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Effect of magnesium supplementation on type 2 diabetes associated cardiovascular risk factors: a systematic review and meta-analysis

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Abstract

Background: Cardiovascular disorders remain the leading cause of death in type 2 diabetic patients. In the present study, a systematic review and a meta-analysis of randomised controlled trials (RCTs) were conducted aiming to evaluate the effect of magnesium supplementation on type 2 diabetes (T2D) associated cardiovascular risk factors in both diabetic and nondiabetic individuals.

Methods: PubMed, Scopus, Cochrane, Web of Science and Google Scholar databases were searched from inception to 30 June 2016 aiming to identify RCTs evaluating the effect of magnesium supplementation on T2D associated cardiovascular risk factors. The data were analysed using a random effect model with inverse variance methodology. Sensitivity analysis, risk of bias analysis, subgroup analysis, meta-regression and publication bias analysis were also conducted for the included studies using standard methods.

Results: Following magnesium supplementation, a significant improvement was observed in fasting plasma glucose (FPG) [weighted mean difference (WMD) = −4.641 mg dL^{-1}, 95% confidence interval (CI) = −7.602, −1.680, $P = 0.002$], high-density lipoprotein (HDL) (WMD = 3.197 mg dL^{-1}, 95% CI = 1.455, 4.938, $P < 0.001$), low-density lipoprotein (LDL) (WMD = −10.668 mg dL^{-1}, 95% CI = −19.108, −2.228, $P = 0.013$), plasma triglycerides (TG) (WMD = −15.323 mg dL^{-1}, 95% CI = −28.821, −1.826, $P = 0.026$) and systolic blood pressure (SBP) (WMD = −3.056 mmHg, 95% CI = −5.509, −0.603, $P = 0.015$). During subgroup analysis, a more beneficial effect of magnesium supplementation was observed in diabetic subjects with hypomagnesaemia.

Conclusions: Magnesium supplementation can produce a favourable effect on FPG, HDL, LDL, TG and SBP. Therefore, magnesium supplementation may decrease the risk T2D associated cardiovascular diseases, although future large RCTs are needed for making robust guidelines for clinical practice.

Introduction

Type 2 diabetes (T2D) is a life style disorder characterised by insulin resistance in insulin sensitising organs and impaired insulin secretion by pancreatic β-cells [(1)]. An epidemiological outbreak of T2D is a major concern for the world healthcare system, generating a large healthcare burden across the globe. The prevalence of diabetes has been speculated to increase from 250 million at present to 592 million by 2035 [(2,3)]. Developing countries are at higher risk (69%) compared to developed countries (20%) [(4,5)].Cardiovascular disorders (CVD) remain the

leading cause of death in T2D patients [6,7]. Various risk factors associated with CVD include hypertension, dyslipidaemia, impaired glucose metabolism and smoking. The overall risk of CVD associated morbidity and motility in T2D involves a complex interplay between these factors [8,9]. The focus of current patient oriented T2D therapy is on controlling hyperglycaemia, along with decreasing the risk of CVD to improve the quality of life and life expectancy of T2D patients [10].

Long-term hyperglycaemia results in macro- and microvascular complications in T2D. Elevated glucose levels cause glycation of lipoproteins within the body. Glycated lipoproteins have differential handling by lipoprotein receptors, which potentiates atherogenicity. Moreover, glycated lipoprotein has increased susceptibility towards oxidation, which increases oxidative stress in T2D patients. Diabetic dyslipidaemia (also known as atherogenic dyslipidaemia) is prevalent in T2D patients at high risk of macrovascular complications. It is characterised by elevated triglyceride (TG) remnants and small dense low-density lipoprotein (LDL) levels, along with decreased high density-lipoprotein (HDL) levels. Elevated blood pressure (BP) also increases the risk of CVD. It has been reported that, with each 10 mmHg increase in systolic blood pressure (SBP), the risk of CVD increases by 15%. Therefore, consideration should be given to CVD associated risk factors along with hyperglycaemia in the management of T2D. Management of diabetic dyslipidaemia and BP is demonstrated to be more beneficial than targeting hyperglycaemia alone for decreasing the risk of macro- and microvascular complications in T2D [11,12].

Life style modifications and adjuvant dietary supplementation are areas of active research in the management of T2D. Magnesium (Mg) supplementation is included among them. Mg is the fourth most abundant cation in the human body with maximum intracellular distribution (99%) [13]. The ARIC study demonstrated an inverse association between serum magnesium levels and the risk of developing T2D in the general population, which suggests a beneficial role of Mg in the prevention of T2D [14]. Mg is essential cofactor of more than 300 enzymes (including enzymes involved in glycolysis). Therefore, Mg is critical for intracellular carbohydrate metabolism [15]. It also acts as a cofactor of tyrosine kinase enzyme and thus is involved in post-receptor signalling of insulin. Mg regulates the release of calcium from the rough endoplasmic reticulum (as a cofactor of CaATPase) in pancreatic β-cells, thus modulating insulin secretion from the pancreas [16–18]. Mg produces a positive effect on diabetic dyslipidaemia by modulating the activity of lipoprotein lipase (LPL), desaturase (DS) and lecithin-cholesterol acyl transferase (LCAT). Impaired activity of LPL and DS leads to elevated TG levels and an increased saturated to unsaturated fatty acid ratio, respectively. This results in increased vulnerability to macrovascular changes associated with T2D. In addition, LCAT plays a critical role in maintaining lipoprotein balance within the body. An impairment in activities of LPL and LCAT results in increased TG, LDL and very LDL (VLDL) and decreased HDL [12]. Mg also decreases BP by causing vascular smooth muscle relaxation, which results in decreased vascular tone [11]. Inflammation and oxidative stress in T2D are also reported to be associated with hypomagnesaemia (HM) because serum Mg levels are inversely associated with C-reactive protein, interleukin (IL)-1β, IL-6, inducible nitric oxide synthase, interferon-γ and malondialdehyde levels [15,17]. Therefore, HM may be a critical risk factor for T2D and other associated co morbidities.

Various cross-sectional and longitudinal studies confirms the association of Mg intake with insulin sensitivity and glucose homeostasis [19–28]. Two meta-analyses [29,30] have been conducted aiming to determine the effect of Mg supplementation on insulin sensitivity and glucose homeostasis (involving an intervention duration of 4–24 weeks with both organic and inorganic salt forms). Both studies confirmed the significant association of Mg intake with insulin sensitivity and glucose homeostasis. However, in a meta-analysis by Song *et al.*,[29] the long-term effect of Mg supplementation was uncertain (as was evident from glycated haemoglobin levels), whereas, in a meta-analysis by Simental-Mendia *et al.* [30], the effect of Mg supplementation on CVD risk factors was not evaluated. Various observational studies also suggest a beneficial role of Mg in reducing the risk of CVD [31–38].

In the present study, we performed a systematic review and meta-analysis of randomised controlled trials (RCTs) to evaluate the beneficial effect of Mg supplementation on T2D associated CVD risk factors. The present meta-analysis includes studies carried out in T2D subjects or in populations at high risk of T2D.

