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Improved Magnesium Levels in Morbidly Obese Diabetic and Non-diabetic Patients After Modest Weight Loss

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Abstract

Serum magnesium (Mg) is reported to be reduced in individuals with obesity, hypertension, and diabetes mellitus and has been suggested as a marker for metabolic syndrome. We have studied changes in serum Mg concentrations in a group of obese patients ($n = 92$) with and without diabetes mellitus after weight loss induced by dieting and bariatric surgery. At inclusion, 11% (10/92) of the population had severe Mg deficiency (< 0.75 mmol/L) and median serum Mg was lower in diabetic ($n = 20$) compared to non-diabetic ($n = 72$) patients ($p = 0.002$). A weight loss of 10 kg after 8 weeks of lifestyle interventions was accompanied by increased serum Mg of about 5% in both diabetic and non-diabetic patients. Serum Mg remained stable thereafter in the non-diabetic patients, while it continued to increase in the diabetic patients after bariatric surgery. Six months after bariatric surgery, there was no significant difference in serum Mg concentration between the groups ($p = 0.08$). The optimal range of circulating Mg concentration is not known, but as even small increments in serum Mg are reported to lower the risk of cardiovascular and ischemic heart disease, our results are interesting in a public health perspective.

Keywords Bariatric surgery · Diabetes mellitus · Magnesium · Metabolic syndrome · Obesity · Weight loss

Introduction

Obesity induces a variety of physiological changes, predisposing the individual to comorbidities like type 2 diabetes, hypertension, dyslipidemia, and coronary heart disease [1]. This is particularly alarming, given the fact that obesity prevalence is increasing worldwide [2]. Weight loss is associated with improvement in metabolic function [3] and can be achieved by lifestyle interventions, dieting, and physical exercise [4]; however, most individuals fail to maintain the weight loss and return to their initial weight [5]. Alternatively, morbidly obese patients may be referred to bariatric surgery [6], which is associated with long-term weight loss and reduced prevalence of obesity-related comorbidities [7].

Serum magnesium (Mg) is reported to be reduced in individuals with obesity [8], diabetes, and hypertension [9] and has been suggested as a marker and possible pathogenic factor in the cascade of signs and symptoms characterizing metabolic syndrome [8, 10]. Increased serum Mg concentrations have been reported after bariatric surgery-induced weight loss [11]. Mg, the second most abundant intracellular cation in the body, is known to be an essential cofactor in more than 300 enzymatic reactions. The electrolyte is taken up in the intestine, stored in the bone, and excreted by the kidneys. Studies have suggested a role for parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) for regulating Mg absorption [12], but Mg homeostasis is still not well understood. Mg is vital for activation of the insulin receptor β-subunit, and patients with type 2 diabetes are reported to have lower serum Mg concentrations compared to controls [13]. Additionally, Mg supplementation is considered to have a beneficial effect on insulin resistance [14].

We have studied changes in serum Mg concentrations in a group of patients with a BMI ≥ 35, who underwent lifestyle interventions followed by Roux-en-Y gastric bypass (RYGB) during a period of 14 months. The purpose was to study

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changes in serum Mg related to weight loss and a diagnosis of diabetes mellitus.

Materials and Methods

Subjects

Patients aged 18 to 60 years eligible for bariatric surgery due to a BMI $\geq$ 40 kg/m^2 or a BMI $\geq$ 35 with serious weight-related comorbidities like type 2 diabetes or cardiovascular disease ($n = 159$) were consecutively recruited at Innlandet Hospital Trust, Gjøvik, Norway, during a period from 2012 to 2014. Exclusion criteria were major psychiatric disorders, serious somatic disorders not related to obesity, alcohol or drug addiction, former obesity surgery, and other major abdominal surgeries. The present study is part of a larger study program on bio-psycho-social impacts of morbid obesity. The enrolled patients took part in an initial 8-week course of nutritional counseling and physical exercise, followed by laparoscopic gastric bypass. Information about diet and use of supplements, control of weight and blood pressure, and blood sampling was done at inclusion, after the first 8 weeks (i.e., immediately preoperatively), and 6 and 12 months after surgery.

Ethical approval of the protocol was obtained by the Regional Committee for Medical and Health Research Ethics (REK), Region South-East, Norway, ref. number 2012/1394. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients before enrolment.

Micronutrient Supplements

During the 8-week course of lifestyle intervention before surgery, no supplements were recommended, but eight patients continued previously prescribed supplements (per oral folate, vitamin B_{12} and vitamin B_6 combination ($n = 3$), vitamin D-calcium combination ($n = 2$), multivitamin/mineral supplement ($n = 2$), and intramuscular vitamin B_{12} injections ($n = 1$)).

