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Review

Influence of Magnesium Sulphate on Cholecystokinin, Hunger, and Obesity

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Abstract. *Aim:* Magnesium has many important functions in the body and one of its less known roles is its contribution to weight management. It triggers the release of cholecystokinin from the small intestines, which leads to suppression of hunger, lowers food intake, and reduces body weight. In this article we reviewed research that investigates this process as well as the individual steps of this pathway. *Methods:* Comprehensive literature search was done in September 2019 with several databases using the key words "magnesium AND (cholecystokinin OR hunger OR obesity)" and research was critically evaluated. *Results:* The ability of magnesium to stimulate the release of cholecystokinin was demonstrated in many animal and human studies. The influence of cholecystokinin on hunger/satiety sensation and or food intake was shown in several experimental models. Some studies demonstrated the overall link between magnesium intake and obesity. *Conclusions:* Even if there is still some controversy, most of the studies show that magnesium suppresses hunger, lowers food intake, and reduces body weight. The most probable mechanism is through magnesium stimulating cholecystokinin, which plays an important inhibitory role in the control of feeding behavior.

Key words: magnesium, intake, cholecystokinin, obesity

Introduction

Magnesium

Magnesium (Mg) is one of the most abundant minerals of the human body and has many important biochemical and physiological functions. Among intracellular cations it is the second most abundant after potassium and among all cations it is the fourth most prevalent. Magnesium is crucial for a broad range of physiological functions; it is a cofactor in more than 250 enzymatic reactions, including macronutrient metabolism, oxidative phosphorylation, nucleic acid and protein synthesis, neuromuscular functionality, and the regulation of secretion of some hormones (1,2). In some pathophysiological conditions such as diabetes mellitus or neurological disorders (particularly depression), magnesium deficiency may worsen the conditions. Since it participates in muscle function, cardiac processes, energy metabolism, and the maintenance of healthy bones, sufficient intake of magnesium is very important for athletes. One of its lesser known but no less important roles is to participate in weight management, which will be reviewed in this article (Figure. 1). Comprehensive literature search was performed in September 2019 with several databases (PubMed, Scopus, Web of Science, and Google Scholar) using the key words "magnesium AND (cholecystokinin OR hunger OR obesity)" and research articles that were found were critically evaluated.

Magnesium is known to cause the release of cholecystokinin (CCK) from the small intestinal mucosa (3) and CCK is known to suppress hunger and lower food intake (4,5).

Current Mg recommendations for adults are 350 mg/day for men and 300 mg/day for women in the

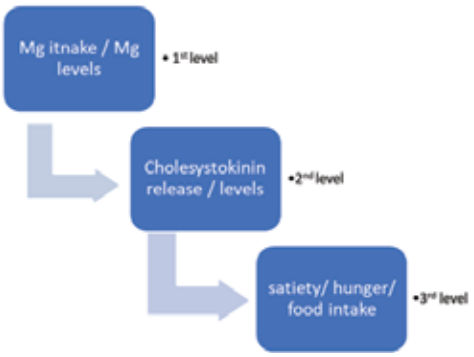

Figure 1. Flowchart presentation of the processes reviewed in this article. The process can be divided into 3 levels and 2 stages connecting them: the influence of Mg (1st level) on cholecystokinin (2nd level) and the influence of cholecystokinin (2nd level) on satiety, hunger, or food intake (3rd level).

EU. During pregnancy and physical activity, the need for magnesium rises approximately 20-30% (6). Good dietary sources of Mg include rice bran (781 mg /100 g), pumpkin seeds (592 mg /100 g), flax (392 mg / 100 g), Brazil nuts (376 mg / 100 g), sesame seeds (351 mg /100 g), and chia seeds (335 mg/100 g) (7,8).

Some mineral waters are also excellent sources of Mg, as they can contain up to 1040 mg /L of Mg (see Table 1) (9,10), with Donat Mg from Rogaška Slatina (Slovenia) being by far the richest (it contains magnesium in the form of sulphate).

Schneider et al.'s study (11) compared the Mg bioavailability from four mineral waters with different types of mineralization (e.g. SO_4^{2-}, HCO_3^-, calcium) with the Mg bioavailability from bread and food supplements. A single center, randomized, controlled trial with a crossover design with 22 healthy men and women was conducted. The results of serum and urine analysis indicated that Mg bioavailability was comparable between mineral waters with different mineralization levels, bread, and food supplements. Specifically, Mg bioavailability was not influenced by the presence of SO_4^{2-}, HCO_3^- or calcium. Thus, mineral water with higher concentrations of Mg constitutes a calorie-free Mg source that contributes to optimal Mg levels.