Methods

Search strategy and selection criteria

A search was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (2009) [39]. We searched PubMed, Scopus, Cochrane, Web of Science and Google Scholar databases from inception to 30 June 2016, including articles in press and online ahead of publication using a search strategy with Medical Search history (MeSH) terms: (randomised controlled trial OR Controlled trials OR randomised OR Placebo) AND (Magnesium OR Magnesium therapy OR Magnesium supplementation) AND (NIDDM OR Type 2 Diabetes OR Type II Diabetes

OR Non-Insulin Dependent Diabetes OR Insulin resistance OR Insulin sensitivity OR Hyperglycaemia OR Impaired glucose tolerance). Truncations (*) were used at appropriate places to ensure that all variations of search terms were included. The search was restricted to the English language only. Wherever studies were available as an online abstract or were inaccessible, their full text was obtained either from the journal publisher or from the study authors by personal request. Additional information wherever required was obtained from the corresponding author of a study by request. Studies compliant with the following inclusion criteria were included in present systematic review:

- RCTs with parallel or cross-over design
- Enrolled participants ≥18 years of age
- Participants were either T2D or at high risk of developing T2D (e.g. prediabetics, hypertensive, overweight or obese)
- Evaluated effect of Mg supplementation (both organic and inorganic) on T2D associated CVD risk factors
- A supplementation duration of at least 1 month
- The presence of sufficient data to interpret pre- and post-treatment changes in desired outcomes.

Studies not compliant with the above inclusion criteria were excluded. We also excluded case controlled studies, multiple reports of same trial and observational studies (cross-sectional as well as longitudinal designs).

Both investigators in the present study carried out an independent search for suitable trials and evaluated titles and abstracts during prescreening. After prescreening, the full text of the remaining studies was evaluated for potential inclusion in the present systematic review. Any discrepancy regarding the decision for including or excluding a particular study was resolved after mutual discussion.

Data collection and quality assessment

Data collection forms were developed in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions* [40]. Each study was given with a unique study ID (an integer) and the following information was extracted from the included studies:

- Last name of first author and year of publication
- Number of participants in both treatment and control group (in cross-over studies, same number of participants considered in both groups)
- Population characteristics, including age, body mass index, HM or normomagnesaemic (NM)
- Dose of Mg and its related salt form
- Duration of supplementation
- Baseline and final values in each group for any of:

Fasting plasma glucose (FPG), fasting plasma insulin (FPI), glycated haemoglobin (HbA_{1C}), total cholesterol (TC), HDL, LDL, TG, SBP and diastolic blood pressure (DBP)

Assessment of the risk of bias was performed in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions* [40]. Separate forms were generated for each study with its unique study ID (initially assigned during data collection). Each study was evaluated for its sequence generation method, allocation of sequence concealment, blinding and dropout details, selective outcome reporting and other potential sources of bias.

Data synthesis and analysis

Collected data of different outcomes, wherever needed, was converted into uniform measurement units using established conversion factors. FPG, TC, HDL, LDL and TG values were recorded as mg dL^{-1}. Insulin values were recorded as μIU mL^{-1}. SBP and DBP values were recorded as mmHg. These measuring units were adopted to increase the utility of systematic review in clinical practice. Comprehensive meta-analysis (CMA), version 2 (Biostat, Eaglewood, NJ, USA) was used for the meta-analysis. Effect of intervention was assessed in form of weighted mean difference (WMD) at a 95% confidence interval (CI). WMD was calculated using inverse variance methodology. The following formulae were used to calculate the change score (or intervention effect):

- For studies in which baseline values were available:

$$\text{Change score} = (T_f - T_b) - (C_f - C_b) \quad (1)$$

where T_f is the final value of outcome in treatment group; T_b is the baseline value of outcome in treatment group; C_f is the final value of outcome in control group; and C_b is the baseline value of outcome in control group.

- For cross-over trials

$$\text{Change score} = T_f - C_f \quad (2)$$

wherever the SEM was reported for a particular group, this was converted to the SD by multiplying it by the square root of number of subjects present in that group. Wherever results were recorded as median value with range, conversion into mean and SD was performed as suggested by Hozo *et al.*[41]. Wherever variation was recorded as range, the SD was calculated by subtracting the lower limit from the upper limit followed by division of outcome with *t*-value at 95% CI. The *t*-value was calculated in EXCEL (Microsoft Corp., Redmond, WA, USA) using the formula: =tinv(1−0.95, n−1), where, *n* is the number of subjects in a particular group. Random effect

model (DerSimonian-Laird method) and a generic inverse variance method were used for meta-analysis. Inter-study variability was assessed by the Cochrane Q and I^2 index [40]. Sensitivity analysis was performed as suggested by the *Cochrane Handbook of Systematic Reviews of Interventions* [40] via the 'leave-out one method'. In this method, one study was removed at a time and the meta-analysis was repeated with the remaining treatment arms and any effect of elimination on summary estimate was evaluated.

Subgroup analysis

Subgroup analysis was performed to assess the effect of population and intervention characteristics on outcome measure. There were two population based subgroup analysis criteria: diabetic or nondiabetic population and HM (<0.74 mmol L^{-1} or 1.8 mg dL^{-1}) or NM (≥ 0.74 mmol L^{-1} or 1.8 mg dL^{-1}) population. Intervention subgroup analysis had two criteria: ≤ 3 months of treatment duration or >3 month treatment duration and the type of magnesium salt used in intervention (inorganic or organic). Variation among subgroups was evaluated on the basis of the P-value at 95% CI.

Meta-regression

Weighted random effect meta-regression was performed to evaluate the association between possible confounders and outcome measure. In the present analysis, elemental magnesium dose per day and treatment duration (in weeks) were considered as possible confounders.

Assessment of publication bias

Publication bias was analysed by visual assessment of asymmetry in Begg's funnel plot. Kendall's tau with continuity correlation, Egger's linear regression test, corrected effect size test (trim and fill test) and the classical Fail safe N test were also used to assess the effect of publication bias on reported outcome.

Results

We found 88 records during the initial search of all databases. Of these, 35 were non-original records. Twenty three did not meet the inclusion criteria. The remaining studies were considered after analysing the full text. Of these, two studies [42,43] were excluded because one [42] was a case–control study and the other [43] was a conference abstract (i.e. no data were available). The full text of one study [44] was not available online. On request, the journal publisher provided the full text. The design details of two studies [44,45] were obtained from their corresponding authors on request. Finally, 28 studies were included in the present review [46–71]. In accordance with the PRISMA statement, the details of the search strategy and its outcomes are presented in Fig. 1.

A total of 1694 subjects were included in present study. Of these, 834 subjects belong to the treatment arm, whereas 860 belong to the placebo arm. Studies were conducted from 1989 to 2015. A summary of selected studies is provided in the Supporting information (Table S1).

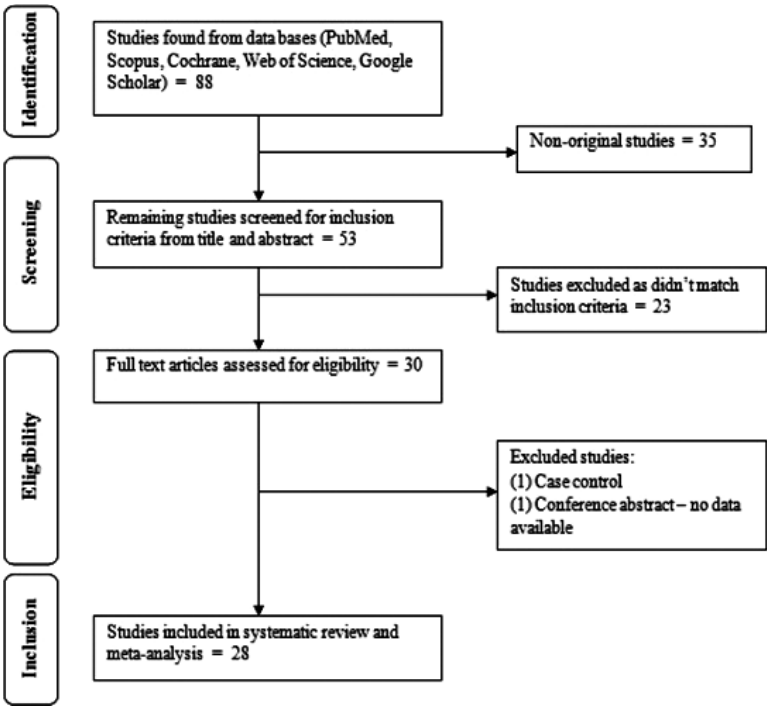


Figure 1 Details of the search strategy and its outcomes.