After surgery, the patients were recommended a daily iron (100 mg), calcium (1000 mg), and vitamin D (20 μg) supplement for 6 months; intramuscular vitamin B_{12} injections (1 mg) every third month; and lifelong daily multivitamin/mineral supplements. Over-the-counter multivitamin/mineral supplements in Norway contain 5–10 μg vitamin D and up to 100 mg Mg per tablet.

Biochemical Analyses

Serum Mg and HbA1c were analyzed on Cobas c501 (Roche Diagnostics, USA) and serum PTH (1–84) and vitamin D were analyzed on Cobas e601 (Roche Diagnostics, USA) at a routine laboratory at Innlandet Hospital Trust, Gjøvik, Norway.

Roux-en-Y Bariatric Surgery Procedure

The surgical technique of laparoscopic Roux-en-Y gastric bypass (RYGB) involves transection of the upper part of the stomach leaving about 30 mL, which is then anastomosed with the distal jejunum, resulting in bypass of the remaining major part of the stomach, duodenum, and proximal jejunum. The smaller functional stomach pouch results in earlier satiety and thus restricted food intake. Furthermore, the food in this stomach pouch bypasses the duodenum and enters directly into the distal jejunum, leading to malabsorption of calories and nutrients in the small intestine.

Statistical Analysis

Results are presented as mean and standard deviation (SD), compared by Student's *t* test or ANOVA, and median and interquartile range (IQR), compared by Mann-Whitney *U* test or Kruskal-Wallis test. Chi-square test was used for categorical data. Spearman correlations were used to explore relationships between data.

Data on blood pressure (BP) at inclusion and 6 months after bariatric surgery were missing for 33/92 patients (36%), and paired sample test was used when comparing the change in BP for the remaining 59 patients.

Graphical illustrations of the relationship between serum Mg and weight loss in kilograms after 8 weeks of lifestyle interventions were obtained by generalized additive models (GAM) and corrected for a diagnosis of diabetes.

The SPSS statistical package (version 23, IBM®SPSS®, Chicago, IL, USA) and the package "mgcv" in R, version 3.3 (The R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses. Two-sided p-values < 0.05 were considered statistically significant.

Results

Demographics

Among the 159 enrolled patients, 92 had available data on serum Mg and were included in the study. After 8 weeks of lifestyle interventions, 81 patients (88%) returned for bariatric surgery. After bariatric surgery, 79 patients (86%) returned for follow-up after 6 months and 74 patients (80%) returned after 12 months.

At inclusion, 20 of the 92 (22%) patients had a diagnosis of diabetes mellitus confirmed by HbA1c. Demographic characteristics according to diabetes mellitus at inclusion are given in

Table 1. Apart from a higher percentage of patients with hypertension and a lower percentage of women in the diabetic group, no significant differences in baseline characteristics were observed between the diabetic and non-diabetic patients.

Information on the use of supplements were available for 59 of the 92 patients (64%) at inclusion and 48% of these reported regular use of multivitamin/mineral supplements, with no significant difference between the groups ($p = 0.29$). At inclusion, there were no significant differences in serum levels of Mg and vitamin D according to the use of supplements ($p = 0.38$).

Weight Loss in Diabetic and Non-diabetic Patients

Total mean weight loss from inclusion to 12 months after surgery in the diabetic group was 36.1 (SD 12.6) kg (subdivided into: mean 10.7 (SD 4.6) kg after 8 weeks, 21.5 (6.7) kg 6 months after surgery, and 4.0 (5.3) kg 12 months after surgery). In the non-diabetic group, total mean weight loss was 42.3 (SD 12.0) kg, (subdivided into: mean 9.3 (SD 4.7) kg after 8 weeks, 26.2 (7.9) kg 6 months after surgery, and 6.6 (6.9) kg 12 months after surgery).

Changes in Serum Mg, HbA1c, PTH, and Vitamin D after Weight Loss in Diabetic and Non-diabetic Patients

At inclusion, median serum Mg was significantly lower in diabetic compared to non-diabetic patients (Table 2). Ten of 92 (11%) patients had a severe Mg deficiency, defined as a serum Mg < 0.75 mmol/L, and this was more prevalent in diabetic (6/20, 30%) than in non-diabetic patients (4/72, 6%) ($p = 0.002$).