Body Weight Regulation

The global obesity epidemic is a public health problem that requires the full attention of the scientific community. The common path in all methods of weight regulation is the sensation of satiety or hunger. The human body uses the energy consumed by food very economically; when we consume more than we need, the energy is stored in the body and thus the body weight rises. If we consume only 10% more calories than we utilize, we gain 14 kg per year, or 70 kg in 5 years. Alternately, if we consume that much less, our weight will be reduced by the same amount. The math behind the calorie balance is simple, but the physiology and psychology that regulate the sensation of hunger and satiety and dictates how many calories we consume is much more complex. Our sensation of

Table 1. The selection of mineral water brands with the highest Mg content.

Mineral water brand	Mg content (mg / L)	region
Donat Mg	1000	Europe
Apollinaris	126	Europe
Mendocino	120	North America
Gerolsteiner	112	Europe
Adobe Springs	96	North America
Radenska	93	Europe
Vichi Celestins	60	Europe
San Pellegrino	57	Europe
Valser	55	Europe
Vichy Springs	48	North America
Contrexe´ville	45	Europe

hunger is reduced when we have enough carbohydrates and fats in our body's deposits, when the concentration of these substances is high enough in the blood, or when we have a full digestive tract. This information is brought to the brain by various hormones including cholecystokinin, whose action is linked to magnesium and will be reviewed here. Other substances regulating food consumption are: products of gastrointestinal neuroendocrine cells (ghrelin, leptin, gastric inhibitory polypeptide, orexin, glucagon-like peptide-1, oxyntomodulin, and peptide YY), products of the pancreas (insulin, glucagon, somatostatin, pancreatic polypeptide, and amylin), products from adipocytes (leptin), and products of hypothalamus (endocannabinoids and the recently discovered nesfatin-1) (12–14).

Cholecystokinin

Cholecystokinin (CCK) is a hormone that carries information about the intake of food through the body. It is secreted by the enteroendocrine I-cells located in the proximal small intestine mucosa in response to fat (fatty acids), protein, and other substances (4,5). After a meal, plasma CCK levels increase within 15 minutes, and the lifespan of CCK is only a few minutes (5). It affects several processes including suppression of hunger. The vagal nerve has CCK_1 receptors that can lead to early meal termination and reduce food intake; the hypothalamus also has CCK_1 receptors, which means a direct communication without vagal regulation may exist. The synergistic interaction between CCK and several other anorexigenic peptides also has an important role in food intake regulation.

There are multiple molecular forms of CCK, for example, CCK-8, CCK-33, and CCK-58, with an active site located within the first eight amino acids of the carboxyl terminus and with a sulfate group on the seventh tyrosine residue.

CCK inhibits food intake and gastric emptying, and it also increases pancreatic secretions and gallbladder and smooth muscle contractions. CCK evokes these responses by activating two G protein-coupled receptors: $CCK_1$and CCK_2. CCK_1receptors are located mainly in the gastrointestinal tract whereas CCK_2 receptors are found mainly in the brain. CCK-mediated reduction in food intake (both meal size and the prolongation of the inter-meal interval) occurs by the activation of low-affinity CCK_1 receptors on vagal afferents (4). CCK is involved in both short- and long-term regulation. Short-term regulation is mediated largely through the previously mentioned CCK_1 receptors on vagal afferent neurons, while long-term regulation is more complex and likely involves both peripheral and central sites of action and interactions among various other signaling molecules.

These effects have been examined in many animal and human studies. In one of them (15) partially purified CCK was injected intraperitoneally into rats between a fasting period and food presentation. The hormone produced a large dose-related suppression of intake of both solid and liquid diets. Identical doses of the synthetic terminal octapeptide of cholecystokinin produced identical results. An effective dose of CCK did not suppress drinking after water deprivation. Neither CCK nor the octapeptide produced learning of a taste aversion in bait shyness tests. Secretin, which was used as a control, did not affect feeding.

In another experiment on 7 men and 8 women (16) researchers tested if increased cholecystokinin enhances satiety. Increased cholecystokinin release was achieved by addition of fiber or fat to a low-fat, low-fiber meal. Three isoenergetic breakfast meals were tested in a randomized crossover design: low fiber, low fat; high fiber, low fat; and low fiber, high fat. Blood samples were drawn from subjects after fasting and then at different points in time after test meal consumption for a duration of 6 h. Plasma was analyzed for cholecystokinin, insulin, glucose, and triacylglycerols. Visual analogue scales were used to assess subjects' hunger, desire to eat, fullness, and prospective consumption. In the women, the meals higher in fiber or in fat resulted in greater feelings of satiety and in significantly higher cholecystokinin in responses than did the low-fat, low-fiber meal. In the men, the increase in cholecystokinin concentration did not differ between meals, but the 2 low-fat meals elicited a greater feeling of satiety than did the high-fat meal. The insulin response was significantly higher for the low-fiber, low-fat meal than for the other 2 meals, and the triacylglycerol response was greatest for the high-fat, low-fiber meal. In women, the feeling of satiety caused by cholecystokinin release is enhanced by increasing either the fiber or fat content of a low-fat, low-fiber meal.

CCK_1 receptor agonists for treating obesity have been developed, but have not yet reached clinical practice (17).

