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Evaluating the role of homoeopathically potentised magnesium sulphate 30C on insulin resistance in type 2 diabetes mellitus patients in surat, India: A randomised controlled crossover clinical trial

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***Abstract*---**The World Health Organization has declared type 2 diabetes mellitus (T2DM) to have reached pandemic proportions. The affected population worldwide has increased from 108 million in 1980 to 537 million in 2021. Recent studies have shown that T2DM is often associated with altered magnesium levels. The study aimed to assess the effects of homoeopathically potentised *Magnesium sulphate* 30C on insulin resistance in T2DM patients in Surat, India. The study design was a randomised controlled crossover trial conducted at the ZFR Multi-specialty Homoeopathy Clinic, Surat, India. A total of 79 participants were divided randomly into two groups. One group received the placebo and the other received the potentised *Magnesium sulphate* 30C in the first period (12 weeks). This was followed by a washout period and the groups were crossed over to receive the other intervention, again for 12 weeks. The analysis of variance was used to find the comparisons between both groups for the mean value of glycosylated haemoglobin (HbA1c), fasting blood sugar (FBS), fasting insulin, serum magnesium, homeostatic model assessment for insulin resistance (HOMA-IR), and estimated average glucose levels. HbA1c (%) ($p<0.001$) showed a significant difference between both groups. FBS (mg/dL) ($p=0.246>0.05$), fasting insulin ($p=0.835>0.05$), serum

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magnesium (p=0.470>0.05), HOMA-IR (p=0.257>0.05), and estimated average glucose (p=0.071>0.05) were not significantly different at the end of both study periods. Homoeopathically potentised *Magnesium sulphate* 30C was not found to significantly affect insulin resistance in T2DM patients, although a significant difference was observed in the HbA1c value. Further extensive trials are required that consider differences in the dietary magnesium intake, patients' detailed demographic profile, and estimation of serum lipid markers.

Keywords---Type 2 diabetes mellitus, *Magnesium sulphate*, Insulin, Serum markers.

Introduction

Diabetes is a growing global problem. According to the International Diabetes Federation report, the worldwide diabetes prevalence among adults aged 20-79 years was 4.6% in 2000, which has risen to 8.8% in 2017 [1]. Today, type 2 diabetes (T2DM) is deemed a worldwide pandemic affecting developed and developing countries alike. It has reached proportions to warrant its classification as a significant public health problem. Due to the world population ageing rapidly as well as unhealthy changes in lifestyles resulting in T2DM affecting a higher number of younger individuals, it stands to adversely affect the human race in alarming proportions. Further, for the most part during the disease pathogenesis, the illness is compensated and remains unmanifested. By the time T2DM is diagnosed, it has advanced at the pathophysiological level to advanced insulin resistance with failure. Diabetes is a silent killer that affects almost all organs of the human body. It is responsible for the pathogenesis of cardiovascular illnesses and complications, which again is a major cause of sudden morbidity worldwide (The Emerging Risk Factors Collaboration, 2010). The approach to the management of T2DM is complicated, requiring multi-level interventions, including drug, supplementary, and lifestyle changes. Currently available medications are not adept at handling fluctuations in blood glucose levels, and a combination of drugs with different mechanisms of action is required to tackle this illness. This is because pathogenetically, T2DM involves mechanisms at multiple cellular and organ levels[1].

Magnesium is quite under-reported as an element that has major roles in several life processes. This cation acts as a catalyst for enzymes in several essential cellular reactions, nucleotide processing, cell proliferation, and cell signalling pathways [2]. Carbohydrate metabolism pathways including gluconeogenesis, glycolysis, glycogenesis, Krebs cycle, and lipogenesis need magnesium as a catalyst for several enzymes. Insulin secretion is also magnesium-dependent due to its role in the potassium channel functioning in the beta cells of islet of Langerhans. The action of insulin on tissues like muscle, fat, and liver in response to peripheral glucose levels is a phosphorylation-dependent cascade that uses magnesium at several important steps. Magnesium deficiency manifests itself as peripheral insulin resistance [3]. Thus, the role of magnesium in

carbohydrate metabolism, insulin secretion, and insulin sensitivity/resistance is well-established [4].

