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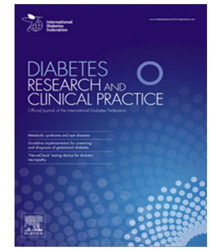

Association of low serum magnesium with diabetes and hypertension: Findings from Qatar Biobank study

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ABSTRACT

Aim: We aimed to examine the association between serum magnesium and diabetes and hypertension among Qatari adults.
Methods: In the cross-sectional study, we used data from 9693 Qatari participants aged 20 years and above attending the Qatar Biobank (QBB) Study. Blood samples were analyzed in a central lab. Habitual food consumption was assessed by a food frequency questionnaire. Reduced rank regression was used to construct magnesium related dietary pattern (MRDP) using serum magnesium as a response variable. Diabetes was defined by blood glucose, HbA1c or known diabetes. Prediabetes was defined as HbA1c between 5.7% and 6.4%. Subclinical magnesium deficiency was defined as serum magnesium <0.85 mmol/L.
Results: The prevalence of diabetes, prediabetes and subclinical magnesium deficiency was 18.9%, 11.5% and 59.5%, respectively. Across the quartiles of serum magnesium from high to low, the prevalence ratios (PR 95%CI) for diabetes were 1.00, 1.35, 1.88, and 2.70 (95%CI 2.38–3.05), respectively (p for trend <0.001). The presence of hypertension significantly increased the probability of diabetes along a wide range of low serum magnesium. A low intake of MRDP was also positively associated with diabetes and high HbA1c.
Conclusion: Subclinical magnesium deficiency is common in Qatar and associates with diabetes, prediabetes and hypertension in Qatari adults.
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1. Introduction

Qatar is one of the nations with the highest prevalence of type 2 diabetes (T2DM) with 18.97% Qatari adults aged 18–64 years had diabetes [1]. Qatari diabetics have fivefold more diabetes risk factors due to lifestyle and environment than others [2], and the reason for this difference is poorly understood. Like other parts of the world, diabetes in Qatar is likely the interplay of gene and environment including an unhealthy diet. High consumption of refined grains, sugar and energy dense processed food is of concern [3]. One of the consequences of this dietary pattern is a low intake of magnesium.

Epidemiological studies suggest that high magnesium intake is associated with a low risk of diabetes [4] and

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metabolic syndrome [5,6] as well as low levels of systematic inflammation [7–9]. Magnesium intake may improve dyslipidemia, oxidative stress and insulin sensitivity among those with type 2 diabetes [10]. Furthermore magnesium supplementation reduces the glucose levels among people with diabetes [11], and the level of inflammation [12].

Subclinical magnesium deficiency is highly prevalent but largely unrecognized [13]. It is because the current reference interval for serum magnesium was based on the distribution in a normal population (i.e. 0.75–0.95 mmol/L) but not based on the association between serum magnesium and health outcomes [14]. Although there was no overt signs of clinical magnesium deficiency in the healthy population, relatively low magnesium status has been found to be associated with several health outcomes including hypertension, cardiovascular diseases and diabetes [14]. The majority of the studies on the association between magnesium status and diabetes have been conducted in the USA, Europe and some Asian countries [15,16].

The major dietary sources of magnesium intake include whole grains, legumes, nuts, and green leafy vegetables. In modern societies, the intake of magnesium is generally below the recommended level. One of the reasons for the inadequate intake of magnesium is a high intake of refined grains (as magnesium is lost during the refining process) and a low intake of whole grains [13].

Despite widely used, the traditional single nutrient intake and disease association approach used in nutritional epidemiology has limitations. It does not consider the potential interactions between nutrients and foods in the diet. There is an increasing number of studies using dietary patterns (especially using the reduced rank regression (RRR) method) and disease association approach [17]. The advantage of the RRR method is that it uses biomarkers (e.g. C reactive protein, lipids) or nutrients as intermedia responses so that it can explore the potential mediation effects of diet on disease. No study has used serum magnesium as an intermediate response variable to construct dietary patterns. A recent study from the QBB cohort which included only 1000 subjects revealed low magnesium levels among diabetics compared to non-diabetics [18].

The current study aimed to assess the association between serum magnesium levels, hypertension and diabetes as well as insulin resistance among adults attending Qatar Biobank study.