Early Works

Investigation on the influence of magnesium on the gastrointestinal tract had already begun at the end of 19th century. The early studies were reviewed in 1939 (18). At that time, it was known that the more dilute the solution of $MgSO_4$, the more rapid the emptying time of the stomach. Concentrated solutions may lengthen this period considerably. The effects of magnesium (Mg) on the gastro-intestinal tract were studied in un-anesthetized dogs with a gastric and intestinal fistula (19).

Another review on cholecystokinin research was published in 1961 (20). It showed that CCK promotes gall bladder contraction and controls digestion in the upper part of the gastro-intestinal tract. This effect of duodenal mucosa extracts was known to be due to a specific hormone, of which the first samples were already obtained and highly purified to be suitable for clinical purposes. In the biologic assay, a dog-unit was defined as the amount of dried material, free of vasodilatory effects, which, when dissolved in normal saline solution and injected intravenously within 10 or 15 sec, causes within the first three minutes an intra-gall bladder pressure rises of 1 cm. This came to be called the cholecystokinetic effect (from the Greek chole "bile", cysto "sac", kinin "move"), which gave the name to the cholecystokinin hormone. The release of the hormone from the duodenal mucosa was known to related to the stimulation of a procain sensitive receptor.

Influence of magnesium on cholecystokinin, hunger sensation and obesity

Animal Studies

A study performed in 1985 (21) examined the effect Mg (in the form of sulphate) on the release of CCK-33, pancreatic polypeptide (PP), and gastrin. Five dogs with pancreatic and gastric fistulas were given 1-h intraduodenal infusions of Mg (4 mmol per kg per hour), or an intravenous bolus followed immediately by a 1-hour infusion of Mg (0.25 mmol/kg bolus, 0.25 mmol per kg per hour). Intraduodenal infusion significantly stimulated CCK-33, PP, and gastrin release. Intravenous Mg increased CCK-33 to 123% of basal levels but did not stimulate PP and gastrin levels.

Mg concentrations in plasma and cells are affected by diet, disease, and genetic factors. This was studied in an experiment from 2007 (22). To characterize the genetic factors involved in the regulation of Mg homeostasis, low and high magnesium status mice were developed by bidirectional selective breeding. The effects of a low-Mg diet on the Mg status parameters were analyzed in these mice. Using a cDNA array, a screen for differential gene expression was performed in kidneys from these animals, fed either a Mg adequate or deficient diet. The Mg-deficient diet significantly affected the plasma, erythrocyte, and urine Mg concentrations in both strains, in similar proportions in the two strains. Furthermore, in response to the Mg-deficient diet, both strains showed changes of the expression of genes primarily belonging to the family of transcription and growth factors (down-regulated). Of the identified genes, five were of particular interest as they were expressed differently in response to the deficient diet in these two strains: osteopontin, the CCK1 receptor, connexin 45, a growth hormone receptor, and BAG1. These results suggest that the two strains exhibit different responses to Mg deficiency. CCK_1 receptor is downregulated in kidneys of mice selected to have low Mg status after 1 week on a Mg-deficient diet.

In a recent study (23), male rats selectively bred for diet-induced obesity (obese-prone) or resistance (obese-resistant) were fed a high-fat, high-energy diet containing moderately low (0.116 g/kg) or normal (0.516 g/kg) Mg levels for 13 weeks. Mg was given in the form of oxide. The growth, body composition, mineral homeostasis, bone development, and glucose metabolism of the rats were examined. The two strains of rats showed differences ($p < 0.05$) in many physical and biochemical measures regardless of diet. Both strains of rats fed the low Mg diet had decreased body

weight, lean body mass, decreased femoral size (width, weight, and volume), and serum Mg and potassium concentrations compared to rats fed the normal Mg diet. The low Mg diet increased serum calcium concentration in both rat strains with a concomitant decrease in serum parathyroid hormone concentration only in the obese-resistant strain. In the femur, Mg concentration was reduced, whereas concentrations of Ca and Na were increased in both strains fed the low Mg diet. Plasma glucose and insulin concentrations in an oral glucose tolerance test were similar in rats fed both diets. A moderately low Mg diet therefore impairs the growth of lean body mass and alters femoral geometry and mineral metabolism in rats fed a high-energy diet.