Magnesium intake has reduced considerably over the years due to food refining and extensive use of insecticides and pesticides [5]. Under these circumstances, we find that magnesium intake from natural sources is often insufficient to meet the recommended daily requirements. Subsequently, many people are deficient in this essential element and manifest non-specific symptoms and signs that may not indicate magnesium deficiency. Diagnostic methods are flawed in their true estimation of a person's magnesium status, and serum or plasma levels are reduced only in severe magnesium deficiency. By the time the deficiency is apparent in serum levels, cellular processes are already compromised, and the disease pathophysiology is already advanced with compensatory mechanisms being stretched to various degrees [6].

The medical science of Homoeopathy is well-established in the treatment of several conditions. It is rich in pharmacologically active products and has innovative methods of drug preparation. The potentisation methods of homoeopathic drug preparation are known to increase the potency while reducing the concentration of the active ingredient during drug treatment [7]. This implies improved efficacy of the drug at lower concentrations of the active ingredient, suggesting lower side effects [8]. Homoeopathy has several potent compounds of magnesium whose roles are well-established in other medical conditions. The role of these compounds in the management of T2DM requires further investigation.

The role of magnesium in the management of T2DM has been studied extensively; evidence for its positive role is compelling although inconclusive [9, 10]. This is an area of urgent and fast-moving research in the scientific and medical community and holds the potential for better management of this debilitating disease. Clinical trials in the homoeopathy field are not organised and hence do not receive recognition. There is an urgent need to conduct clinical trials for homoeopathic preparations in a scientific manner. This is the only way the medical world will look at the vast knowledge base of homoeopathy as an established mode of patient care [11]. It is the need of the hour to blend into the current trends in evidence-based management protocols. Homoeopathy is practiced in India and parts of Europe and has stood the test of time. However, the practitioners and decision-makers need to upscale and revamp the research scenarios to make them visible and acceptable as a science among the more prominent medical fraternity. The urgent need for organised clinical trials and research in homoeopathy has never been felt so strongly. Greater participation of researchers, policymakers, and practitioners is required to prevent homoeopathy from being written off as non-scientific by the research community.

Clinical trials and publications are needed to make public the vast knowledge and wealth of information in the ancient science of homoeopathy. Homoeopathic magnesium preparations are potent, well-

established, and have minimal side effects. However, practitioners and researchers have not researched their role in the management of T2DM. There are no randomised clinical trials assessing the role of potentised magnesium preparations in the management of insulin resistance in people with T2DM [12]. Studies are sparse and not randomised and do not give a clear indication of the process of potentisation used. There is an urgent need to conduct clinical trials with a clear recording of the process of potentisation to provide a basis for promoting further research [13]. In this context, the study aimed to evaluate the effect of supplementation with homoeopathically potentised *Magnesium sulphate* 30C on insulin resistance in patients with T2DM.

Materials and Methods

Study design

This study was a randomised controlled crossover trial of a homoeopathic remedy. The participants were divided randomly into two groups, one received the placebo, and the other group received the active ingredient i.e., the potentised *Magnesium sulphate* 30C. These two groups were then crossed over, and the intervention was reversed with the placebo group receiving the active drug and vice versa.

Study Setting

The study included participants from the city of Surat, India, and it was conducted at the ZFR Multi-specialty Homoeopathy Clinic, Surat. A random selection of 76 consecutive patients having T2DM and attending the outpatient department was enrolled in the study.

Sample Size

The ideal sample size for the study using matched pair design using G Power software version 3.1 and single-centre design was 68. Accordingly, the study included 76 randomly selected patients with an assumption of a dropout rate of 10%.

Selection Criteria

Patients already diagnosed with T2DM and with proven insulin resistance as measured using the homeostatic model assessment (HOMA) values of beta-cell activity and insulin resistance (IR) with all age groups were included in this study. Patients with type 1 diabetes, as evident in HOMA results of beta-cell activity and increased serum magnesium levels, were excluded from the study.