Assessment of the risk of bias

Under sequence generation analysis, no study was found to have a high risk of bias. Allocation concealment was unclear in all studies. Blinding of participants, personnel and outcome assessors was associated with a low risk of bias. There was only one study by Solati *et al.* [66] that was associated with a high risk of bias. All studies reported adequate data for inclusion in the meta-analysis. No study included in the present meta-analysis was found to have a high risk for selective reporting outcomes (see Supporting information, Table S2).

Effect on outcomes related to type 2 diabetes associated cardiovascular disease related risk factors

The effect of Mg supplementation of FPG, FPI, HbA_{1C}, TC, HDL, LDL, TG, SBP and DBP was assessed via meta-analysis of 27, 15, 14, 15, 20, 12, 21, 19 and 19 treatment arms. After Mg supplementation, significant improvement was observed in FPG (WMD = -4.641 mg dL^{-1}, 95% CI = -7.602, -1.680, $I^2 = 83.353$, $P = 0.002$) (Fig. 2), HDL (WMD = 3.197 mg dL^{-1}, 95% CI = 1.455, 4.938, $I^2 = 67.250$, $P = 0.00032$) (Fig. 2), LDL (WMD = -10.668 mg dL^{-1}, 95% CI = -19.108, -2.228, $I^2 = 71.201$, $P = 0.013$) (Fig. 2), TG (WMD = -15.323 mg dL^{-1}, 95% CI = -28.821, -1.826, $I^2 = 53.267$, $P = 0.026$) (Fig. 2) and SBP (WMD = -3.056 mmHg, 95% CI = -5.509, -0.603, $I^2 = 59.191$, $P = 0.015$) (Fig. 2). Insignificant improvement or no improvement was observed in FPI (WMD = -0.481μIU mL^{-1}, 95% CI = -1.462, -0.500, $I^2 = 57.774$, $P = 0.336$) (Fig. 2), HbA_{1C} (WMD = -0.001%, 95% CI = -0.132, 0.130, $I^2 = 0.000$, $P = 0.989$) (Fig. 2), TC (WMD = -4.323 mg dL^{-1}, 95% CI = -10.841, 2.195, $I^2 = 55.102$, $P = 0.194$) (Fig. 2) and DBP (WMD = -1.369 mmHg, 95% CI = -3.023, 0.285, $I^2 = 64.749$, $P = 0.105$) (Fig. 2). As is evident from the value of I^2, the included studies had moderate to considerable heterogeneity associated with them.

Sensitivity analysis (leave-out one method) showed that results were robust and were not over influenced by the results of a particular study.

Subgroup analysis

Both population and interventional subgroup analysis did not show any significant variation in the case of HbA_{1C} and TC at 95% CI. A significant differential effect was observed in rest of outcomes at 95% CI (see Supporting information, Table S3). In the diabetic versus nondiabetic population, significant differences were observed in FPG ($P = 0.003$), HDL ($P < 0.001$), LDL ($P = 0.003$) and TG ($P = 0.041$), whereas an insignificant difference was observed in the case of FPI ($P = 0.301$). Statistically significant variation was also observed among the HM and NM groups in the case of FPG ($P = 0.001$), FPI ($P = 0.013$), HDL ($P < 0.001$) and LDL ($P = 0.039$), whereas variation was insignificant in the case of TG ($P = 0.797$). Different Mg salts had a variable effect only in the case of FPG ($P < 0.001$) and HDL ($P < 0.001$) at 95% CI, whereas, there was no differential effect on other outcomes. Duration of therapy (≤3 months or >3 months) also had a significant variable effect for all outcomes except in the case of FPI ($P = 0.171$).

Meta-regression analysis

At 95% CI, elemental Mg dose was found to be inversely associated with FPG ($P = 0.084$), TC ($P = 0.002$), HDL ($P < 0.001$), LDL ($P = 0.008$), TG ($P = 0.028$), SBP ($P < 0.001$) and DBP ($P < 0.001$) (see Supporting information, Fig. S1). Duration of therapy had inverse association with FPG ($P < 0.001$) only when the rest of parameters did not show a significant association at 95% CI (see Supporting information, Fig. S2).

Risk of publication bias

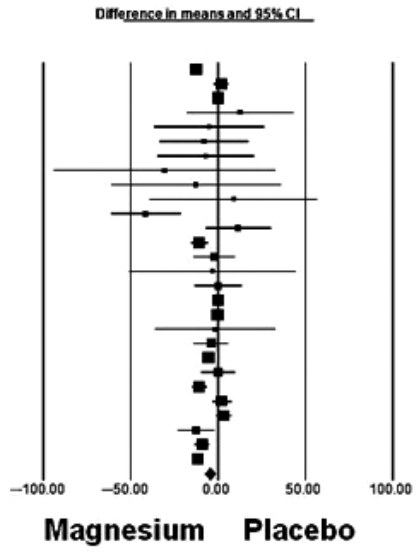
Visual evaluation of funnel plot for all outcomes (see Supporting information, Fig. S3) was performed. Data related to Kendall's tau with continuity correlation, Egger's linear regression test, trim and fill test and the fail safe *N* test for all outcomes are shown in the Supporting information (Table S4). The trim and fill test shows imputation of three studies and one study in the case of FPI and TG, respectively, although there was no significant variation in the outcome summary estimate. Egger's regression test showed significant variation only in the case of TG ($P = 0.015$), whereas all other outcomes did not show any significant bias in any of the tests.

Discussion

Hyperglycaemia plays an important role in the development of macro- and microvascular complications in T2D because it affects the glycation of lipoproteins as and also increases their vulnerability towards oxidation [11,12]. We observed an overall beneficial effect of Mg supplementation on FPG. We also observed a differential effect of Mg supplementation during subgroup analysis. A significant beneficial effect of Mg supplementation was observed in the diabetic population with hypomagnesaemia. Hence, analysis of baseline serum Mg levels may be important before rationalising Mg supplementation. Significant variation was also observed in the case of treatment duration. Both short-term and long-term therapy were found to be effective in the management of FPG, although >3 months of supplementation produces a greater beneficial effect on