2. Methods

2.1. *Study design and sample*

The Qatar Biobank Study started in 2012 and aimed to recruit 60,000 participants aged above 18 years who are Qatari nationals or those lived in the country above 15 years. The detail of the study design was published elsewhere [19]. By end of 2018, about 15,000 participants took part in the study. A self-administered questionnaire was used to collect sociodemographic information, lifestyle factors and dietary habits. Information of health condition, family history of diseases, and medication use were collected during a nurse interview. Participants were invited to have a health examination in the Qatar Biobank facility at Hamad Medical City. Blood samples were collected for measurement of 66 biomarkers including magnesium and C-reactive protein. In the current analysis, we included a random sample of 9693 Qatari participants aged 20–67 years who gave blood samples, had measured serum magnesium and completed the food frequency questionnaire. Those with missing values of serum magnesium or food intake or age <20 years were excluded. All participants gave informed consent. The Qatar Biobank study was approved by the Institutional Review Board from the Hamad Medical Corporation Ethics Committee. The current analysis was approved under the IRB exempted category (Ex-2018-RES-ACC-0125-0069).

2.2. *Outcome variable: Diabetes, insulin resistance and glycemic control*

Diabetes was defined based on the following criteria: fasting blood glucose ≥7 mmol/L or random blood glucose ≥11.0 mmol/L, or HbA1c ≥6.5%, or self-reported diabetes [20]. Prediabetes was defined as HbA1c between 5.7% and 6.4%.

The homeostasis model of assessment of insulin resistance (HOMA-IR) was used to evaluate insulin resistance (fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L)/22.5) [21]. We define HOMA-IR ≥2.8 as having insulin resistance based on the ROC analysis using diabetes as an outcome measure.

2.3. *Exposure variable: Serum magnesium, magnesium related dietary pattern (MDRP)*

Serum magnesium was measured in a central laboratory of the Qatar Biobank Study using an automated colorimetric method (Magnesium Gen.2 from Roche Diagnostics, Indianapolis, IN). The assay's coefficients of variations are 0.3%–0.8%. Subclinical magnesium deficiency was defined as serum magnesium <0.85 mmol/L [14].

Habitual food intake was assessed by a food frequency questionnaire (FFQ). The FFQ included 102 commonly consumed food items in Qatar. It was developed based on the FFQ used in the European Prospective Investigation of Cancer (EPIC) study. However, it has not been validated in Qatar. The FFQ asked participants to report their usual intake (never to ≥2 times/day). In the analysis, the food frequency consumption was recoded to times/week based on the following rules: never or rarely (0), 1–3 times per month (0.5), 1–3 times per week (2), 4–6 times per week (5), once per day (7) and two or more times per day (14). Based on the similarity of nutrient profiles or culinary use, food intake was collapsed into 38 food groups before further analysis.

MRDP was constructed using RRR analysis with the intakes of 38 collapsed food groups as input variables. PROC PLS statement in SAS (SAS Institute Inc., Cary, North Carolina) was used to conduct RRR analysis using serum magnesium as the response variable [17]. MRDP score was calculated as the sum of the products of the factor loading coefficients and standardized weekly intake of each food group associated with the pattern.

2.4. Covariates

The following variables were treated as covariates in the analysis: age, gender, education (low: primary and secondary school; medium: technical or professional school; high: university and postgraduate degree), leisure time physical activity level (metabolic equivalent of task (MET), recoded as tertiles), smoking (non-smokers, ex-smokers and current smokers). Overweight was defined as a BMI of 25.0–29.9 kg/m^2; obesity is defined as a BMI $\geq$ 30 kg/m^2. C-reactive protein was used as an indicator of inflammation and recoded into <6 mg/L or $\geq$6 mg/L. A family history of diabetes was defined as having a sibling with diabetes. Hypertension was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg, or having known hypertension. Kidney function was evaluated by the estimated glomerular filtration rate (eGFR). eGFR was calculated by the adaptation of the CKD-EPI creatinine equation [22]. Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min/1.73 m^2. Participants were asked about the use of medication for the treatment of diabetes and hypertension. However, information on the specific type of medicine was not available except insulin use.