Screening and baseline evaluations

The participants were initially screened for fasting blood glucose level (mg/dL), fasting insulin level (mg/dL), glycosylated haemoglobin (HbA1C) (DCCT percentage), insulin resistance on HOMA index for beta-cell function and insulin resistance status, and serum magnesium levels (mg/dL). Together, these

investigations were grouped as the Mag-In package for this study investigating the effect of potentised magnesium on insulin sensitivity. The participants were randomly assigned to the control and test groups in a blind fashion. Each group initially comprised 38 participants. The intervention or test group received *Magnesium sulphate* 30C at bedtime for 12 consecutive weeks along with the usual prescribed dosage of oral hypoglycaemic agents. The control or placebo group received a placebo at bedtime daily for 12 weeks like the drug and the usual prescribed dosage of oral hypoglycaemic agents. This 12-week period was followed by collection of blood samples from all participants for the same Mag-In package tests that were conducted at the beginning of the study. Then, there was a crossover of the two arms or groups with the participants in the test group were swapped to the placebo group and vice versa. There was an intervening 2-week wash over period to prevent interference due to carry-over effect.

Outcome Measures

The primary outcome measure for evaluating participants' insulin resistance is the HOMA index. The HOMA-IR is calculated from fasting insulin levels and serves as a surrogate assessment of insulin resistance. Investigations were carried out in weeks 0, 12, and 26. The investigations included Glycosylated haemoglobin (HbA1c) levels, fasting blood sugar, fasting serum insulin, serum magnesium and HOMA-IR grouped together as the Mag-In test package for convenience and to convey that the investigations are being performed as part of the clinical study. Pathological investigations were performed in an impartial manner similar to any other blood samples, and there was no special treatment for these samples.

Statistical analysis

Data were presented as mean ± SD. Comparisons between groups were made using one-way and two-way analysis of variance (ANOVA). A P-value <0.05 was deemed statistically significant.

Results and Discussion

Initially, we had included 93 patients with T2DM in our study. Fourteen patients did not complete the first follow-up or did not complete the crossover study. Hence, these 14 were excluded from the study, and the final analysis was performed on 79 patients.

Baseline Characteristics

The mean age of the patients was 56.61 ± 10.10 years. The male: female ratio was 1.54:1.00. In terms of oral hypoglycaemic agent being used, metformin was used by 68 (86.1%) patients, followed by glimepiride by 51 (64.6%) and teneligliptin by 15 (19%) patients. Most commonly patients were taking 2 drugs (45.6%). Majority of the patients had deranged HbA1c (78.5%) and FBS levels (64.6%). According to HOMA-IR, 56 (70.9%) patients had insulin resistance. Estimated average glucose (eAG) was more than 126 mg/dL in 75 (94.9%) patients. The data are summarised in Table 1.

Table 1: Summary of baseline characteristics

Characteristics	Mean ± SD
Age	56.61 ± 10.10 years
HbA1c	7.85 ± 1.71%
FBS	134.99 ± 54.08 mg/dL
Fasting insulin	14.81 ± 15.94 µIU/mL
Serum magnesium	1.97 ± 0.24 mg/dL
HOMA-IR	5.31 ± 6.76
eAG	178.43 ± 49.07 mg/dL

Crossover analyses

There was no statistically significant effect of period or treatment-period interaction (P>0.05); in other words, the effect can be attributed to drug or placebo. At a confidence interval of 95%, we can say that the true population value for the magnitude of the treatment effect lies between -0.7222 to -0.1897. There was an impact of treatment on the HbA1c (%) (P=0.001). There was no statistically significant effect of period or treatment-period interaction (P>0.05), and neither was there any effect of drug/placebo on FBS (P>0.05), so the treatment/placebo did not affect the FBS. There was no statistically significant effect of period or treatment-period interaction (P>0.05), and neither was there an effect of drug/placebo on fasting insulin (P>0.05), so the treatment/placebo had no effect on the fasting insulin. There was no statistically significant effect of period or treatment-period interaction (P>0.05), and neither was there an effect of drug/placebo on serum magnesium (P>0.05), so the treatment/placebo had no effect on the serum magnesium. There was no statistically significant effect of period or treatment-period interaction (P>0.05), and neither was there an effect of drug/placebo on HOMA-IR (P>0.05), so the treatment/placebo had no effect on the HOMA-IR. There was no statistically significant effect of period or treatment-period interaction (P>0.05), and neither there was an effect of drug/placebo on eAG (mg/dL) (P>0.05), so the treatment/placebo had no effect on the eAG (mg/dL). The results are summarised in Table 2.