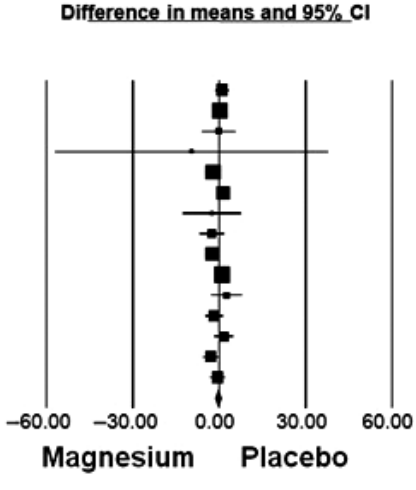
(a)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value
Paolisso 1989	−12.600	1.423	2.025	−15.389	−9.811	−8.854	0.000
Paolisso 1992	1.800	2.142	4.590	−2.399	5.999	0.840	0.401
Paolisso 1994	0.000	1.200	1.441	−2.353	2.353	0.000	1.000
Gullestad 1994	12.600	15.490	239.944	−17.760	42.960	0.813	0.416
Purvis 1994	−5.100	16.263	264.480	−36.975	26.775	−0.314	0.754
Corica 1994	−8.000	13.109	171.851	−33.694	17.694	−0.610	0.542
Eriksson 1995	−7.200	14.059	197.662	−34.756	20.356	−0.512	0.609
de Valk 1998	−30.600	32.418	1050.955	−94.139	32.939	−0.944	0.345
Lima 1998(a)	−12.600	24.713	610.743	−61.037	35.837	−0.510	0.610
Lima 1998(b)	9.000	24.505	600.488	−39.029	57.029	0.367	0.713
Rhodriguez 2003	−41.400	10.240	104.860	−61.470	−21.330	−4.043	0.000
Lal 2003	11.500	9.521	90.645	−7.161	30.161	1.208	0.227
Guerrero-Romero 2004	−10.800	2.509	6.294	−15.717	−5.883	−4.305	0.000
Yokota 2004	−2.000	6.096	37.160	−13.948	9.948	−0.328	0.743
Barragan-Rodriguez 2008	−3.200	24.230	587.091	−50.690	44.290	−0.132	0.895
Guerrero-Romero 2009	0.000	6.893	47.510	−13.510	13.510	0.000	1.000
Lee 2009	0.000	1.504	2.263	−2.949	2.949	0.000	1.000
Barbagallo 2010	−0.200	1.474	2.172	−3.089	2.689	−0.136	0.892
Chacko 2011	−1.700	17.682	312.659	−36.356	32.956	−0.096	0.923
Mooren 2011	−3.960	5.075	25.751	−13.906	5.986	−0.780	0.435
Guerrero-Romero 2011	−5.400	1.653	2.733	−8.640	−2.160	−3.266	0.001
Navarrete-Cortes 2014	0.000	5.091	25.917	−9.978	9.978	0.000	1.000
Solati 2014	−10.700	2.110	4.452	−14.835	−6.565	−5.071	0.000
de Souza e Silva 2014	2.000	2.799	7.832	−3.485	7.485	0.715	0.475
Cosaro 2014	3.240	2.385	5.689	−1.435	7.915	1.358	0.174
Simental-Mendia 2014	−12.600	5.518	30.448	−23.415	−1.785	−2.283	0.022
Rhodriguez-Moran 2014	−9.200	2.159	4.662	−13.432	−4.968	−4.261	0.000
Guerrero-Romero 2015	−11.400	1.206	1.454	−13.763	−9.037	−9.455	0.000
	−4.641	1.511	2.282	−7.602	−1.680	−3.072	0.002



(b)

Study name	Difference in means	Lower limit	Upper limit	P-Value
Paolisso 1989	1.000	−1.498	3.498	0.433
Paolisso 1992	0.150	−1.114	1.414	0.816
Rhodriguez 2003	−0.230	−6.265	5.805	0.940
Guerrero-Romero 2004	−9.600	−57.079	37.879	0.692
Yokota 2004	−2.190	−3.568	−0.812	0.002
Lee 2009	1.300	−0.812	3.412	0.228
Chacko 2011	−2.600	−12.855	7.655	0.619
Mooren 2011	−2.500	−6.830	1.830	0.258
Guerrero-Romero 2011	−2.340	−4.247	−0.433	0.016
Navarrete-Cortes 2014	1.040	0.222	1.858	0.013
Solati 2014	2.550	−3.074	8.174	0.374
de Souza e Silva 2014	−1.900	−5.090	1.290	0.243
Cosaro 2014	1.500	−1.928	4.928	0.391
Rhodriguez -Moran 2014	−3.000	−5.723	−0.277	0.031
Guerrero-Romero 2015	−0.600	−3.222	2.022	0.654
	−0.481	−1.462	0.500	0.336



(c)

Study name	Difference in means	Lower limit	Upper limit	P-Value
Gullestad 1994	0.400	−0.418	1.218	0.338
Corica 1994	−0.100	−0.749	0.549	0.763
Eibl 1995	−0.200	−0.958	0.558	0.605
Eriksson 1995	0.400	−0.432	1.232	0.346
de Valk 1998	0.000	−0.894	0.894	1.000
Lima 1998(a)	0.200	−0.753	1.153	0.681
Lima 1998(b)	−0.300	−1.381	0.781	0.587
Rhodriguez 2003	−2.100	−3.522	−0.678	0.004
Barragan-Rodriguez 2008	−0.100	−1.232	1.032	0.862
Guerrero-Romero 2009	0.200	−0.685	1.085	0.658
Chacko 2011	0.100	−1.284	1.484	0.887
Navarrete-Cortes 2014	−0.200	−1.462	1.062	0.756
Solati 2014	0.290	−0.649	1.229	0.545
Cosaro 2014	0.000	−0.152	0.152	1.000
	−0.001	−0.132	0.130	0.989

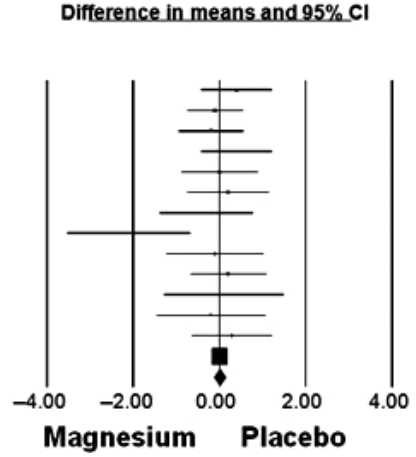
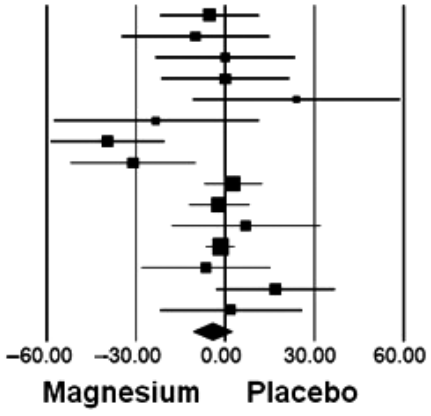


Figure 2 Meta-analysis of the effect of magnesium supplementation on: (a) fasting plasma glucose, (b) fasting plasma insulin, (c) glycated haemoglobin, (d) total cholesterol, (e) high-density lipoprotein, (f) triglycerides, (g) low-density lipoproteins, (h) systolic blood pressure and (i) diastolic blood pressure ($P < 0.05$).

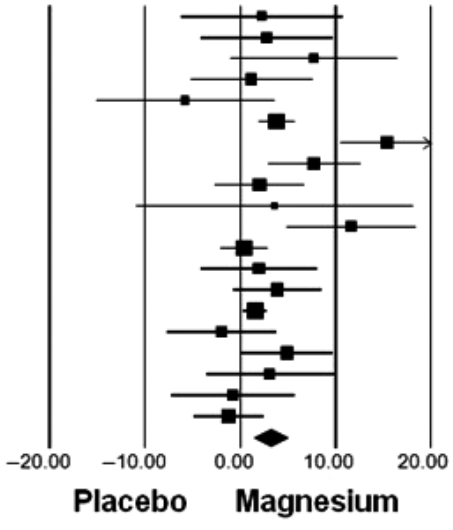
(d)