Median serum Mg increased by 5% in the diabetic patients and by 6% in the non-diabetic patients after a modest weight loss induced by 8 weeks of lifestyle interventions (Table 2). At this time point, we observed a dose-response relationship between serum Mg and weight loss in kilograms corrected for a diagnosis of diabetes (Fig. 1).

After bariatric surgery, serum Mg continued to increase to a total of 12% in the diabetic patients, while it remained stable in the non-diabetic patients (Table 2). Six months after surgery, all patients had a serum Mg concentration ≥ 0.75 mmol/L.

HbA1c was significantly reduced from inclusion to 12 months after surgery in both diabetic (− 23%, $p < 0.001$) and non-diabetic patients (− 7%, $p < 0.001$) (Table 2). In the diabetic patients, serum Mg was inversely correlated to HbA1c at inclusion (Spearman's rho − 0.31, $p = 0.19$), and after 8 weeks (rho − 0.52, $p = 0.05$), but not after bariatric surgery ($p > 0.4$). In the non-diabetic patients, there was a positive correlation between Mg and HbA1c which gradually decreased from inclusion (rho = 0.32, $p = 0.006$) to 12 months after surgery (rho = 0.18, $p = 0.18$).

Median PTH level was significantly higher in non-diabetic compared to diabetic patients at inclusion. During follow-up, the level increased somewhat in the diabetics (7%) and was significantly reduced in non-diabetic patient (− 14%) (Table 2).

Median vitamin D was higher in diabetic patients compared to non-diabetics at inclusion and showed no significant change after weight loss in diabetics. In non-diabetic patients, vitamin D concentrations increased by 49% during follow-up (Table 2).

Changes in Blood Pressure 6 Months After Bariatric Surgery

Data on BP was available for 59 patients both at inclusion and 6 months after bariatric surgery. Mean systolic BP was

Table 1 Baseline characteristics in diabetic and non-diabetic patients admitted for bariatric surgery ($n = 92$)

Parameters	Diabetic patients $N = 20$	Non-diabetic patients $N = 72$	p value
Age, years, mean (SD)	45.5 (8.1)	42.1 (8.8)	0.12[1]
Female gender, n (%)	11 (55)	57 (79)	0.03[2]
BMI, kg/m^2, mean (SD)	41.8 (4.1)	42.6 (4.1)	0.42[1]
Waist circumference, cm, mean (SD)	133 (11)	127 (13)	0.12[1]
Systolic blood pressure, mm Hg, mean (SD)[3]	139 (10)	141 (17)	0.72[1]
Diastolic blood pressure, mm Hg, mean (SD)[3]	89 (12)	88 (7)	0.71[1]
Current diagnosis of hypertension, n (%)	13 (65)	19 (29)	0.003[2]
Daily smoker, n (%)	4 (20)	14 (20)	0.64[2]
Fulltime occupation, n (%)	6 (30)	37 (54)	0.12[2]
Married/cohabitant, n (%)	15 (88)	55 (89)	0.96[2]

[1] Compared by Student's t test

[2] Compared by Pearson chi-square test

[3] $N = 74$, missing data for 18 patients

Table 2 BMI and biochemical parameters in patients before and after weight loss in diabetic and non-diabetic patients\

Parameters	At inclusion		After 8 weeks of diet and physical exercise		After gastric bypass				p value[1] Kruskal-Wallis	
	$N = 92$				6 months		12 months			
			$N = 81$		$N = 79$		$N = 74$			
	Diabetic $N = 20$	Non-diabetic $n = 72$	Diabetic $N = 15$	Non-diabetic $n = 66$	Diabetic $N = 16$	Non-diabetic $n = 63$	Diabetic $N = 14$	Non-diabetic $n = 60$	Diabetic $N = 14$	Non-diabetic $n = 60$
Body mass index, kg/m^2	41.5 (39.2, 43.7)	41.7 (39.5, 45.0)	37.6 (36.4, 40.4)	39.0 (36.7, 41.1)	30.8 (28.1, 33.6)	30.4 (27.6, 33.1)	29.7 (27.3, 33.1)	27.7 (24.9, 30.0)	< 0.001	< 0.001
p value[2]	0.47		0.20		0.55		0.15			
Serum magnesium, mmol/L	0.77 (0.73, 0.85)	0.83 (0.78, 0.90)	0.81 (0.76, 0.89)	0.88 (0.82, 0.93)	0.82 (0.79, 0.87)	0.87 (0.81, 0.89)	0.86 (0.82, 0.90)	0.88 (0.83, 0.92)	0.001	0.003
p value[2]	0.007		0.03		0.08		0.56			
HbA1c	7.3 (6.7, 8.5)	5.4 (5.1, 5.6)	6.3 (6.1, 7.0)	5.2 (5.0, 5.5)	5.5 (5.2, 6.5)	4.9 (4.7, 5.2)	5.6 (5.1, 6.2)	5.0 (4.8, 5.1)	< 0.001	< 0.001
p value[2]	< 0.001		< 0.001		< 0.001		< 0.001			
PTH, pmol/L	5.0 (2.9, 6.9)	6.6 (5.0, 7.9)	4.4 (4.0, 5.1)	5.3 (4.1, 7.3)	5.5 (3.8, 6.9)	5.5 (4.5, 6.5)	5.4 (4.6, 6.5)	5.8 (4.5, 6.9)	0.16	0.004
p value[2]	0.006		0.03		0.45		0.70			
Vitamin D, nmol/L	64 (55, 72)	47 (37, 67)	63 (47, 96)	53 (31, 76)	75 (53, 88)	68 (52, 87)	70 (58, 91)	70 (53, 88)	0.10	< 0.001
p value[2]	0.03		0.13		0.81		0.79			