2.5. Data analyses

Serum magnesium and MRDP score were recoded into quartiles. Data were reported as means ± SD and the chi square test was used to compare differences between groups for categorical variables and ANOVA for continuous variables. Poisson regression models with robust variance were used to assess the association (prevalence ratio (PR)) between the exposure variables (i.e. serum magnesium and MDRP) and outcomes (diabetes, insulin resistance, poor glycemic control) [23]. PR derived from Poisson regression is a better measurement of the association than odds ratio from logistic regression when the prevalence of the outcome is above 10%. A set of three models were used: model 1 adjusted for age and gender; model 2 further adjusted for smoking, education, physical activity and intake of fruits and vegetables; and model 3 further adjusted for BMI (normal, overweight and obese) and CRP. In sensitivity analyses, we further adjusted for eGFR after excluded those with eGFR <90 mL/min/1.73 m^2. The multiplicative interaction between magnesium, MRDP and hypertension was tested by adding the product term of the two variables in the multivariable model. *Marginsplot* command in Stata was used to visually present the interaction. The non-linear association between the duration and diabetes was tested using logistic regression with the adjustment of age and gender. The association was visually presented using margins and marginsplot command in Stata. The association between serum magnesium/magnesium related dietary pattern and log transformed HOMA-IR was assessed using quantile regression with the adjustment of age, gender, BMI, smoking, education and physical activity. All the analyses were performed using STATA 15.1 (Stata Corporation, College Station). Statistical significance was considered when $p < 0.05$ (two sided).

3. Results

3.1. Descriptive results

The mean ± SD serum magnesium was 0.83 ± 0.07 mmol/L and 98.9% of the participants had serum magnesium between 0.65 and 1.05 mmol/L (Supplement Fig. 1). The prevalence of subclinical magnesium deficiency was 59.5% (53.0% in men and 65.0% in women). In those with diabetes, the prevalence of subclinical magnesium deficiency was 77.2%.

In the sample, 1834 subjects (18.9%) had diabetes (18.3% of men and 19.5% of women). A total of 1639 subjects (16.9%) were previously diagnosed with diabetes; 78% of them recorded the year of onset of diabetes providing an average duration of diabetes of 11.4 ± 8.4 years; 423 (25.8%) were using insulin and 1153 (70.4%) were under treatment with other medication for diabetes. Two percent of the cohort had newly discovered diabetes and 11.5% had prediabetes. The prevalence of CKD was 0.77%. Overall, 994 participants had eGFR below 90 mL/min/1.73 m^2. Table 1 shows the sample characteristics across quartiles of serum magnesium levels. Women were more likely to have low magnesium than men. Across the quartiles of serum magnesium from high to low, the prevalence of obesity, hypertension, dietary supplement use and high CRP increased but the education and physical activity level decreased. There was no difference in fruit and vegetable intake by quartiles of serum magnesium level. Participants in the first quartile of serum magnesium were older than other groups. The prevalence of poor glycemic control was 49.9% among those with known diabetes and increased with the decrease of serum magnesium level. There was a non-linear association between the duration of diabetes and subclinical magnesium deficiency; the probability of magnesium deficiency increased with duration of diabetes up to ~14 years and decreased after 20 years (Supplement Fig. 2).

MRDP was characterized by a high intake of red meat, nuts, soup, and coffee but a low intake of white bread, biryani, Arabic bread, and cooked vegetables (Supplement Fig. 3). The pattern explained 0.90% of the variance of serum magnesium. No participants reported using magnesium supplement other than the use of multiple vitamin and minerals supplement (n = 5740, 59.2%).

3.2. Association between serum magnesium and diabetes

Low serum magnesium was positively associated with diabetes and undiagnosed diabetes. The prevalence of diabetes was 10.2%, 13.2%, 18.2% and 34.1% across quartiles of serum magnesium from high to low, respectively. In the fully adjusted model, across quartiles of serum magnesium from high to low, the prevalence ratios (PR 95%CI) for diabetes were 1.00, 1.35, 1.88, and 2.70 (95%CI 2.38–3.05), respectively (p for trend <0.001) (Table 2). A similar trend was observed for undiagnosed diabetes with PRs across quartiles of magnesium of 1.00, 1.29, 2.31, and 2.22 (95%CI 1.49–3.31) (p for trend <0.001), respectively. Further adjusting for hypertension medication did not change the above association (data not shown).

Table 1 – Sample characteristics by quartiles of serum magnesium.