Study name	Difference in means	Lower limit	Upper limit	*P*-Value
Purvis 1994	−5.300	−21.798	11.198	0.529
Corica 1994	−9.900	−34.767	14.967	0.435
Eibl 1995	0.000	−23.356	23.356	1.000
Eriksson 1995	0.000	−21.428	21.428	1.000
de Valk 1998	23.980	−10.793	58.753	0.177
Rhodriguez 2003	−23.200	−57.664	11.264	0.187
Lal 2003	−39.600	−58.771	−20.429	0.000
Guerrero-Romero 2004	−30.940	−52.005	−9.875	0.004
Yokota 2004	2.600	−7.229	12.429	0.604
Lee 2009	−1.930	−12.125	8.265	0.711
Mooren 2011	6.960	−18.033	31.953	0.585
Navarrete-Cortes 2014	−1.610	−6.556	3.336	0.523
Solati 2014	−6.500	−28.265	15.265	0.558
de Souza e Silva 2014	17.000	−2.982	36.982	0.095
Cosaro 2014	1.940	−21.879	25.759	0.873
	−4.323	−10.841	2.195	0.194



(e)

Study name	Difference in means	Lower limit	Upper limit	*P*-Value
Purvis 1994	2.300	−6.165	10.765	0.59434
Corica 1994	2.790	−4.130	9.710	0.42943
Eibl 1995	7.730	−1.044	16.504	0.08421
Eriksson 1995	1.160	−5.273	7.593	0.72378
de Valk 1998	−5.800	−15.183	3.583	0.22569
Rhodriguez 2003	3.860	1.949	5.771	0.00008
Lal 2003	15.400	10.488	20.312	0.00000
Guerrero-Romero 2004	7.740	2.887	12.593	0.00177
Yokota 2004	2.000	−2.709	6.709	0.40521
Barragan-Rodriguez 2008	3.600	−10.952	18.152	0.62777
Guerrero-Romero 2009	11.600	4.777	18.423	0.00086
Lee 2009	0.380	−2.115	2.875	0.76534
Mooren 2011	1.940	−4.147	8.027	0.53218
Guerrero-Romero 2011	3.870	−0.747	8.487	0.10042
Navarrete-Cortes 2014	1.550	0.331	2.769	0.01269
Solati 2014	−1.950	−7.672	3.772	0.50419
de Souza e Silva 2014	4.900	0.078	9.722	0.04639
Cosaro 2014	3.100	−3.588	9.788	0.36363
Rhodriguez -Moran 2014	−0.800	−7.328	5.728	0.81017
Guerrero-Romero 2015	−1.200	−4.877	2.477	0.52238
	3.197	1.455	4.938	0.00032



(f)

Study name	Difference in means	Lower limit	Upper limit	*P*-Value
Purvis 1994	0.500	−21.816	22.816	0.96497
Corica 1994	−8.700	−32.226	14.826	0.46857
Eibl 1995	−7.730	−29.649	14.189	0.48944
Rhodriguez 2003	−3.870	−42.198	34.458	0.84313
Lal 2003	−48.000	−66.558	−29.442	0.00000
Guerrero-Romero 2004	−34.800	−55.812	−13.788	0.00117
Lee 2009	−3.090	−11.825	5.645	0.48808
Mooren 2011	11.600	−9.676	32.876	0.28526
Navarrete-Cortes 2014	−11.220	−15.015	−7.425	0.00000
Solati 2014	−26.770	−43.856	−9.684	0.00213
de Souza e Silva 2014	12.000	−7.714	31.714	0.23285
Cosaro 2014	−0.390	−23.888	23.108	0.97405
	−10.668	−19.108	−2.228	0.01324

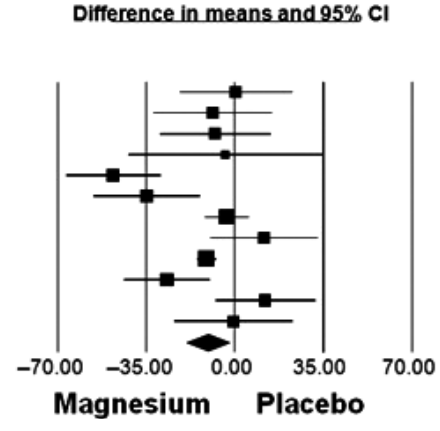
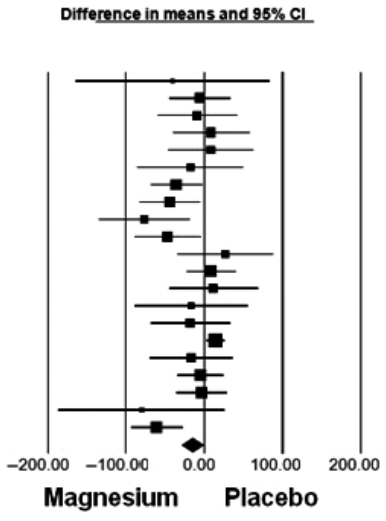


Figure 2 Continued.

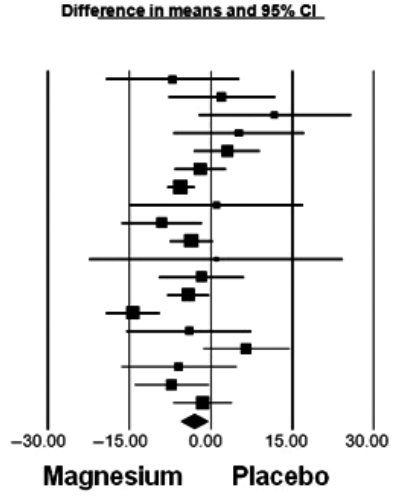
(g)

Study name	Difference in means	Lower limit	Upper limit	*P*-Value
Purvis 1994	−40.740	−164.487	83.007	0.51876
Corica 1994	−6.100	−45.474	33.274	0.76140
Eibl 1995	−8.850	−60.233	42.533	0.73568
Eriksson 1995	8.850	−40.237	57.937	0.72381
de Valk 1998	7.970	−46.810	62.750	0.77552
Rhodriguez 2003	−17.720	−85.528	50.088	0.60852
Lal 2003	−35.500	−68.964	−2.036	0.03760
Guerrero-Romero 2004	−44.280	−82.868	−5.692	0.02451
Yokota 2004	−76.600	−134.841	−18.359	0.00994
Barragan-Rodriguez 2008	−47.000	−89.571	−4.429	0.03047
Guerrero-Romero 2009	26.570	−34.889	88.029	0.39681
Lee 2009	8.860	−22.791	40.511	0.58324
Chacko 2011	11.400	−45.233	68.033	0.69319
Mooren 2011	−16.830	−89.753	56.093	0.65102
Guerrero-Romero 2011	−17.710	−69.044	33.624	0.49893
Navarrete-Cortes 2014	14.180	2.006	26.354	0.02243
Solati 2014	−16.800	−69.835	36.235	0.53469
de Souza e Silva 2014	−5.000	−34.743	24.743	0.74179
Cosaro 2014	−3.540	−36.373	29.293	0.83264
Rhodriguez -Moran 2014	−80.200	−186.555	26.155	0.13942
Guerrero-Romero 2015	−60.600	−93.419	−27.781	0.00030
	−15.323	−28.821	−1.826	0.02608



(h)

Study name	Difference in means	Lower limit	Upper limit	*P*-Value
Purvis 1994	−7.010	−19.261	5.241	0.26208
Eriksson 1995	2.000	−7.799	11.799	0.68913
de Valk 1998	11.800	−2.250	25.850	0.09974
Rhodriguez 2003	5.200	−6.800	17.200	0.39569
Lal 2003	3.000	−3.095	9.095	0.33466
Guerrero-Romero 2004	−2.000	−6.759	2.759	0.41016
Yokota 2004	−5.500	−8.027	−2.973	0.00002
Barragan-Rodriguez 2008	1.100	−14.792	16.992	0.89208
Guerrero-Romero 2009	−9.100	−16.496	−1.704	0.01588
Lee 2009	−3.600	−7.658	0.458	0.08211
Barbagallo 2010	1.000	−22.328	24.328	0.93304
Mooren 2011	−1.700	−9.619	6.219	0.67395
Guerrero-Romero 2011	−4.200	−8.101	−0.299	0.03485
Solati 2014	−14.400	−19.345	−9.455	0.00000
de Souza e Silva 2014	−4.000	−15.562	7.562	0.49774
Cosaro 2014	6.500	−1.453	14.453	0.10916
Simental-Mendia 2014	−5.900	−16.518	4.718	0.27611
Rhodriguez -Moran 2014	−7.200	−14.045	−0.355	0.03924
Guerrero-Romero 2015	−1.500	−6.930	3.930	0.58825
	−3.056	−5.509	−0.603	0.01460