The aim of another study (24) was to investigate whether deep-sea water (DSW) enriched with Mg and Ca has beneficial lipid metabolic effects. In vitro research indicated that DSW significantly decreased intracellular triglyceride and glycerol-3-phosphate dehydrogenase activity in 3T3-L1 adipocytes. DSW also inhibited the gene levels of adipocyte differentiation, lipogenesis, and adipocytokines, and up-regulated gene levels of lipolysis and fatty acid oxidation. In this study, the results showed that body weight, liver, adipose tissue, hepatic triglycerides and cholesterol, and serum parameters in the high-fat diet (HFD) + DSW groups were significantly lower compared to the HFD group. Moreover, the fecal output of total lipids, triglycerides, and cholesterol in the HFD+ DSW groups was significantly higher than that of the HFD group. Regarding gene expression, DSW significantly increased the gene levels of lipolysis and fatty acid oxidation and decreased the gene levels of adipocytokine in the adipose tissue of rats with HFD-induced obesity. These results indicate a potential molecular mechanism by which DSW can suppress obesity in rats with HFD-induced obesity through lipolysis and fatty acid oxidation. Many studies have indicated that DSW enriched with Mg and Ca prevents and treats several chronic diseases, including diabetes and obesity (25),(26). A previous study indicated that drinking deep-sea water inhibits the adipogenesis of 3T3-L1 adipocytes and attenuates high-fat/cholesterol diet-induced cardiovascular disorders in hamsters.

Another experiment (27) explored the effects of Mg in the form of sulphate on dynamic changes in glucose and lactate levels in the muscles, blood, and brains of exercising rats using a combination of auto-blood sampling and micro dialysis. Sprague-Dawley rats were pretreated with saline or magnesium sulfate ($MgSO_4$, 90 mg/kg, i.p.) 30 min before treadmill exercise (20 m/min for 60 min). The muscle, blood, and brain glucose levels immediately increased during exercise, and then gradually decreased to near basal levels in the recovery periods of both groups. These glucose levels were significantly enhanced to approximately two-fold ($P<0.05$) in the Mg group. Lactate levels in the muscles, blood, and brains rapidly and significantly increased in both groups during exercise, and brain lactate levels in the Mg group further elevated ($P<0.05$) beyond those in the control group during exercise. Lactate levels significantly decreased after exercise in both groups. In conclusion, Mg enhanced glucose availability in the peripheral and central systems and increased lactate clearance in muscles during exercise.

A recent study (28) determined the effects of hypomagnesaemia on energy homeostasis and lipid metabolism mainly in obesity and type 2 diabetes. Results of the study underline the pivotal function of Mg in maintaining a healthy energy metabolism. Mice ($n = 12$/group) were fed either a low-fat diet (LFD) or a high-fat diet (HFD) (10% or 60% of total energy) in combination with a normal- or low-Mg content (0.21% or 0.03%) for 17 weeks. Mg was added to the diet in the form of oxide. Metabolic cages were used to investigate food intake, energy expenditure and respiration. Blood and tissues were taken to study metabolic parameters and mRNA expression profiles respectively. They showed that low dietary Mg intake ameliorates HFD-induced obesity in mice (47.00 ± 1.53 g vs 38.62 ± 1.51 g in mice given a normal Mg-HFD and low Mg-HFD respectively, $p < 0.05$). Consequently, fasting serum glucose levels decreased and insulin sensitivity improved in low Mg-HFD-fed mice. Moreover, HFD-induced liver steatosis was absent in the low Mg group. In hypomagnesaemic HFD-fed mice, mRNA expression of key lipolysis genes increased in epididymal white adipose tissue, corresponding to reduced lipid storage and high blood lipid levels. Low Mg-HFD-fed mice had increased brown adipose tissue Ucp1 mRNA expression and a

higher body temperature. No difference was observed in energy expenditure between the two HFD groups. Mg-deficiency therefore reduces HFD-induced obesity in mice through enhanced adipose tissue activity.

Human Studies

In an old study (3) Mg in the form of sulphate was given orally to 20 patients with irritable bowel syndrome at a dose 100 mg/kg in 150 ml water). A rapid increase in colonic segmental motor activity (onset within two to six minutes in most cases) was seen (percentage activity increased from 16.2 to 23.7 P<0.05; mean wave amplitude from 7.1 to 9.1 cm H_20, NS; motility index from 144 to 259, P<0.01). This increase was most marked in 10 patients who complained of attacks of abdominal pain after food (16.1 to 29.8 %, P<0 01; 6.8 to 9.6 cm H_20, P<0.05; 135 to 350, P<0.05), and after the $MgSO_4$ three of these patients experienced an attack of their usual pain. These findings provide further evidence that 'functional' abdominal pain after food may in some cases be related to an exaggerated intestinal motor response to CCK.

In the same year, another study from the same authors about $MgSO_4$ (29,30) was published. It showed that all the known actions of $MgSO_4$ on the gut are closely similar to reported actions of cholecystokinin, which is released from the intestinal mucosa in response to $MgSO_4$ and other salts. These results showed that the action of the saline purgatives is not brought about by osmotic effects but is in large part due to the actions of CCK on the gastrointestinal tract.

Another experiment (31) tried to assess the effects of Mg chloride or $MgSO_4$ on the release of cholecystokinin from the duodenum. Outputs of trypsin and bilirubin were quantified during perfusion of the duodenum with isotonic solutions of these salts. Net intestinal water transport was also quantified. The results suggest that Mg ions in the duodenum are a relatively weak stimulus to the pancreas and gallbladder, an action not augmented by the concomitant presence of the sulfate ion; Mg in this study was a weak stimulant of cholecystokinin release. Furthermore, Mg chloride inhibited net jejunal water absorption and $MgSO_4$ was even more potent, promoting net water secretion, effects which cannot be entirely attributed to cholecystokinin release.