	Q1 N = 2,423	Q2 N = 2,423	Q3 N = 2,424	Q4 N = 2,423	p-value
Magnesium (mmol/L)	0.74 (0.04)	0.81 (0.01)	0.85 (0.01)	0.91 (0.04)	<0.001
Age	41.1 (11.7)	38.9 (11.2)	39.4 (11.3)	40.3 (11.4)	<0.001
Gender					<0.001
Male	923 (38.1%)	1031 (42.6%)	1174 (48.4%)	1382 (57.0%)	
Female	1500 (61.9%)	1392 (57.4%)	1250 (51.6%)	1041 (43.0%)	
Education					<0.001
Low	521 (21.5%)	390 (16.1%)	335 (13.8%)	350 (14.5%)	
Medium	721 (29.8%)	715 (29.5%)	673 (27.8%)	635 (26.2%)	
High	1180 (48.7%)	1318 (54.4%)	1416 (58.4%)	1437 (59.3%)	
Smoking					<0.001
Non	1714 (70.7%)	1634 (67.4%)	1557 (64.2%)	1403 (57.9%)	
Smoker	364 (15.0%)	432 (17.8%)	454 (18.7%)	582 (24.0%)	
Ex-smoker	345 (14.2%)	357 (14.7%)	413 (17.0%)	438 (18.1%)	
Leisure time physical activity (MET hours/week)	18.1 (39.2)	19.9 (39.8)	20.4 (36.5)	23.4 (43.3)	<0.001
BMI (kg/m^2)	30.9 (6.4)	29.9 (6.2)	29.4 (6.0)	29.0 (5.6)	<0.001
BMI categories					<0.001
Normal	381 (15.7%)	506 (20.9%)	545 (22.5%)	555 (22.9%)	
Overweight	787 (32.5%)	813 (33.6%)	862 (35.6%)	925 (38.2%)	
Obese	1253 (51.8%)	1103 (45.5%)	1017 (42.0%)	941 (38.9%)	
Ferritin (μg/L)	64.3 (110.1)	66.2 (81.5)	76.2 (92.7)	85.1 (88.2)	<0.001
CRP > 6 mg/L	764 (31.5%)	613 (25.3%)	551 (22.7%)	527 (21.7%)	<0.001
Dietary supplement use	1502 (62.0%)	1465 (60.5%)	1397 (57.6%)	1376 (56.8%)	<0.001
Vitamin D or Calcium supplement use	110 (4.5%)	115 (4.7%)	91 (3.8%)	69 (2.8%)	0.003
Vegetable intake (times/week)	19.2 (15.3)	19.1 (15.5)	18.5 (15.1)	18.7 (15.3)	0.40
Fruit intake (times/week)	8.3 (7.7)	8.2 (7.4)	8.2 (7.3)	8.2 (7.5)	0.93
eGFR (mL/min/1.73 m^2)	108.6 (15.7)	110.0 (14.3)	108.2 (14.5)	106.0 (15.3)	<0.001
CKD	29 (1.2%)	15 (0.6%)	11 (0.5%)	20 (0.8)	0.021
C-peptide (nmol/L)	2.4 (1.5)	2.2 (1.3)	2.2 (1.4)	2.3 (1.3)	0.011
HbA1C (mmol/L)	6.2 (1.7)	5.6 (1.1)	5.5 (0.9)	5.4 (0.7)	<0.001
HbA1C ≥ 7 mmol/L among known diabetes (%)	60.3	44.0	38.8	30.7	<0.001
Hypertension	489 (20.2%)	277 (11.4%)	290 (12.0%)	311 (12.8%)	<0.001
Diabetes	826 (34.1%)	441 (18.2%)	320 (13.2%)	247 (10.2%)	<0.001
Prediabetes (HbA1c = 5.7–6.4%)	216 (8.9%)	263 (10.9%)	303 (12.5%)	328 (13.5%)	<0.001
Normal HbA1C with no diabetes and no prediabetes	1381(57.0%)	1719(71.0%)	1801(74.3%)	1848(76.3%)	<0.001
HOMA-IR > 2.8 (for fasting samples)	663(42.3%)	518(24.5%)	471 (29.4%)	465 (28.3%)	<0.001
Family history of diabetes	814 (33.6%)	672 (27.7%)	607 (25.0%)	632 (26.1%)	<0.001
Insulin use	231 (9.5%)	86 (3.5%)	60 (2.5%)	46 (1.9%)	<0.001
Diabetes medication other than insulin	615 (25.4%)	260 (10.7%)	162 (6.7%)	116 (4.8%)	<0.001
Hypertension medication use	394 (16.3%)	212 (8.7%)	190 (7.8%)	194 (8.0%)	<0.001

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures.

Low serum magnesium was also positively associated with insulin resistance. In the fully adjusted model, the PRs (95%CI) for insulin resistance across quartiles of serum magnesium from high to low were 1.00, 1.03 (0.93–1.14), 1.12 (1.02–1.24), and 1.26 (1.15–1.37) (p for trend <0.001), respectively.