(i)

Study name	Difference in means	Lower limit	Upper limit	*P*-Value
Purvis 1994	−2.270	−9.928	5.388	0.56127
Eriksson 1995	−1.000	−6.542	4.542	0.72361
de Valk 1998	5.800	0.179	11.421	0.04314
Rhodriguez 2003	3.600	−3.831	11.031	0.34233
Lal 2003	5.450	2.013	8.887	0.00189
Guerrero-Romero 2004	−0.100	−4.136	3.936	0.96127
Yokota 2004	−4.000	−9.093	1.093	0.12369
Barragan-Rodriguez 2008	−0.200	−3.203	2.803	0.89614
Guerrero-Romero 2009	−4.100	−7.842	−0.358	0.03174
Lee 2009	−2.100	−5.201	1.001	0.18437
Barbagallo 2010	−3.000	−5.530	−0.470	0.02014
Mooren 2011	−1.600	−7.864	4.664	0.61666
Guerrero-Romero 2011	−3.810	−7.393	−0.227	0.03714
Solati 2014	−7.150	−11.350	−2.950	0.00085
de Souza e Silva 2014	−0.100	−5.682	5.482	0.97199
Cosaro 2014	1.700	−1.489	4.889	0.29609
Simental-Mendia 2014	−1.900	−8.556	4.756	0.57584
Rhodriguez -Moran 2014	−8.000	−12.288	−3.712	0.00026
Guerrero-Romero 2015	−0.900	−5.374	3.574	0.69340
	−1.369	−3.023	0.285	0.10473

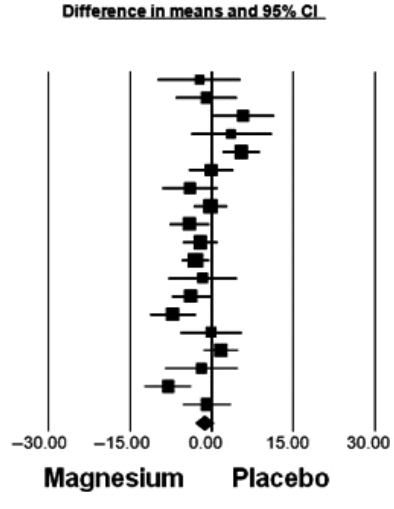


Figure 2 Continued.

FPG ($P = 0.001$). Our results regarding the short-term beneficial effect of Mg supplementation on FPG are different from the results reported by Simental- Mendia *et al.* [30] and this may be the result of a greater number of clinical studies being included in the present meta-analysis.

Mg affects insulin secretion by modulating the opening of a voltage-gated calcium channel in the pancreatic β-cell [16,17]. The included studies did not check the effect of Mg supplementation on insulin secretion, although they reported its effect on FPI. Overall, we did not observe any significant effect of Mg on FPI but, during subgroup analysis, a significant improvement in FPI was observed in the HM population ($P = 0.013$). Hence, adequate intracellular Mg levels may play an important role in insulin secretion.

We did not find any beneficial effect of Mg supplementation on HbA_{1C} during the overall and subgroup analysis. This might be a result of the shorter treatment duration. The actual effect of intervention on HbA_{1C} can be assessed with a treatment duration longer than 3–4 months. Therefore, to determine the effect of Mg supplementation on HbA_{1C}, longer duration trials are needed.

Serum Mg levels are reported to be associated with improved serum levels of VLDL, LDL, HDL and TG [31–38]. Our results depict an overall beneficial effect of Mg on TG, HDL and LDL. Significant variation was observed among diabetic or nondiabetic populations, as well as HM or NM populations, and also with ≤3 months or >3 months of treatment duration. The results of the present study show a positive effect of Mg supplementation on diabetic dyslipidaemia, with a more pronounced effect in HM patients. A beneficial effect of Mg supplementation on HDL and LDL can be obtained after short-term usage, whereas long-term usage is required to obtain a beneficial effect on TG. Hence, Mg supplementation may produce a beneficial effect in diabetic dyslipidaemia. Our results did not show any beneficial effect of Mg supplementation (both overall and at subgroup levels) on TC levels. Interestingly, we found a positive effect of Mg supplementation on HDL levels in the NM population. This may be because of considerable heterogeneity associated with the subgroup or it could be related to the fact that all treatment arms in NM subgroup had mean baseline HDL levels ≤50 mg dL^{-1}. Normal HDL levels ranges from 40 to 60 mg dL^{-1}. Mg supplementation may shift these baseline values towards the higher side of the normal range. Nevertheless, our hypothesis needs clinical validation.

As discussed earlier, an elevated BP also increases the risk of CVD. During the meta-analysis, we found an overall moderate beneficial effect of Mg supplementation on SBP, although there was no effect on DBP, which may be because of the high degree of heterogeneity associated with the population. It is important to note that only four studies were carried out in hypertensive subjects. Hence, more trials need to be conducted in T2D patients with HT to determine any beneficial effect of Mg on SBP and DBP.

Subgroup analysis of different salt forms shows a significant variable effect on various outcomes. This might be the result of a quantitative interaction occurring during the meta-analysis because more studies were conducted with an inorganic salt form. Therefore, to increase the power of the analysis and to assess the effect of the dose of Mg on various confounders, we converted the dose of all salts forms into their elemental Mg content. Meta regression analysis showed an inverse association between Mg dose and all outcomes (except FPI and HbA_{1C}). From the meta-analysis data, it was evident that significant beneficial effects can be obtained with an elemental Mg dose of 300–400 mg. Nevertheless, the bioavailability aspect of different salts of Mg should be considered before making any clinical decision.

There are several limitations of the present meta-analysis that deserves attention.

First, the included studies had a small population size. Second, although beneficial effects were observed in HM populations, the majority of trials were either conducted in NM or did not consider baseline serum Mg levels. Third, fewer trials were conducted in HT patients. Hence, although we observed an overall beneficial effect of Mg supplementation on SBP, its effects in HT patients are still uncertain. Fourth, during the meta-regression analysis, we converted the dose of magnesium salts into their elemental magnesium content, whereas we did not consider the bioavailability aspects of different salts, therefore possibly introducing biasness into the analysis. Organic forms are reported to be more bioavailable than inorganic forms because of a higher solubility in the gastrointestinal milieu [72]. Fifth, obesity is reported to be associated with an increased risk of CVD [73], although the majority of included trials did not correlate body weight to CVD, which can be a potential source of bias. Finally, bias in the results can also be introduced as a result of factors affecting lipid levels within the body. These include renal disease, hypothyroidism, genetically determined lipoprotein disorder, alcohol abuse and oestrogen replacement therapy [10]. Such factors were not considered in any of the included studies.

Conclusions

The present meta-analysis indicates that Mg supplementation can produce a favourable effect on FPG, TG, HDL, LDL and SBP in T2D patients with HM, although current

research is not sufficient for making robust guidelines for clinical practice. There is an urgent need for large RCTs focussing on the many unexplored aspects of Mg supplementation in T2D associated CVD. Noteworthy among them are a consideration of body weight as a possible confounder for CVD development, bioavailability aspects of different salt forms of Mg, various conditions affecting the lipid metabolism in the body and the effect of Mg supplementation in T2D patients with HT.