A further study (32) determined the effects of oral $MgSO_4$ on gallbladder contraction and release of CCK in male volunteers; $MgSO_4$ (25 g in 100 ml distilled water) was given by mouth to five fasting adult males. Plasma samples were collected for measurement of CCK by specific radioimmunoassay. Gallbladder volumes were determined from sonograms obtained from a phased-array real-time ultrasound scanner. Basal concentrations of CCK (82.2 ± 10.1 pg/ml) increased significantly at 20 minutes after oral $MgSO_4$ (113.8 ± 7.1 pg/ml) and reached a maximal value at 50 minutes (150.0 ± 42.0 pg/ml). The mean basal volume of the gallbladder was 30.8 ± 5.3 cm3 and maximum reduction of gallbladder volume (to one third of original) was achieved at 50 minutes after ingestion of $MgSO_4$. Linear regression analysis showed a close correlation (r = -0.9337) between plasma concentrations of CCK and gallbladder size in response to $MgSO_4$. Oral $MgSO_4$ also caused a significant increase in serum gastrin (from basal of 51.4 ± 9.9 pg/ml to 69.8 ± 15.5 pg/ml at 5 min); there was no significant correlation between gastrin release and gallbladder contraction. This study provided direct evidence that the mechanism of magnesium sulfate-stimulated gallbladder contraction occurs through the release of CCK and shows a close correlation between CCK release and contraction of the gallbladder. The main conclusion was that plasma CCK concentrations were increased significantly in response to oral $MgSO_4$.

Another experiment (33) sought to investigate whether artificially-induced accelerated small intestinal transit activates the ileal brake mechanism. Eight healthy volunteers (four female, four male; age 21 +- 3 years) participated in four experiments: (a) meal with either oral $MgSO_4$ or placebo; and (b) fasting with either oral $MgSO_4$ or placebo. Antroduodenal motility was recorded by perfusion manometry. Duodenocaecal transit time was determined by the lactulose H_2 breath test. Gall-bladder volume was measured by ultrasound at regular intervals, and blood samples were drawn for determination of cholecystokinin and peptide YY (RIA). Twenty-four-hour fecal weight and fat excretion were determined. $MgSO_4$ significantly accelerated duodenocaecal transit time and increased fecal fat and

weight in all subjects. $MgSO_4$ significantly delayed the reoccurrence of phase III and affected antroduodenal motility during fasting but not after meal ingestion. Postprandial gall-bladder relaxation and postprandial peptide YY release were significantly increased during the $MgSO_4$ experiment compared to placebo.

The aim of a clinical randomized, double-blind, placebo-controlled study (34) was to determine whether oral Mg supplementation (in the form of Mg chloride solution) improves both insulin sensitivity and metabolic control in type 2 diabetic subjects with decreased serum Mg levels. A total of 63 subjects with type 2 diabetes and decreased serum Mg (serum levels 0.74 mM) treated by glibenclamide received either 50 ml $MgCl_2$ solution (containing 50 g $MgCl_2$ per 1,000 ml solution) or placebo daily for 16 weeks. Chronic diarrhea, alcoholism, use of diuretic and/or calcium antagonist drugs, and reduced renal function were exclusion criteria. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the parameter of insulin sensitivity and glucose and HbA1casparameters of metabolic control. At the end of the study, subjects who received Mg supplementation showed significant higher serum Mg concentration (0.74 +/-0.10 vs. 0.65 +/-0.07mM, P=0.02) and lower HOMA-IR index (3.8 +/-1.1 vs. 5.0 +/-1.3, P=0.005), fasting glucose levels (8.0 +/-2.4 vs. 10.3 +/-2.1 mM, P=0.01), and HbA1c (8.0 +/-2.4 vs. 10.1 +/-3.3%, P=0.04) than control subjects. Oral supplementation with $MgCl_2$ solution therefore restores serum Mg levels and improves insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum Mg levels.

The aim of a double-blind, placebo-controlled, randomized trial on 74 healthy middle-aged overweight women (35) was to examine whether Mg could improve body composition and muscle strength. Volunteers ($25 \leq BMI \leq 30$ kg/m^2) received either 250 mg Mg in the form of Mg oxide or placebo daily for 8 weeks. Body composition was assessed using Bioelectrical Impedance Analysis (BIA). Handgrip strength and knee extension strength were measured with isometric dynamometry. Functional mobility was assessed using Time Get Up and Go Test (TGUG). A significant increase in mean lean body mass was observed (P=0.05) accompanied with a significant decrease in fat mass (P=0.02) solely in the Mg group at the end of 8 weeks compared to baseline values but the changes were not significant when compared to placebo group. Hand-grip strength and TGUG improved in the Mg group compared to baseline but not significantly when compared to placebo. There were no significant differences in increasing knee extension strength in the Mg group as compared with placebo. Baseline values of serum Mg and muscle strength of participants did not indicate any influences on response to Mg supplementation.