Low serum magnesium was positively associated with prediabetes. Compared with the highest quartile of serum magnesium, the lowest quartile had a PR of 1.19 (95% CI 1.02–1.39) after adjusting for sociodemographic and lifestyle factors (Model 2). The association was attenuated after further adjustment of BMI, CRP and hypertension.

A significant inverse association of serum magnesium/magnesium related dietary pattern with log HOMA-IR levels was observed. The association between serum magnesium and log HOMA-IR appeared to be greater when the quantile levels of log HOMA-IR were higher (Supplement Fig. 4).

3.3. *Association between MRDP and diabetes*

A low intake of MRDP was associated with an increased likelihood of having diabetes. In the fully adjusted model, across the quartiles of MRDP from high to low, the PRs (95%CI) for diabetes were 1.00, 1.07 (0.96–1.20), 1.06 (0.95–1.19) and 1.18 (1.06–1.33), respectively (Table 3). In sensitivity analyses, the above association remained unchanged with further adjustment of eGFR after excluded those with eGFR below 90 mL/min/1.73 m^2.

There was no association between MRDP and undiagnosed diabetes or insulin resistance. However, MRDP was associated with log transformed HOMA-IR. After adjusting for age, gender, smoking, physical activity, education, and family history of diabetes, across the quartiles of dietary pattern from high to low, the regression coefficients for log HOMA-IR was 0, 0.02 (-0.02, 0.07), 0.03(−0.02, 0.07) and 0.06(0.01–0.10) (p for trend 0.021), respectively (data not shown).

Table 2 – Prevalence ratio (95%CI) for diabetes and undiagnosed diabetes by quartiles of serum magnesium.

	Q1 (Low)	Q2	Q3	Q4 (High)	p for trend
Diabetes					
Model 1	3.15 (2.79–3.57)	2.03 (1.77–2.33)	1.39 (1.20–1.62)	1.00	<0.001
Model 2	2.86 (2.53–3.23)	1.91 (1.67–2.19)	1.36 (1.18–1.57)	1.00	<0.001
Model 3	2.70 (2.38–3.05)	1.88 (1.64–2.16)	1.35 (1.17–1.56)	1.00	<0.001
Sensitivity analysis	2.73 (2.36–3.16)	1.90 (1.62–2.22)	1.41 (1.19–1.67)	1.00	<0.001
Undiagnosed diabetes					
Model 1	2.42 (1.62–3.61)	2.55 (1.74–3.72)	1.34 (0.89–2.03)	1.00	<0.001
Model 2	2.33 (1.56–3.48)	2.48 (1.70–3.62)	1.34 (0.89–2.02)	1.00	<0.001
Model 3	2.22 (1.49–3.31)	2.31 (1.58–3.37)	1.29 (0.86–1.94)	1.00	<0.001
Sensitivity analysis	2.24 (1.38–3.63)	2.59 (1.64–4.10)	1.47 (0.90–2.41)	1.00	<0.001
Insulin resistance					
Model 1	1.47 (1.34–1.62)	1.21 (1.09–1.34)	1.07 (0.96–1.19)	1.00	<0.001
Model 2	1.40 (1.28–1.54)	1.17 (1.06–1.29)	1.06 (0.95–1.17)	1.00	<0.001
Model 3	1.26 (1.15–1.37)	1.12 (1.02–1.24)	1.03 (0.93–1.14)	1.00	<0.001
Sensitivity analysis	1.32 (1.19–1.46)	1.17 (1.05–1.30)	1.08 (0.97–1.21)	1.00	<0.001
Poor glycemic control among known diabetes					
Model 1	1.83 (1.50–2.22)	1.29 (1.04–1.61)	1.18 (0.93–1.49)	1.00	<0.001
Model 2	1.82 (1.49–2.21)	1.29 (1.04–1.60)	1.17 (0.93–1.48)	1.00	<0.001
Model 3	1.77 (1.46–2.14)	1.28 (1.03–1.59)	1.17 (0.93–1.47)	1.00	<0.001
Sensitivity analysis	1.81 (1.45–2.26)	1.33 (1.04–1.70)	1.15 (0.88–1.50)	1.00	<0.001
Prediabetes					
Model 1	1.23 (1.05–1.43)	1.17 (1.01–1.35)	1.11 (0.97–1.27)	1.00	0.005
Model 2	1.19 (1.02–1.39)	1.14 (0.98–1.31)	1.09 (0.95–1.25)	1.00	0.018
Model 3	1.12 (0.96–1.30)	1.09 (0.94–1.25)	1.07 (0.93–1.22)	1.00	0.137
Sensitivity analysis	1.15 (0.97–1.36)	1.12 (0.96–1.31)	1.05 (0.91–1.23)	1.00	0.073

Model 1 adjusted for age and gender.
Model 2 further adjusted for education, smoking, leisure time physical activity, family history of diabetes.
Model 3 further adjusted for BMI, hypertension and CRP.
Sensitivity analysis: model 3 further adjusted for eGFR after excluded those with eGFR < 90 mL/min/1.73 m^2.