Table 2: Summary of crossover analyses

Measurement	Treatment difference (Mean ± SE)	95% CI	*p*-value
HbA1c	-0.46 ± 0.133	(-0.72 to –0.19)	**0.001***
FBS	-4.16 ± 3.515	(-11.18 to 2.91)	0.246
Fasting Insulin	-0.53 ± 2.547	(-2.80 to 2.26)	0.835
Serum magnesium	0.03 ± 0.045	(-0.03 to 0.06)	0.470
HOMA-IR	-1.61 ± 1.408	(-2.21 to 0.60)	0.257
eAG	-11.02 ± 6.023	(-11.51 to 0.49)	0.071

Figure 1: Comparison of mean HbA1c during the study and placebo periods

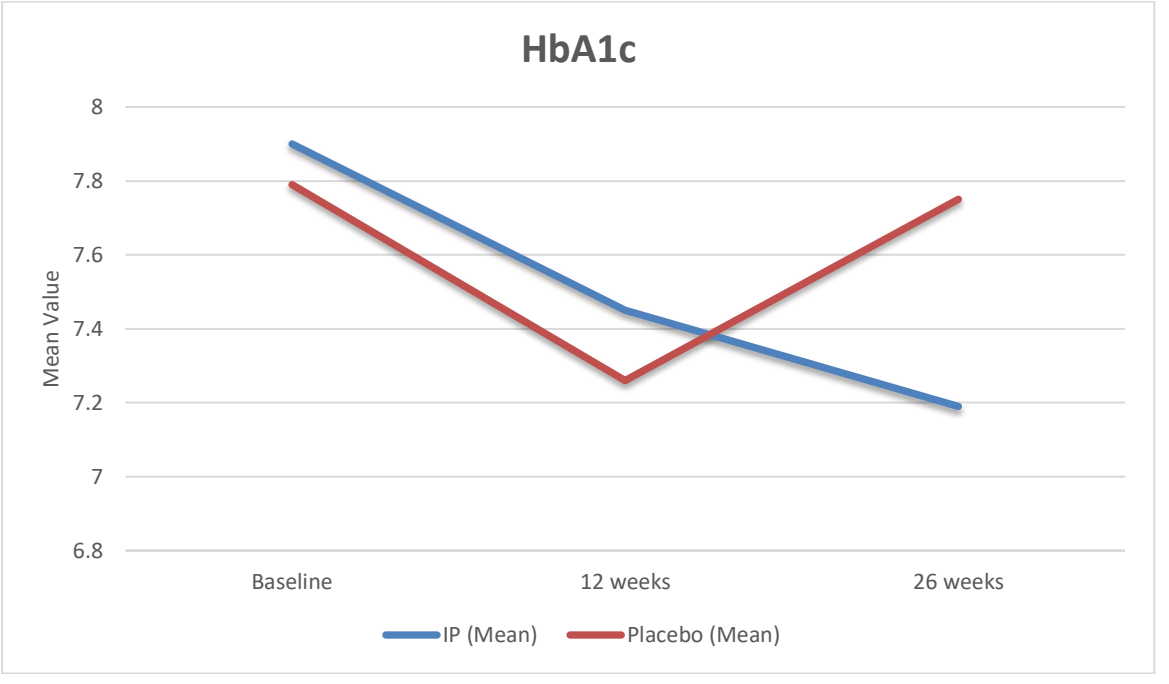


Figure 2: Comparison of mean of fasting blood sugar during the study and placebo period