Transparency declaration

Both HV and RG affirm that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. The reporting of this work is compliant with PRISMA guidelines, 2009.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
No funding is declared.
HV conceived and developed the study protocol, conducted the study and drafted the initial manuscript. RG conducted the study, interpreted the data and critically reviewed the manuscript. Both HV and RG approved the final manuscript submitted for publication.

References

1. Kaku K (2010) Pathophysiology of type 2 diabetes and its treatment policy. *Japan Med Assoc J* **53**, 41–46.
2. Guariguata L, Whiting DR, Hambleton L *et al.* (2014) Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* **103**, 137–149.
3. Zimmet PZ, Magliano DL, Herman WH *et al.* (2014) Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol* **2**, 56–64.
4. Whiting DR, Guariguata L, Weil C *et al.* (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* **94**, 311–321.
5. Shaw JW, Sicree RA & Zimmet PZ (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* **87**, 4–14.
6. Joseph JJ & Golden SH (2014) Type 2 diabetes and cardiovascular disease: what next? *Curr Opin Endocrinol Diabetes Obes* **21**, 109–120.
7. Sattar N (2013) Revisiting the links between glycaemia, diabetes and cardiovascular disease. *Diabetologia* **56**, 686–695.
8. Boden WE, Probstfield JL, Anderson T *et al.* (2011) Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* **365**, 2255–2267.
9. HTC Group, Landray MJ, Haynes R *et al.* (2014) Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* **371**, 203–212.
10. Taskinen MR & Boren J (2015) New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis* **239**, 483–495.
11. Georg P & Ludvik B (2000) Lipids and diabetes. *J Clin Basic Cardiol* **3**, 159–162.
12. Viljoen, A & Wierzbicki, AS. Dyslipidemia: diabetes lipid therapies. In: *Textbook of Diabetes*. pp. 672–683 [Holt RIG, Cockram CS, Flyvbjerg A & Goldstein BJ, editors]. Boston, MA: Blackwell Science; 2010.
13. Halacheva L, Kolev N & Kostov K (2015) Basics of magnesium homeostasis. *Science & Technologies* **5**, 33–37.
14. Raynor LA, Pankow JS, Duncan BB *et al.* (2013) Novel risk factors and the prediction of type 2 diabetes in the atherosclerosis risk in communities (ARIC) study. *Diabetes Care* **36**, 70–76.
15. Barbagallo M & Dominguez LJ (2015) Magnesium and type 2 diabetes: an update. *Int J Diabetes Clin Res* **2**, 1–5.
16. Sales CH & Pedrosa LFC (2006) Magnesium and diabetes mellitus: their relation. *Clin Nutr* **25**, 554–562.
17. Long S & Romani AMP (2014) Role of cellular magnesium in human diseases. *Austin J Nutr Food Sci* **2**, 1051.
18. Chaudhary DP, Sharma R & Bansal DD (2010) Implications of magnesium deficiency in type 2 diabetes: a review. *Biol Trace Elem Res* **134**, 119–129.
19. Rao YS & Rao VD (2016) Serum magnesium levels in type 2 diabetes. *Int J Res Med Sci* **4**, 991–994.
20. Ramadass S, Basu S & Srinivasan AR (2015) Serum magnesium levels as an indicator of status of diabetes mellitus type 2. *Diabetes Metab Syndr* **9**, 42–45.
21. Chutia H & Lynrah KG (2015) Association of serum magnesium deficiency with insulin resistance in type 2 diabetes mellitus. *J Lab Physicians* **7**, 75–78.
22. El-said NH, Sadik NA & Mohammed NA (2015) Magnesium in type 2 diabetes mellitus and its correlation with glycemic control. *Int J Res Med Sci* **3**, 1958–1963.
23. Kulkarni AG, Shendge SK & Shinde V (2014) Study of serum magnesium levels in type 2 diabetes mellitus. *IOSR-JDMS* **13**, 115–119.

24. Hruby A, Meigs JB, O'Donnell CJ *et al.* (2014) Higher magnesium intake reduces risk of impaired glucose and insulin metabolism and progression from prediabetes to diabetes in middle-aged americans. *Diabetes Care* **37**, 419–427.
25. Hyassat D, Sitri EA, Batieha A *et al.* (2014) Prevalence of hypomagnesaemia among obese type 2 diabetic patients attending the National Center for Diabetes, Endocrinology and Genetics (NCDEG). *Int J Endocrinol Metab* **12**, e17796.
26. Mamatha BV, Shankarprasad DS & Manjula R (2014) A comparative study of serum magnesium in type 2 diabetes mellitus patients and non-diabetics and its correlation with glycemic status. *Int J Bioassays* **3**, 3395–3398.
27. Maula MG, Sarkar CR, Zahid AR *et al.* (2013) Serum magnesium level in type II diabetes mellitus. *Dinajpur Med Col J* **6**, 123–127.
28. Evangelopoulos AA, Vallianou NG, Panagiotakos DB *et al.* (2008) An inverse relationship between cumulating components of the metabolic syndrome and serum magnesium levels. *Nutr Res* **28**, 659–663.
29. Song Y, He K, Levitan EB *et al.* (2006) Effects of oral magnesium supplementation on glycaemic control in type 2 diabetes: a meta-analysis of randomized double blind controlled trials. *Diabet Med* **23**, 1050–1056.
30. SimentalMendía LE, Sahebkar A & RodríguezMorán M (2016) Guerrero Romero F. A systematic review and meta-analysis of randomized controlled trials on the effects of magnesium supplementation on insulin sensitivity and glucose control. *Pharmacol Res* **111**, 272–282.
31. Walter RM Jr, Uriu-Hare JY, Olin KL *et al.* (1991) Copper, zinc, manganese, and magnesium status and complications of diabetes mellitus. *Diabetes Care* **14**, 1050–1056.
32. Antin SS, Kashinkunti M, Kataria AV *et al.* (2014) A cross sectional study of fasting serum magnesium levels in the patients with type 2 diabetes mellitus and its relation to diabetic complications. *Sch J App Med Sci* **2**, 502–506.
33. Khubchandani AS & Sanghani H (2013) Study of serum magnesium and HbA_{1C} in diabetic patients along with changes in their lipid profiles. *IJCP* **23**, 717–719.
34. Wang J, Persuitte G, Olendzki BC *et al.* (2013) Dietary magnesium intake improves insulin resistance among non-diabetic individuals with metabolic syndrome participating in a dietary trial. *Nutrients* **5**, 3910–3919.
35. Mishra S, Padmanaban P, Deepti GN *et al.* (2012) Serum magnesium and dyslipidemia in type-2 diabetes mellitus. *Biomed Res* **23**, 295–300.
36. Rasheed H, Elahi S & Ajaz H (2012) Serum magnesium and atherogenic lipid fractions in type II diabetic patients of Lahore, Pakistan. *Biol Trace Elem Res* **148**, 165–169.
37. Agrawal P, Arora S, Singh B *et al.* (2011) Association of macrovascular complications of type 2 diabetes mellitus with serum magnesium levels. *Diabetes Metab Syndr* **5**, 41–44.
38. Haglin L, Bäckman L & Tornkvist B (2011) A structural equation model for assessment of links between changes in serum triglycerides,-urate, and -glucose and changes in serum Calcium, -magnesium and -phosphate in type 2 diabetes and non-diabetes metabolism. *Cardiovasc Diabetol* **10**, 116.
39. Liberati A, Altman DG, Tetzlaff J *et al.* (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* **6**, e1000100.
40. Deeks JJ, Higgins JPT & Altman DG (2008) Analysing data and undertaking meta-analyses. In: *Cochrane Handbook of Systemic Reviews of Interventions*. pp. 243–296 [Higgins JPT & Green S, editors]. Chichester: John Wiley & Sons Ltd.
41. Hozo SP, Djulbegovic B & Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* **20**, 13.
42. Singh YR, Verma S, Agrawal D *et al.* (2015) A study of magnesium supplementation on glycemic control in patients of type-2 diabetes mellitus. *IJCAP* **2**, 26–30.
43. Ble-Castillo JL, Navarrete-Cortes A, Guerrero-Romero F *et al.* (2014) Effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients. *Atherosclerosis* **235**, e84–e191.
44. Lal J, Vasudev K, Kela AK *et al.* (2003) Effect of oral magnesium supplementation on lipid profile and blood glucose of patients with type 2 diabetes mellitus. *JAPI* **51**, 37–42.
45. Yokota K, Kato M, Lister F *et al.* (2004) Clinical efficacy of magnesium supplementation in patients with type 2 diabetes. *J Am Coll Nutr* **23**, 506S–509S.
46. Paolisso G, Sgambato S, Pizza G *et al.* (1989) Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care* **12**, 265–269.
47. Paolisso G, Sgambato S, Gambardella A *et al.* (1992) Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* **55**, 1161–1167.
48. Paolisso G, Scheen A, Cozzolino D *et al.* (1994) Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients. *J Clin Endocrinol Metab* **78**, 1510–1514.
49. Gullestad L, Jacobsen T & Dolva LO (1994) Effect of magnesium treatment on glycemic control and metabolic parameters in NIDDM patients. *Diabetes Care* **17**, 460–461.
50. Purvis JR, Cummings DM, Landsman P *et al.* (1994) Effect of oral magnesium supplementation on selected cardiovascular risk factors in non-insulin-dependent diabetics. *Arch Fam Med* **3**, 503–508.
51. Corica F, Allegra A, Di Benedetto A *et al.* (1994) Effects of oral magnesium supplementation on plasma lipid