3.4. *Interaction between serum magnesium and hypertension*

There was a significant interaction between serum magnesium and hypertension in relation to diabetes ($p < 0.001$). Subjects with hypertension and low serum magnesium level had a significantly high marginal probability of diabetes (Fig. 1). However, no such interaction was observed between MRDP and hypertension.

Serum magnesium and MRDP were positively associated with hypertension after adjustment for age, gender, smoking, education, BMI and physical activity (Supplement Fig. 5).

4. Discussion

In this large cross-sectional study, we found that low serum magnesium is positively associated with diabetes, prediabetes, insulin resistance, and poor glycemic control. There was a significant interaction between serum magnesium and hypertension in relation to diabetes. Subjects with low serum magnesium and hypertension had a high likelihood of having diabetes. A low intake of MRDP was also positively associated with diabetes, and poor glycemic control. The strength of the association between dietary pattern and diabetes was weaker than the association between serum magnesium and diabetes. Among those with known diabetes, the duration of diabetes was positively associated with subclinical magnesium deficiency.

4.1. *Comparison with other studies-high prevalence of subclinical magnesium deficiency*

High prevalence of subclinical magnesium deficiency (~60%) was previously reported in several western countries and Iran [13,14,24]. However, the prevalence of subclinical magnesium deficiency in our study was much higher than the findings from Iran. In Iran, the prevalence of hypomagnesemia (serum magnesium <0.75 mmol/L) was 4.6% among participants of the Tehran Lipid and Glucose Study [24]. Using the same cut-off of 0.75 mmol/L, we found that the prevalence of hypomagnesemia was 9.8% in our sample. Consistent with current knowledge, in our study the risk of having subclinical magnesium deficiency increased with the duration of diabetes among those with known diabetes. It suggests that low serum magnesium levels may be a consequence of having diabetes in the sample.

4.2. *Association of low serum magnesium with diabetes and insulin resistance*

Our findings of the positive association between low magnesium and diabetes and insulin resistance are in line with findings from other countries [14]. In a 10 year follow-up study, it has been shown that low serum magnesium concentration

Table 3 – Prevalence ratio (95%CI) for diabetes and undiagnosed diabetes by quartiles of magnesium related dietary pattern.

	Q1 (Low)	Q2	Q3	Q4 (High)	p for trend
Diabetes					
Model 1	1.29 (1.15–1.45)	1.10 (0.98–1.24)	1.12 (1.00–1.26)	1.00	<0.001
Model 2	1.24 (1.11–1.39)	1.08 (0.96–1.21)	1.09 (0.97–1.23)	1.00	<0.001
Model 3	1.18 (1.06–1.33)	1.06 (0.95–1.19)	1.07 (0.96–1.20)	1.00	0.005
Sensitivity analysis	1.18 (1.04–1.33)	1.04 (0.92–1.18)	1.05 (0.93–1.19)	1.00	0.012
Undiagnosed diabetes					
Model 1	1.11 (0.75–1.64)	0.91 (0.62–1.32)	0.78 (0.53–1.16)	1.00	0.519
Model 2	1.12 (0.76–1.65)	0.90 (0.62–1.32)	0.78 (0.52–1.16)	1.00	0.503
Model 3	1.00 (0.68–1.48)	0.85 (0.58–1.24)	0.71 (0.48–1.06)	1.00	0.823
Sensitivity analysis	1.03 (0.67–1.59)	0.76 (0.49–1.17)	0.63 (0.39–1.00)	1.00	0.755
Insulin resistance					
Model 1	1.06 (0.96–1.17)	0.98 (0.89–1.08)	1.01 (0.92–1.12)	1.00	0.366
Model 2	1.04 (0.94–1.14)	0.96 (0.87–1.06)	1.00 (0.91–1.11)	1.00	0.671
Model 3	0.99 (0.91–1.09)	0.94 (0.86–1.03)	0.98 (0.89–1.07)	1.00	0.705
Sensitivity analysis	1.00 (0.90–1.10)	0.95 (0.86–1.05)	0.96 (0.87–1.07)	1.00	0.909
Poor glycemic control among known diabetes					
Model 1	1.21 (1.04–1.41)	1.19 (1.02–1.38)	1.09 (0.93–1.28)	1.00	0.007
Model 2	1.20 (1.03–1.40)	1.18 (1.01–1.38)	1.09 (0.93–1.27)	1.00	0.009
Model 3	1.17 (1.01–1.37)	1.17 (1.00–1.37)	1.08 (0.92–1.27)	1.00	0.021
Sensitivity analysis	1.24 (1.05–1.47)	1.22 (1.02–1.45)	1.13 (0.95–1.34)	1.00	0.007
Prediabetes					
Model 1	1.08 (0.93–1.25)	1.01 (0.87–1.17)	1.00 (0.86–1.16)	1.00	0.339
Model 2	1.03 (0.89–1.20)	0.97 (0.84–1.13)	0.97 (0.84–1.13)	1.00	0.676
Model 3	1.00 (0.86–1.16)	0.96 (0.83–1.11)	0.93 (0.81–1.08)	1.00	0.935
Sensitivity analysis	0.93 (0.79–1.09)	0.91 (0.78–1.07)	0.83 (0.70–0.98)	1.00	0.608