One study (36) examined the relationship between body weight status and hypomagnesemia (serum Mg concentration≤0.74 mM) in apparently healthy subjects. A total of 681 healthy individuals aged 30 to 65 years were enrolled in a cross-sectional study. Exclusion criteria were extreme exercise, chronic diarrhea, alcohol intake, diuretics use, smoking, oral Mg supplementation, diabetes, malnutrition, hypertension, liver disease, thyroid disorders, and renal damage. Based on Body Mass Index (BMI), the participants were defined as: normal weight (BMI<25 kg/m^2); overweight (BMI≥25<30 BMI kg/m^2); and obese (BMI≥30 kg/m^2). The multivariate logistic regression analysis showed that dietary Mg intake (OR 2.11; 95%CI 1.4–5.7) but not obesity (OR 1.53; 95%CI 0.9–2.5), overweightness (OR 1.40; 95%CI 0.8–2.4), nor normal weightiness (OR 0.78; 95%CI 0.6–2.09) were associated with hypomagnesemia. A subsequent logistic regression analysis adjusted by body mass index, waist circumference, total body fat, systolic and diastolic blood pressure, and triglycerides levels showed that hyperglycemia (2.19; 95%CI 1.1–7.0) and dietary Mg intake (2.21; 95%CI 1.1–8.9) remained associated with hypomagnesemia. Results of this study showed that body weight status is not associated with hypomagnesemia and that, irrespective of obesity, hyperglycemia is a cause of hypomagnesemia in non-diabetic individuals.

In Vitro Studies

In old research (37), scientists have succeeded in proving that $MgSO_4$ actually evacuates the gall bladder, first by the injection of a foreign substance into the

bile as an indicator, and secondly by direct observation with the use of the duodenal tube in laparotomy.

The relationship between insulin and Mg has also been reviewed (38). In particular it has been shown that Mg plays the role of a second messenger for insulin action; on the other hand, insulin itself has been demonstrated to be an important regulatory factor of intracellular Mg accumulation. Conditions associated with insulin resistance, such as hypertension or aging, are also associated with low intracellular Mg contents. In diabetes mellitus, it has been suggested that low intracellular Mg levels result from both increased urinary losses and insulin resistance. The extent to which such a low intracellular Mg content contributes to the development of macro- and micro angiopathy remains to be established. Reduced intracellular Mg content might contribute to the impaired insulin response and action which occurs in Type 2 (non-insulin-dependent) diabetes mellitus. Chronic Mg supplementation can contribute to an improvement in both islet Beta-cell response and insulin action in non-insulin-dependent diabetic subjects.

The effect of Mg on the secretory responses and the mobilization of calcium (Ca) and Mg evoked by CCK-8 in the exocrine rat pancreas was investigated in one study (39). Both these cations were added to the perfusion solution in the form of chloride. In the isolated, intact, perfused pancreas, CCK-8 (10^{-10} M) produced marked increases in juice flow and total protein output in zero and normal (1.1 mM) extracellular Mg compared to a much-reduced secretory response in elevated (5 mM and 10 mM) extracellular Mg. Similar effects of perturbation of extracellular Mg on amylase secretion and $^{45}Ca^{2+}$ uptake (influx) were obtained in isolated pancreatic segments. In pancreatic acinar cells loaded with the fluorescent bioprobe fura-2 acetomethylester (AM), CCK-8 evoked marked increases in cytosolic free Ca concentration in zero and normal extracellular Mg compared to a much-reduced response in elevated extracellular Mg. Pretreatment of acinar cells with either dibutyryl cyclic AMP (DB^2 cAMP) or forskolin had no effect on the CCK-8 induced changes in cytosolic free Ca^{2+} concentration. In magfura-2-loaded acinar cells CCK-8 (10^{-8} M) stimulated an initial transient rise in intracellular free Mg concentration of intracellular Mg followed by a more prolonged and sustained decrease. This response was abolished when sodium Na^+ was replaced with N-methyl-D-glucamine (NMDG). Incubation of acinar cells with 10 mM Mg resulted in an elevation in cytosolic free Mg concentration. Upon stimulation with CCK-8, intracellular Mg concentration decreased only slightly compared with the response obtained in normal extracellular Mg. CCK-8 caused a net effiux of Mg in pancreatic segments; this effect was abolished when extracellular Na^+ was replaced with either NMDG or choline. The results indicate that Mg can regulate CCK-8-evoked secretory responses in the exocrine pancreas possibly via Ca^{2+} mobilization. Moreover, the movement of Mg in pancreatic acinar cells is dependent upon extracellular Na^+.