[1] Median (IQR) compared by Kruskal-Wallis test, for diabetic and non-diabetic patients respectively

[2] Median (IQR) compared by Mann-Whitney U test

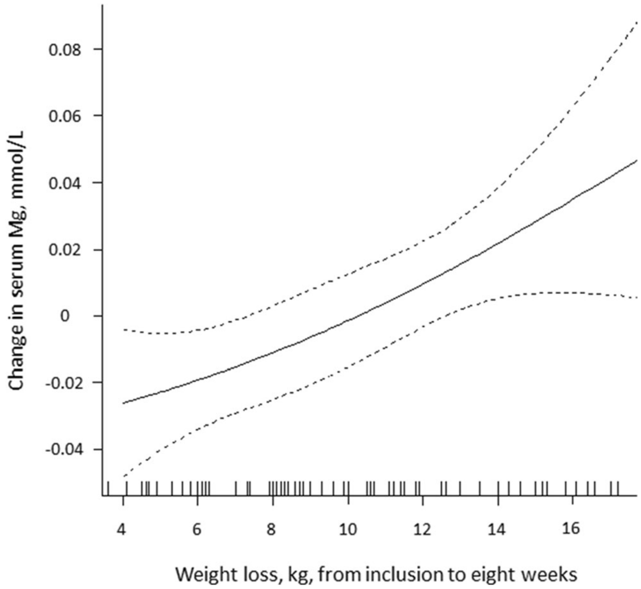

Fig. 1 Change in serum magnesium (Mg), mmol/L, according to weight loss from inclusion to 8 weeks, corrected for a diagnosis of diabetes

significantly reduced from 141 (SD 16) mmHg at inclusion to 126 (SD 15) mmHg6 months after surgery ($p < 0.001$), and mean diastolic BP from 89 (SD 12) mmHg to 82 (SD 11) mmHg ($p = 0.001$). Apart from a positive correlation between systolic and diastolic BP and PTH at inclusion (systolic BP, $r = 0.37$, $p = 0.001$, and diastolic BP, $r = 0.24$, $p = 0.04$), no significant correlations were observed between blood pressure and biochemical parameters at any time point.

Discussion

A modest weight loss of approximately 10 kg after 8 weeks of lifestyle interventions increased serum Mg by about 5% in obese patients. The improvement in Mg levels during this period was not related to intake of supplements. In diabetic patients, serum Mg continued to increase also after surgery, while it remained stable in the non-diabetic patients. Median serum Mg was lower in diabetic than in non-diabetic obese patients at inclusion, but the serum levels became identical 12 months after bariatric surgery. Weight loss significantly reduced HbA1c in both diabetic and non-diabetic patients, and the initial inverse correlation to serum Mg disappeared.

Serum Mg Homeostasis

Serum Mg concentrations are reported to be inversely associated with the incidence of hypertension, type 2 diabetes, and coronary heart disease, but the optimal range of circulating Mg concentration is not known [9]. Since less than 1% of the whole body Mg is present in serum, a serum value within the reference interval does not exclude Mg deficiency, but a serum Mg concentration below 0.75 mmol/L is considered indicative of severe deficiency [15]. In principle, low Mg levels may be due to poor nutrition or absorption, hypercalcemia, hyperthyroidism, hyperaldosteronism, or renal tubular disorders, but factors that control Mg absorption are not well understood. A role for both PTH and the active vitamin D, 1,25-dihydroxyvitamin D, has been proposed, but this is still controversial [12].