Model 1 adjusted for age and gender.
Model 2 further adjusted for education, smoking, leisure time physical activity, family history of diabetes.
Model 3 further adjusted for BMI, hypertension and CRP.
Sensitivity analysis: model 3 further adjusted for eGFR after excluded those with eGFR < 90 mL/min/1.73 m^2.

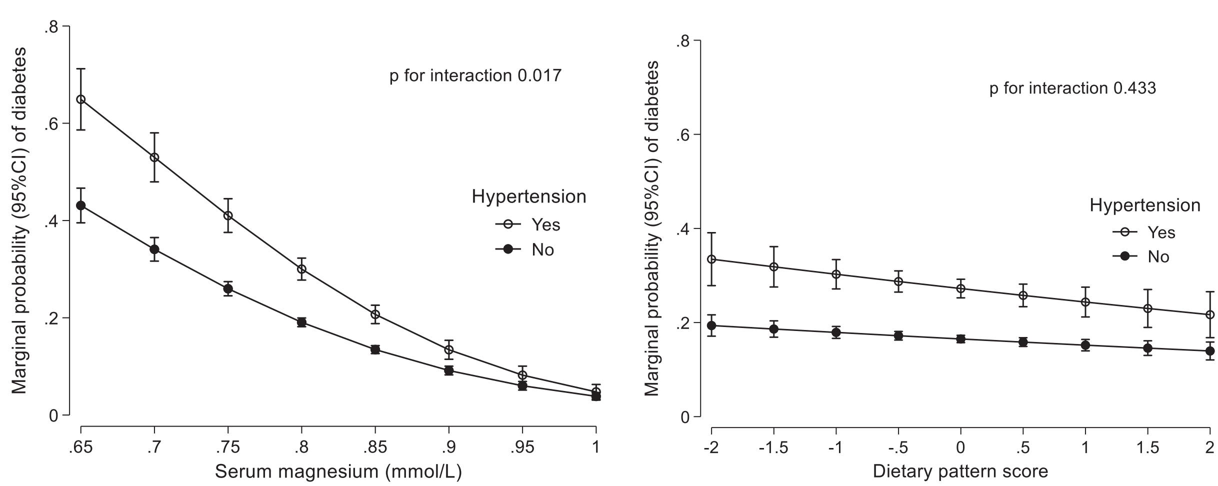

Fig. 1 – Interaction between serum magnesium, magnesium related dietary pattern and hypertension in relation to diabetes. Values were marginal mean probability of diabetes (95%CI) derived from logistic regression adjusted for education, smoking, leisure time physical activity, family history of diabetes using margins command after logistic regression in Stata 15. p for interaction between serum magnesium and hypertension was 0.017. p for interaction between magnesium related dietary pattern and hypertension was 0.433.

(<0.74 mmol/L) was associated with increased risk of developing diabetes among Mexican adults aged 20–65 years [25]. Randomized clinical trials found that magnesium supplementation improves insulin sensitivity [26].

In our study, diabetes duration was associated with magnesium deficiency; this raises the hypothesis that renal dysfunction associated with diabetes may lead to magnesium loss.