Conclusion

The ability of magnesium (Mg) to stimulate the release of cholecystokinin (CCK) was demonstrated in many studies, including in dogs (21) and in humans (31,32). In all these studies, the Mg in the form of suphate was used. Expression of CCK1 receptor gene was also found to depend on Mg content in food (22).

There is also one study in rats (23) and one in mice (28) that, on the contrary, indicate that low Mg in the diet can decrease the body weight, but these two studies used Mg in the form of oxide.

The influence of cholecystokinin on hunger/satiety sensation and or food intake was shown in several experimental models including human and animal. Intraperitoneal application of CCK or synthetic terminal octapeptide of CCK to rats after fasting (15) produced a large dose-related suppression of intake of both solid and liquid diets.

Some studies also demonstrated the overall link between enhanced Mg intake and treatment of obesity (food consumption or absorption, body fat mass) in animals (24) ,(25),(26) and humans (33,35). Again, in most studies, the Mg in the form of sulfate was used. Apart from body weight also other parameters (liver tests, adipose tissue, hepatic triglycerides and cholesterol) were significantly lowered by addition of Mg to the diet (24).

One study, on the other hand, demonstrated that low intake of magnesium was associated with hypomagnesemia, but they did not find any association of hypomagnesemia with body weight status (36).

Even if there is still some controversy, most of the studies show that magnesium suppresses hunger, lowers food intake, and reduces body weight. The most probable mechanism is through magnesium stimulating CCK, which plays an important inhibitory role in the short-term control of feeding behavior. The influence of the anions that are accompanying the Mg was not systematically investigated, but there are some indications that sulphate ion can play an important role too.

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References

1. Wolf FI, Trapani V. Cell (patho)physiology of magnesium. Clinical Science. 2008.
2. Whang R, Hampton EM, Whang DD. Magnesium homeostasis and clinical disorders of magnesium deficiency. Annals of Pharmacotherapy. 1994.
3. Harvey RF, Read AE. Effects of oral magnesium sulphate on colonic motility in patients with the irritable bowel syndrome. Gut. 1973 Dec;14(12):983–7.
4. Sayegh AI. The Role of Cholecystokinin Receptors in the Short-Term Control of Food Intake. In: Progress in Molecular Biology and Translational Science. 1st ed. Elsevier Inc.; 2013. p. 277–316.
5. Chen Y. Regulation of food intake and the development of anti-obesity drugs. Drug Discov Ther. 2016;10(2):62–73.
6. EFSA NDA Panel (EFSA Panel on Dietetic Products N and A. Scientific opinion on dietary reference values for magnesium: dietary reference values for magnesium. EFSA J. 2015;13:4186.
7. USDA National Nutrient Database for Standard Reference [Internet]. US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. 2018. Available from: https://www.ars.usda.gov/nea/bhnrc/ndl
8. Kreft S, Kolar D, Fatur K. Hungry pumpkin [Internet]. 2019. Available from: www.hungry-pumpkin.com
9. Garzon P, Eisenberg MJ. Variation in the mineral content of commercially available bottled waters: Implications for health and disease. Am J Med. 1998;
10. Bothe G, Coh A, Auinger A. Efficacy and safety of a natural mineral water rich in magnesium and sulphate for bowel function: a double-blind, randomized, placebo-controlled study. Eur J Nutr. 2017;
11. Schneider I, Greupner T, Hahn A. Magnesium bioavailability from mineral waters with different mineralization levels in comparison to bread and a supplement. Food Nutr Res. 2017;
12. Alén F, Ramírez-López MT, Gómez de Heras R, Rodríguez de Fonseca F, Orio L. Cannabinoid Receptors and Cholecystokinin in Feeding Inhibition. Vol. 92, Vitamins and Hormones. 2013. 165–196 p.
13. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature. 2006 Sep;443(7109) :289–95.
14. Prinz P, Stengel A. Control of Food Intake by Gastrointestinal Peptides: Mechanisms of Action and Possible Modulation in the Treatment of Obesity. J Neurogastroenterol Motil. 2017 Apr;23(2):180–96.
15. Gibbs J, Young RC, Smith GP. Cholecystokinin Decreases Food Intake in Rats 1. Obes Res. 1997 May;5(3):284–90.
16. Burton-Freeman B, Davis PA, Schneeman BO. Plasma cholecystokinin is associated with subjective measures of satiety in women. Am J Clin Nutr. 2002 Sep;76(3):659–67.
17. Miller LJ, Desai AJ. Metabolic Actions of the Type 1 Cholecystokinin Receptor: Its Potential as a Therapeutic Target. Trends Endocrinol Metab. 2016 Sep;27(9):609–19.
18. Lium R, Florey HW. The action of magnesium sulphate on the intestine of the cat. Q J Exp Physiol Cogn Med Sci. 1939 Aug;29(3):303–19.
19. Roth GB, Crittenden PJ. Sulphates of Sodium and Magnesium on Gastro-intestinal Activity. Exp Biol Med. 1934 Oct;32(1):91–4.
20. Torsoli A, Ramorino ML, Colagrande C, Demaio G. Experiments with cholecystokinin. Acta radiol. 1961;55(3) :193–206.
21. Inoue K, Fried GM, Wiener I, Sakamoto T, Lilja P, Greeley GH, et al. Effect of divalent cations on gastrointestinal hormone release and exocrine pancreatic secretion in dogs. Am J Physiol Liver Physiol. 2017;248(1):G28–34.
22. Ozgo M, Bayle D, Zimowska W, Mazur A. Effect of a low magnesium diet on magnesium status and gene expression in the kidneys of mice selected for high and low magnesium erythrocyte levels. Magnes Res. 2007;20(2):148–53.
23. Bertinato J, Lavergne C, Rahimi S, Rachid H, Vu NA, Plouffe LJ, et al. Moderately low magnesium intake impairs growth of lean body mass in obese-prone and obese-resistant rats fed a high-energy diet. Nutrients. 2016;8(5).
24. Chang W-T, Lu T-Y, Cheng M-C, Lu H-C, Wu M-F, Hsu C-L. Deep Sea Water Improves Abnormalities in Lipid Metabolism through Lipolysis and Fatty Acid Oxidation in High-Fat Diet-Induced Obese Rats. Mar Drugs. 2017 Dec;15(12):386.
25. Ha BG, Moon D-S, Kim HJ, Shon YH. Magnesium and calcium-enriched deep-sea water promotes mitochondrial biogenesis by AMPK-activated signals pathway in 3T3-L1 preadipocytes. Biomed Pharmacother. 2016 Oct;83:477–84.