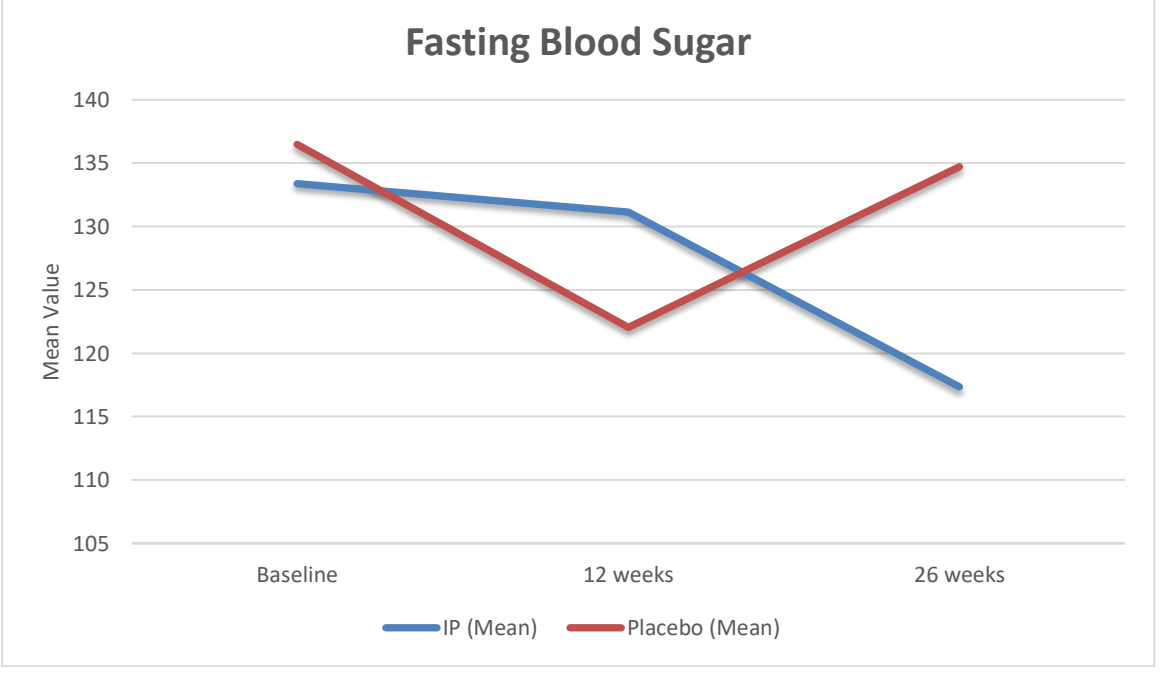


Figure 3: Comparison of means of fasting insulin during the study and placebo periods