concentrations in patients with non-insulin-dependent diabetes mellitus. *Magnes Res* **7**, 43–47.
52. Eibl NL, Kopp HP, Nowak HR *et al.* (1995) Hypomagnesemia in type II diabetes: effect of a 3-month replacement therapy. *Diabetes Care* **18**, 188–192.
53. Eriksson J & Kohvakka A (1995) Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab* **39**, 217–223.
54. de Valk HW, Verkaaik R, van Rijn HJ *et al.* (1998) Oral magnesium supplementation in insulin-requiring type 2 diabetic patients. *Diabet Med* **15**, 503–507.
55. de Lordes Lima M, Cruz T, Pousada JC *et al.* (1998) The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* **21**, 682–686.
56. Rodríguez-Moran M & Guerrero-Romero F (2003) Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care* **26**, 1147–1152.
57. Guerrero-Romero F, Tamez-Perez HE, González-González G *et al.* (2004) Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. *Diabetes Metab* **30**, 253–258.
58. Barragan-Rodríguez L, Rodríguez-Moran M & Guerrero-Romero F (2008) Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. *Magnes Res* **21**, 218–223.
59. Guerrero-Romero F & Rodríguez-Moran M (2009) The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial. *J Hum Hypertens* **23**, 245–251.
60. Lee S, Park HK, Son SP *et al.* (2009) Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults. *Nutr Metab Cardiovasc Dis* **19**, 781–788.
61. Barbagallo M, Dominguez LJ, Galioto A *et al.* (2010) Oral magnesium supplementation improves vascular function in elderly diabetic patients. *Magnes Res* **23**, 131–137.
62. Chacko SA, Sul J, Song Y *et al.* (2011) Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. *Am J Clin Nutr* **93**, 463–473.
63. Mooren FC, Kruger K, Volker K *et al.* (2011) Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects – a double-blind, placebo-controlled, randomized trial. *Diabetes Obes Metab* **13**, 281–284.
64. Guerrero-Romero F & Rodriguez-Moran M (2011) Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. *Eur J Clin Invest* **41**, 405–410.
65. Navarrete-Cortes A, Ble-Castillo JL, Guerrero-Romero F *et al.* (2014) No effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia. *Magnes Res* **27**, 48–56.
66. Solati M, Ouspid E, Hosseini S *et al.* (2014) Oral magnesium supplementation in type II diabetic patients. *Med J Islam Repub Iran* **28**, 67.
67. De Souza E, Silva MLL, Cruz T *et al.* (2014) Magnesium replacement does not improve insulin resistance in patients with metabolic syndrome: A 12-week randomized double-blind study. *J Clin Med Res* **6**, 456–462.
68. Cosaro E, Bonafini S, Montagnana M *et al.* (2014) Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome. *Nutr Metab Cardiovasc Dis* **24**, 1213–1220.
69. Simental-Mendia LE, Rodriguez-Moran M & Guerrero-Romero F (2014) Oral magnesium supplementation decreases C-reactive protein levels in subjects with prediabetes and hypomagnesemia: a clinical randomized double-blind placebo-controlled trial. *Arch Med Res* **45**, 325–330.
70. Rodriguez-Moran M & Guerrero-Romero F (2014) Oral magnesium supplementation improves the metabolic profile of metabolically obese, normal-weight individuals: a randomized double-blind placebo-controlled trial. *Arch Med Res* **45**, 388–393.
71. Guerrero-Romero F, Simental-Mendia LE, Hernandez-Ronquillo G *et al.* (2015) Oral magnesium supplementation improves glycaemic status in subjects with prediabetes and hypomagnesaemia: a double-blind placebo-controlled randomized trial. *Diabetes Metab* **41**, 202–207.
72. Coudray C, Rambeau M, Feillet-Coudray C *et al.* (2005) Study of magnesium bioavailability from ten organic and inorganic Mg salts in Mg-depleted rats using a stable isotope approach. *Magnes Res* **18**, 215–223.
73. Mathieu P, Lemieux I & Després JP (2010) Obesity, inflammation, and cardiovascular risk. *Clin Pharmacol Ther* **87**, 407–416.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Figure S1. Meta-regression analysis of the effect of elemental magnesium dose on: (a) fasting plasma glucose, (b) fasting plasma insulin, (c) glycated haemoglobin, (d) total cholesterol, (e) high-density lipoprotein, (f) triglycerides, (g) low-density lipoproteins, (h) systolic blood pressure and (i) diastolic blood pressure ($P < 0.05$).
Figure S2. Meta-regression analysis of effect of duration of therapy on: (a) fasting plasma glucose, (b)

fasting plasma insulin, (c) glycated haemoglobin, (d) total cholesterol, (e) high-density lipoprotein, (f) triglycerides, (g) low-density lipoproteins, (h) systolic blood pressure and (i) diastolic blood pressure ($P < 0.05$).

Figure S3. Funnel plots for assessment of publication bias: (a) fasting plasma glucose, (b) fasting plasma insulin, (c) glycated haemoglobin, (d) total cholesterol, (e) high-density lipoprotein, (f) triglycerides, (g) low-density lipoproteins, (h) systolic blood pressure and (i) diastolic blood pressure ($P < 0.05$).

Table S1. Summary of the different studies included in the systematic review.

Table S2. Assessment of the risk of bias in accordance with the Cochrane risk of bias assessment tool.

Table S3. Subgroup analysis of various study outcomes at a 95% confidence interval.

Table S4. Assessment of the risk of publication bias.