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Effect of oral magnesium sulfate administration on blood pressure and lipid profile in streptozocin diabetic rat

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Abstract

Approximately one-third of patients with type 1 diabetes develop a variety of complications as a result of mechanisms that are not completely understood. However, insufficient metabolic control seems to play a major role. Other factors such as magnesium (Mg) could also be of importance. We designed this study to elucidate the effect of oral magnesium administration on plasma lipid profile and mesenteric fat in male Wistar rats. Animals were divided into 4 groups ($n=10$ in each group): one group served as control, while the other groups were made diabetic with a single i.v. injection of 40 mg/kg streptozocin. Animals in which the diabetic state lasted for 10 days were referred as acute diabetic rats, whereas those in which the diabetes lasted for 8 weeks were defined as chronic diabetics. Mg-treated chronic diabetic received 10 g/l of $MgSO_4$ added to the drinking water (0.46 g/24 h) for eight weeks following which the left common carotid artery was cannulated for continuous recording of blood pressure. Blood glucose, magnesium and lipid profiles levels were also determined. Diabetes induction caused plasma glucose, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), total cholesterol and triglyceride concentrations to increase, however plasma Mg level was decreased. Administration of $MgSO_4$ for eight weeks caused the return of the above factors to their normal levels. Mg concentrations also increased but failed to reach normal levels. Diabetes induction caused mesenteric fat/body weight ratio to increase, but administration of $MgSO_4$ reduced the ratio to normal levels. In addition, Mg administration returned systolic blood pressure to the normal level. Our results support the hypothesis that Mg may play a part in the management of diabetes and the prevention of its vascular complications in streptozocin-induced diabetic rats and it may be useful in the treatment of hyperlipidaemia in diabetic case.

Keywords: Diabetes; Lipid profile; Magnesium; Blood pressure; Mesenteric fat

1. Introduction

Magnesium is an essential cation playing a crucial role in many physiological functions (Laires et al., 2004). It is critical in energy-requiring metabolic processes, protein synthesis, hormone secretion and intermediary metabolism (Laires et al., 2004). Its deficiency is frequently observed in diabetes (Laires et al., 2004; Djurhuus et al., 1999). Approximately one-third of patients with type 1 diabetes develop a variety of complications (Djurhuus et al., 2001). The mechanism(s) leading to these complications is not completely understood. But insufficient metabolic control seems to play a major role (Djurhuus et al., 2001). Other factors such as magnesium could also be of importance (Djurhuus et al., 2001). Long diabetes duration, poor glycemic control, hypertension and dyslipidemia can lead to the development of diabetic vascular complications (Jenkins et al., 2003). Clinical atherosclerotic disease is positively associated with total and low density lipoprotein (LDL) cholesterol and inversely associated with high density lipoprotein (HDL) cholesterol (Choi et al., 2006). An atherogenic lipid profile is observed in 50–75% of patients with diabetes and is predominately characterized by elevated levels of triglycerides and apolipoprotein B, decreased levels of HDL cholesterol, and LDL (Saad et al., 2004).

Among all the investigated obesity indexes, the mesenteric fat thickness showed the highest correlations with total cholesterol, LDL triglycerides, fasting plasma glucose and

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systemic blood pressure (Liu et al., 2003; Ishikawa and Koga, 1998). Kuriyama et al. (2002) have reported that accumulation of intra-abdominal visceral fat is closely associated with increased incidence of metabolic complications in obesity. Mesenteric fat, a reflection of visceral adiposity, may play an important role in the pathogenesis of metabolic syndrome and cardiovascular diseases (Liu et al., 2006). In our previous study (Soltani et al., 2005a,b) we observed that baseline perfusion pressure of the mesenteric vascular bed in chronic diabetic rats treated with Mg is significantly lower than in non-treated diabetic rats. Measurement of mesenteric fat thickness may be a useful indicator of regional fat distribution in the assessment of cardiovascular risks (Liu et al., 2006).

Reports on the effect of magnesium on lipid profile in diabetic patients are controversial. While some indicate that administrating magnesium supplementation to the diabetic patients did not improve lipid levels (de Valk et al., 1998), others showed beneficial effects on lipid profile (Lal et al., 2003; Singh et al., 1991, 1990; Corica et al., 1994; Anetor et al., 2002).

To address this issue we designed a study to elucidate the effect of oral magnesium administration on plasma mesenteric fat, triglycerides, HDL and total cholesterol levels.

2. Materials and methods

2.1. Animals

The animals were handled in accordance with the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" (http://www.nap.edu/readingroom/books/labrats/). Male Wistar rats, weighing 180–250 g were used. All animals were maintained at a constant temperature of 22±2 °C with fixed 12:12-h light–dark cycle. Nutritionally balanced pellets and water were freely available. Animals were divided into four groups (10 rats in each group): control, acute diabetic, chronic diabetic and Mg-treated chronic diabetic.