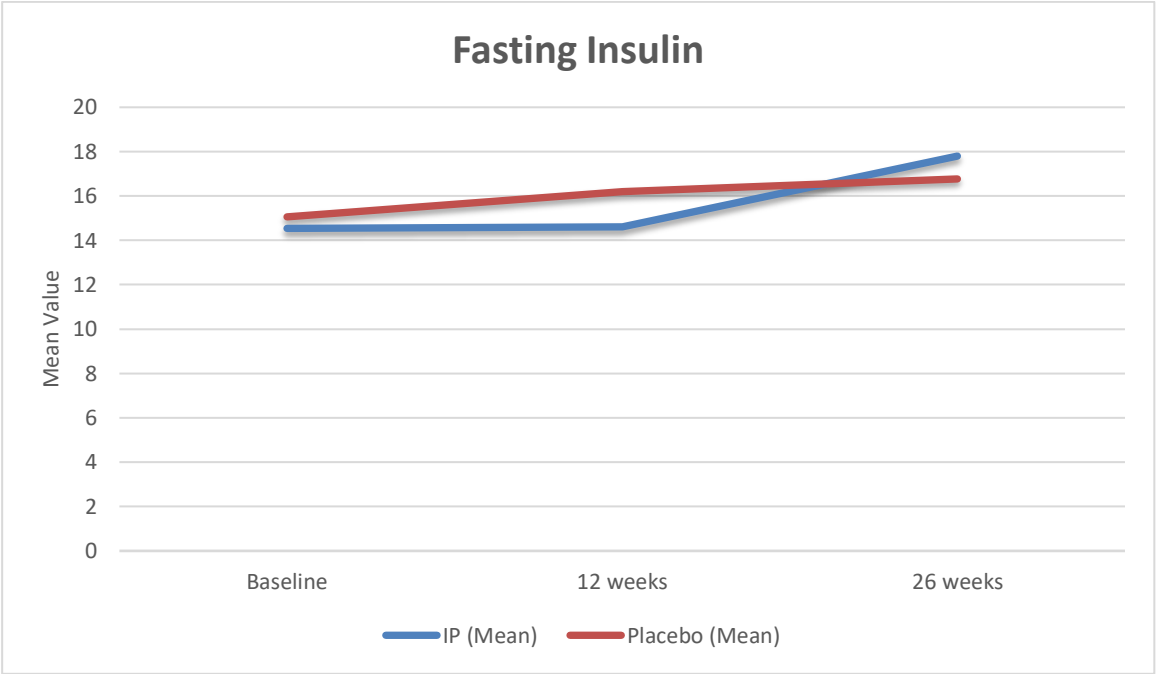


Figure 4: Comparison of means of serum magnesium levels during the study and placebo periods