26. Wang L-C, Lung T-Y, Kung Y-H, Wang J-J, Tsai T-Y, Wei B-L, et al. Enhanced Anti-Obesity Activities of Red Mold Dioscorea When Fermented Using Deep Ocean Water as the Culture Water. Mar Drugs. 2013 Oct;11(10):3902–25.
27. Chen H-Y, Cheng F-C, Pan H-C, Hsu J-C, Wang M-F. Magnesium Enhances Exercise Performance via Increasing Glucose Availability in the Blood, Muscle, and Brain during Exercise. Lluch GL, editor. PLoS One. 2014 Jan;9(1):e85486.
28. Kurstjens S, Overmars-Bos C, Bindels RJM, Hoenderop JGJ, de Baaij JHF, van Diepen JA, et al. Magnesium deficiency prevents high-fat-diet-induced obesity in mice. Diabetologia. 2018;61(9):2030–42.
29. Harvey RF, Read AE. SALINE PURGATIVES ACT BY RELEASING CHOLECYSTOKININ. Lancet. 1973 Jul;302(7822):185–7.
30. Harvey RF, Read AE. Mode of action of the saline purgatives. Am Heart J [Internet]. 1975 Jun;89(6):810–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/0002870375901994
31. Malagelada JR, Holtermuller KH, McCall JT, Go VL. Pancreatic, gallbladder, and intestinal responses to intraluminal magnesium salts in man. Am J Dig Dis. 1978 Jun;23(6):481–5.
32. Inoue K, Wiener I, Fagan CJ, Watson LC, Thompson JC. Correlation Between Gallbladder Size and Release of Cholecystokinin After Oral Magnesium Sulfate in Man. Ann Surg. 1983 Apr;197(4):412–5.
33. Vu, Nouwens, Biemond, Lamers, Masclee. The osmotic laxative magnesium sulphate activates the ileal brake. Aliment Pharmacol Ther. 2000 May;14(5):587–95.
34. Rodriguez-Moran M, Guerrero-Romero F. Oral Magnesium Supplementation Improves Insulin Sensitivity and Metabolic Control in Type 2 Diabetic Subjects: A randomized double-blind controlled trial. Diabetes Care. 2003 Apr;26(4):1147–52.
35. Moslehi N, Vafa M, Sarrafzadeh J, Rahimi-Foroushani A. Does Magnesium Supplementation Improve Body Composition and Muscle Strength in Middle-Aged Overweight Women? A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Biol Trace Elem Res. 2013 Jun;153(1–3):111–8.
36. Guerrero-Romero F, Flores-García A, Saldaña-Guerrero S, Simental-Mendía LE, Rodríguez-Morán M. Obesity and hypomagnesemia. Eur J Intern Med. 2016 Oct;34:29–33.
37. Matsuo I. Magnesium sulphate as a cause of the evacuation of the gallbladder. J Am Med Assoc [Internet]. 1924 Oct 25;83(17):1289. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1924.02660170005002
38. Paolisso G, Scheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. Diabetologia. 1990 Sep;33(9):511–4.
39. Wisdom DM, Salido GM, Baldwin LM, Singh J. The role of magnesium in regulating CCK-8-evoked secretory responses in the exocrine rat pancreas. Mol Cell Biochem. 1996;154(2):123–32.

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