4.3. Refined grain consumption, desalinated water and magnesium intake

Using the RRR method we identified a magnesium related dietary pattern. The pattern is characterized by a high intake of red meat, nuts, coffee and low intake of white bread, Arabic bread, and cooked vegetables. The composition of the MRDP is supported by the fact that red meat, nuts and coffee have high levels of magnesium, while plant-based food including white bread and Arabic bread has low levels of magnesium.

The intake of refined grain (rice and wheat) has been found to be a risk factor for diabetes. It is often attributed to the high glycemic index and glycemic load [27]. However, refined grains have a low content of magnesium due to the refining process. Therefor high intake of refined grain diets may contribute to the diabetes risk. Inadequate intake of magnesium has not been recognized as a problem in Qatar. The latest national report on nutrition did not even report the intake of magnesium [3]. Findings from other countries suggest that suboptimal intake of magnesium is common. For example, about half of Americans consume less than the Estimated Average Requirement for magnesium [28].

In Qatar, a high proportion of drinking water is through the desalination of seawater. The magnesium levels in the water supply and bottled water are around 4 mg/L. Thus, a low level of water magnesium may also contribute to the deficiency of magnesium in the population.

Consistent with the positive association between low serum magnesium and diabetes, there was also a positive association between a low intake of MRDP and diabetes. However, the strength of the association between MRDP and diabetes was weaker than the association between serum magnesium and diabetes. It could be due to the fact that diet is not a strong predictor of serum magnesium. In the study, MRDP can only explain 0.9% of the variance of serum magnesium. This is supported by the current knowledge of the regulation of serum magnesium [13]. Among the determinants of serum magnesium, the use of vitamin D and calcium supplement is not negligible in Qatar. It is known that vitamin D and calcium supplement use increases the risk of magnesium deficiency [13]. Although the prevalence of vitamin D and calcium supplement use was low, the overall dietary supplement was very high (~60%). Dietary aluminum may lead to magnesium deficit by reducing the absorption of magnesium by five folds [29]. Modern lifestyle uses aluminum containing products widely (e.g. aluminum cookware, baking powder, baked goods) and can be a significant contributor to magnesium deficiency. In Qatar, eating deserts is a cultural norm with an average consumption of sugar and sweets of 120 g/d [3]. Although the data on dietary aluminum intake is not available, it is expected that exposure is high. Furthermore, in modern diet, the intake of phosphorus is high [30], which can also contribute to magnesium deficiency [31].

Although this cross-sectional study cannot conclude a causal relationship between magnesium related dietary pattern and diabetes, the findings are in line with other cohort studies. In a *meta*-analysis of 13 prospective cohort studies, Dong *et al* found that every 100 mg/day increment in magnesium intake was associate with a 14% (95%CI 11–18%) decreased risk of diabetes [4]. A strong dose response relationship between MRDP and poor glycemic control among those with diabetes suggest the importance of the magnesium rich diet in the management of diabetes in the study population.

4.4. Interaction between serum magnesium and hypertension

To the best of our knowledge, this is the first study reporting an interaction between serum magnesium and hypertension in relation to diabetes. The role of magnesium in blood pressure regulation has been widely studied. Findings from randomized control trials suggest that magnesium supplementation reduces blood pressure [32]. In the current study, the prevalence of hypertension was the highest in the lowest quartile of serum magnesium. Those with hypertension and low serum magnesium had the highest likelihood of having diabetes. At the serum magnesium level of 0.75 mmol/L, those with hypertension had more than 40% probability of having diabetes. A high intake of magnesium related dietary pattern is associated with a lower prevalence of diabetes and hypertension in our study. Studies are needed to assess whether magnesium supplementation will benefit the control of both hypertension and diabetes in those with subclinical magnesium deficiency.

The study has several limitations. Firstly, the cross-sectional study design does not allow a causal relationship to be made. Secondly, the FFQ does not have information on portion size. We are not able to accurately estimate the intake of magnesium. The association between dietary pattern and diabetes may be under or over estimated. Thirdly, we are unable to adjust for the hypertension and diabetes medication use. The strength of the study is its large sample size and the ability to adjust for a variety of confounding factors.

In conclusion, subclinical magnesium deficiency is common also in Qatar and associates with diabetes and hypertension. Further longitudinal and interventional studies are needed to elucidate the role of magnesium in the etiology of diabetes in the population.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Author contributions

Z.S. contributed to the conception, analysis, and interpretation of data; drafting of the report; and have given approval of the final version for publication. A.B.A.S. contributed to analysis and interpretation of the data, commented on the report, and has given approval of the final version for publication.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107903.

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