rezvankhah@gmail.com](mailto:b.rezvankhah@gmail.com)

ORCID iD: 0000-0002-9922-8966

Mohammad Reza Haeri: [haeri.mr@googlemail.com](mailto:haeri.mr@googlemail.com)

ORCID iD: 0000-0002-1584-5298

Hosein Heydari: [hoseinheydari3375@yahoo.com](mailto:hoseinheydari3375@yahoo.com)

ORCID iD: 0000-0002-8627-9625

Javad Tafaraji: [javad883@yahoo.com](mailto:javad883@yahoo.com)

ORCID iD: 0000-0003-0598-9949

Navid Shafiqh: [navid\\_shafiqh2005@yahoo.com](mailto:navid_shafiqh2005@yahoo.com)

ORCID iD: 0000-0002-1314-296X

Jamshid Ordoni Avval: [mzaj\\_ordoni@yahoo.com](mailto:mzaj_ordoni@yahoo.com)

ORCID ID: 0000-0003-4675-2761

Alireza Rahat Dahmardeh: [Dr.dahmardeh@gmail.com](mailto:Dr.dahmardeh@gmail.com)

ORCID ID: 0000-0002-5705-6481

Niyooosha Masoumzadeh: [passerby\\_62@yahoo.com](mailto:passerby_62@yahoo.com)

ORCID ID: 0000-0002-2222-4713

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