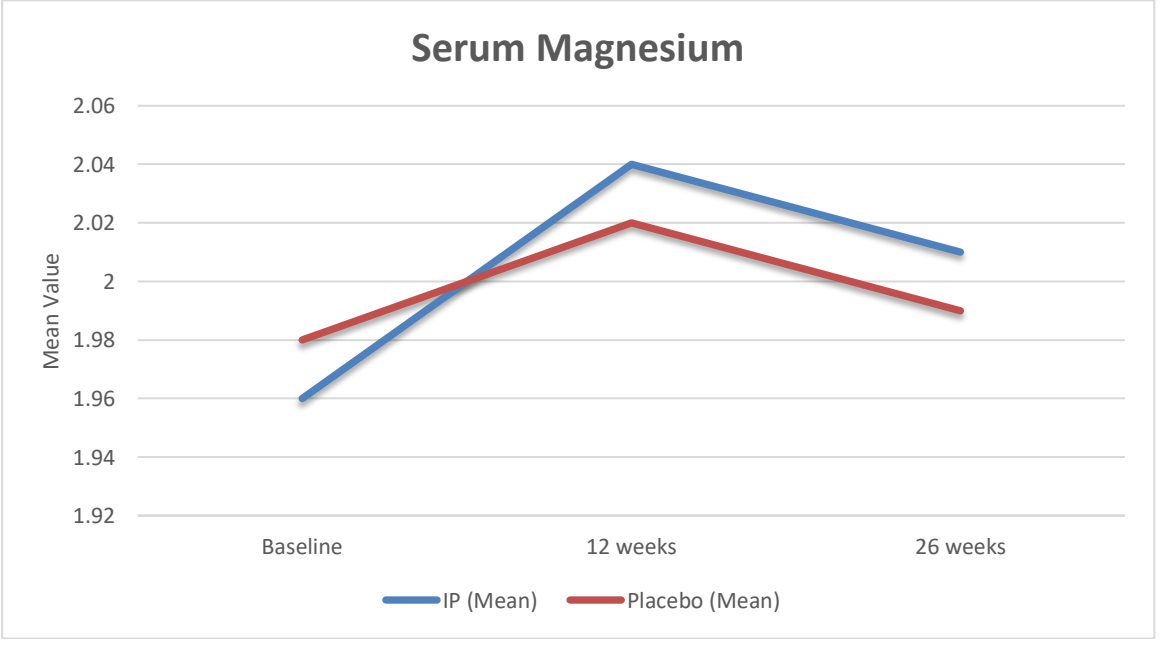


Figure 5: Comparison of means of HOMA-IR during the study and placebo periods

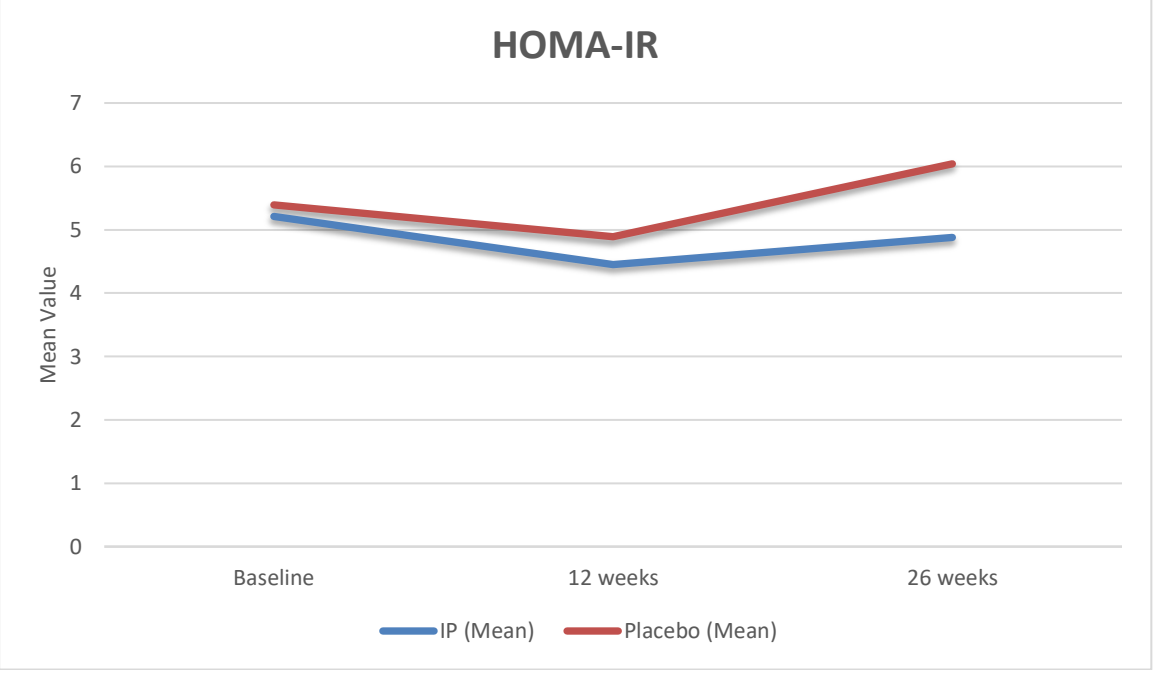
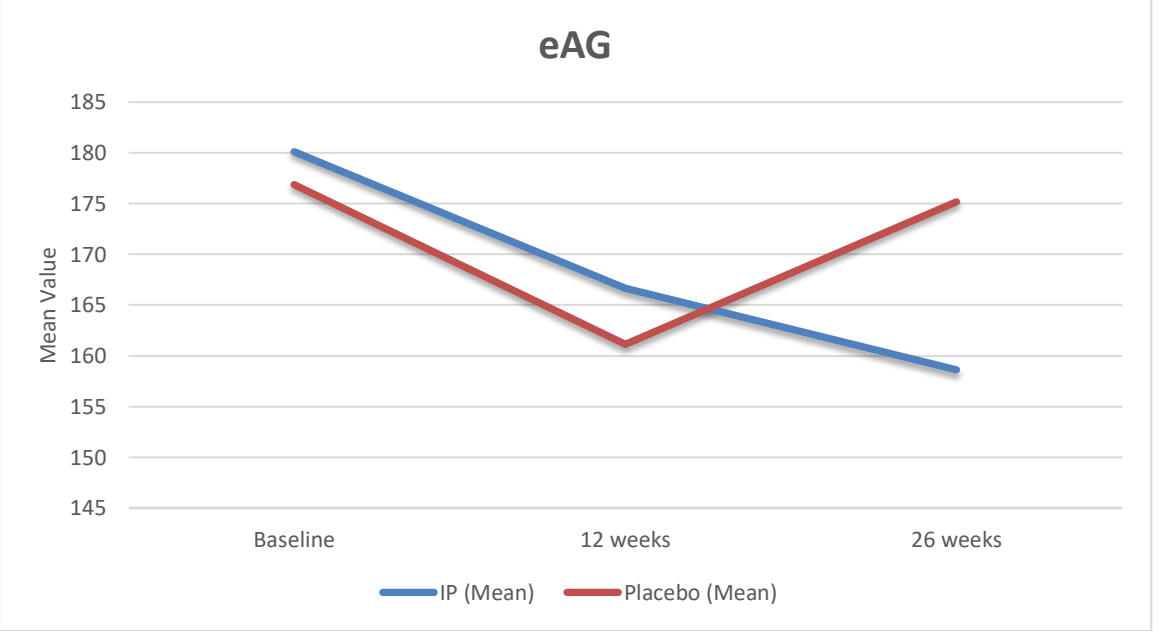