In the present study, vitamin D was given as a supplement after bariatric surgery, and the levels increased in both groups, significantly only in the non-diabetics who had a lower serum vitamin D concentration at inclusion compared to the diabetic patients. As diabetic patients have regular medical checkups, vitamin deficiencies are more likely to be diagnosed and treated, which might explain the higher vitamin D status in diabetics compared to non-diabetics at inclusion.

Median PTH level was lower at inclusion and increased slightly in diabetic patients, while it decreased during follow-up in the non-diabetics. However, neither PTH nor vitamin D concentrations were correlated to serum Mg at inclusion or during follow-up.

Inadequate Mg concentrations are seen in 35% of obese patients prior to bariatric surgery [16]. The low serum Mg concentrations observed in obese individuals have recently been proposed to be due to hyperglycemia rather than obesity in non-diabetic individuals [10]. In our population of obese patients, there was an initial inverse correlation between HbA1c and serum Mg, which disappeared after weight loss. The reduction in HbA1c following weight loss might have contributed to the increment in serum Mg in both diabetic and non-diabetic patients. Low Mg levels in diabetics may in part be precipitated by glucose-induced osmotic diuresis and reduced tubular reabsorption of Mg [17]. In diabetic patients, serum Mg is found to be 0.08 mmol/L lower compared to controls [18]. Thus, our result of 0.06 mmol/L lower median serum Mg in diabetic compared to non-diabetic obese patients is in accordance with previous observations.

Mg Concentrations after Bariatric Surgery

Different methods of bariatric surgery are associated with different effects on Mg status, but the results are conflicting, as gastric bypass is reported to both reduce and increase Mg levels. Dalcanale et al. found that about 30% of patients treated with Roux-en-Y gastric bypass were Mg deficient [19]. However, their data suggest that Mg deficiency was already present preoperatively. Johansson reported a 6% increase in serum Mg, from 0.80 to 0.85 mmol/L, after RYGB, which is in accordance with our observations [20].

Magnesium and Metabolic Syndrome

The prevalence of obesity is increasing worldwide, predisposing the individual to comorbidities like type 2 diabetes, hypertension, and dyslipidemia [21]. Studies find an inverse relation between serum Mg concentrations and blood pressure [22], cardiovascular disease [23], and HbA1c [24]. We did not find any relation between serum Mg and blood pressure at inclusion or during follow-up in the present study, but the number of blood pressure measurements during follow-up was inadequate for definite conclusions.

A deficient magnesium status as found in morbidly obese patients may result in a defective tyrosine-kinase activity at the insulin receptor level and impairment in insulin action with worsening of insulin resistance, and secondary also worsening of other elements in the metabolic syndrome, including the increased risk of cardiovascular events [25].

A dose-response relationship between dietary Mg intake and cardiovascular mortality has been reported [26]. Even small increments in serum Mg are said to lower the risk of cardiovascular and ischemic heart disease [27]. It has been suggested that treatment of hypomagnesaemia might improve glycemic control [28]. In this respect, our observation of increased serum Mg after a modest weight loss in both diabetic and non-diabetic obese patients is of interest in a public health perspective.

Strength and Limitations

There is currently no gold standard for the determination of Mg status. For serum Mg values from 0.75 to 0.85 mmol/L, a loading test is considered to be the most accurate way to assess Mg deficiency. Measurement of Mg in muscle cells or in the bone is another approach; however, these methods still lack standardized protocols and the need for biopsies limits clinical use. Neither of these tests was done in this study, which is a limitation. Another limitation is incomplete data on blood pressure during follow-up, which made it impossible to evaluate clinical effects of weight loss and serum Mg changes.

Conclusion

In our population of obese patients, median serum Mg was initially lower in diabetic compared to non-diabetic patients, but became equal after bariatric surgery. A modest weight loss of approximately 10 kg after 8 weeks of lifestyle interventions increased serum Mg by about 5% in both diabetic and non-diabetic patients. As even small increments in serum Mg are reported to lower the risk of cardiovascular and ischemic heart disease, our results are interesting in a public health perspective.

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Author Contributions S Meyer Mikalsen and A-L Bjørke-Monsen analyzed the data and wrote the paper, J.E. Whist revised the paper, and J Aaseth wrote the paper. All authors approved the final version.

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Compliance with Ethical Standards

Ethical approval of the protocol was obtained by the Regional Committee for Medical and Health Research Ethics (REK), Region South-East, Norway, ref. number 2012/1394. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients before enrolment.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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