Figure 6: Comparison of means of eAG during the study and placebo periods



**: indicates statistical significance*

The results of this study showed a significant reduction in HbA1c values in the intervention group. There was no significant difference between the two groups in terms of FBS, fasting insulin levels, serum magnesium levels, HOMA-IR score, and eAG.

A reduction in HbA1c values is considered as an indicator of treatment effect. In terms of the results of the study, *Magnesium sulphate* 30C shows an effect on the reduction of HbA1c values. In reference to our primary research question, *Magnesium sulphate* 30C did not result in a reduction in HOMA-IR values and therefore indicates no effect on reduction in insulin resistance. As there were no previous studies on the test drug to study its impact on insulin resistance, this study was designed as a pilot. Based on the findings of this study, future projects can be designed considering a need for extended duration and a change in dose.

The outcomes of some prior studies corroborate with the results of the current study. The baseline results of the present study were found to be consistent with [14], in which significant improvement was observed in HbA1C, insulin levels (IL), C-peptide, HOMA. IR, and HOMA.IR% of the intervention group compared to control after three months of intervention. A study by Moran et al. (2003)[15] showed a remarkable increase in serum magnesium levels in comparison to placebo [15]. These results differ from the current study for reasons including but not limited to the use of different formulations, a different dose of magnesium, and a longer duration of the study.

Similarly, Solati et al. administered a higher dosage of magnesium (300 mg) and reported an improvement in FBS and 2-hour postprandial blood glucose levels[16]; however, similar to the current study, there was no significant rise in serum magnesium levels. Romero et al. (2004)[17] also reported improvement in insulin sensitivity by 10% and blood sugar by 37% with daily oral magnesium supplementation (Guerrero-Romero et al., 2004)[17]. Some studies also cite a negative correlation between magnesium, glucose, HbA1c, and HOMA-IR. Chen et al. (2017) showed that magnesium levels had a decreasing trend from normal glucose tolerance group to pre-diabetics to people with diabetes[18]. A meta-analysis done in 2011 reported that a majority of its included studies showing significant inverse relation between magnesium intake and risk of diabetes in a dose-response manner [19]. However, this study did not consider the factors such as geographic region, period of follow-up, sex, or family history of T2DM. Larsson & Wolk (2007b) reported a 15% reduction in the incidence of diabetes[10]. Low magnesium levels have been associated with developing complications of diabetes; at the same time, insulin sensitivity and diabetic complications seem to decrease with adding dietary intake of magnesium [9, 20]. Magnesium regulation in diabetic patients works for correcting complications by neutralising harmful effects of oxidative stress [21]. Another meta-analysis concluded that magnesium supplementation significantly decreased glucose levels [22].

The present study has some limitations. The dietary intake of magnesium of patients was not taken into consideration. A variable dietary intake is expected for each individual who should have been considered during the trial's design. To eliminate this confounding factor, a stratified randomised design could be used based on the serum magnesium levels of the participant. Alternatively, and

additionally, a larger number of participants could be recruited. The current study did not include monitoring the lipid parameters in the patients. Despite the limitations, the present study provides a base for more extensive studies in the future with increased sample size, emphasis on dietary intake, increased dose of magnesium conjugate, alterations in a conjugate of magnesium in the drug, and an increased period of intervention.

Conclusion

Homoeopathically potentised *Magnesium sulphate* 30C was not found to have a significant effect on insulin resistance in T2DM patients, although a significant difference was observed in HbA1c value. Despite the contradictory findings in the present study and the literature, most of the studies discussed here report that low magnesium levels negatively affect glucose regulation; however, this has not been shown in our present study. Furthermore, larger trials are required that consider the dietary intake of magnesium by patients, their detailed demographic profile, and estimation of serum lipid markers.

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