Rats were made diabetic with tail intravenous injection of 40 mg/kg streptozocin. Ten days after diabetes induction, fasting blood glucose level was determined and the presence of diabetes was confirmed by blood glucose levels above 250 mg/dl. Animals in which the diabetes lasted for 10 days were referred to as acute diabetic rats, whereas those in which the diabetes lasted for 8 weeks were defined as chronic diabetics. Mg-treated chronic diabetic rats received 10 g/l of $MgSO_4$ added to the drinking water ten days after diabetes induction, for eight weeks. Water consumption was recorded. The Mg-treated chronic diabetic group appeared to consume significantly lower amounts of water compared to chronic diabetic group (46±4 and 205±3.3 ml/24 h for Mg-treated chronic diabetic and chronic diabetic). So the exact dose of $MgSO_4$ that rats were consuming each day was 0.46 g/24 h.

2.2. Blood pressure measurement

Animals were deprived of food for 14 h and anesthetized with ketamine HCl (50 mg/kg, ip). The left common carotid artery was cannulated for continuous recording of blood pressure for 30 min with a pressure transducer (MLT0380) and Power Lab Recording System (4SP, ADInstruments).

2.3. Biochemical assay

Animals were decapitated after anesthesia with ketamine HCl. Blood samples were taken from the neck vascular trunk in order to determine the glucose, triglycerides, total cholesterol, HDL-cholesterol and magnesium levels by spectrophotometer (UV 3100, Shimadzu) and using appropriate kits (Zistshimi, Tehran. Iran). LDL and very low density lipoprotein (VLDL) cholesterol were calculated by the following formula (Saunders et al., 1999):

$$\text{VLDL} = \text{Triglycerides}/5$$

$$\text{LDL} = \text{Total cholesterol} - \text{HDL cholesterol} - \text{VLDL}$$

2.4. Drugs

Streptozocin was obtained from Pharmacia and Upjohn Co. (Kalamazoo, USA), and dissolved in 1 ml normal saline immediately before use. Magnesium sulfate and ketamine HCl were obtained from Sigma (St. Louis, MO, USA) and (Trittau-Germany) respectively.

2.5. Statistical analysis

Data were expressed as mean±SEM. Differences among groups were evaluated by one-way analysis of variance (ANOVA) with Tukey post-hoc test and differences between two groups were evaluated by *t*-test. The correlation between mesenteric bed weight and LDL and cholesterol levels were studied by Pearson correlation coefficient. $P<0.05$ was selected for acceptance of statistical significance.

3. Results

3.1. Changes in plasma glucose, magnesium and lipid profile

Blood glucose measurements indicated that before diabetes induction, there were no differences among animals in each group. Ten days after diabetes induction by streptozocin injection, glucose plasma level was significantly elevated and Mg plasma level was significantly reduced (Table 1).

Changes in plasma glucose, magnesium, triglycerides, total cholesterol, HDL-cholesterol, LDL and VLDL concentrations were measured in non-diabetic control, acute diabetic, chronic diabetic and magnesium-treated chronic diabetic groups (Fig. 1). Diabetes induction caused plasma glucose, HDL,

Table 1
Plasma glucose and magnesium concentrations before and ten days after diabetes induction (data are expressed as mean±SEM)

	Glucose (mg/dl)	Mg (mg/dl)
Before diabetes ($n=40$)	126.64±9.19	3.47±0.41
10 days after diabetes ($n=40$)	297.40±9.81 [a]	2.51±0.11 [a]

[a] $P<0.05$.

LDL, VLDL, total cholesterol and triglyceride concentrations to increase, though plasma magnesium level decreased. Nine weeks following diabetes induction the trends observed in the above factors continued. Administration of magnesium sulfate for eight weeks (from 10th day) caused plasma glucose, LDL, VLDL, total cholesterol and triglyceride concentrations return to their normal levels. Plasma HDL levels were in the Mg-treated chronic diabetic animals compared to the non-diabetic controls. Magnesium concentrations also increased but they never reached the normal levels.

3.2. Changes in mesenteric fat/body weight ratio

Diabetes induction by streptozocin injection caused the mesenteric fat/ body weight ratio to increase, but administration of magnesium sulfate for eight weeks caused this ratio return to the normal level (Fig. 2).

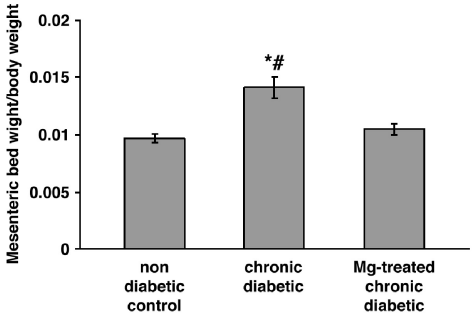

Fig. 2. Mesenteric fat/body weight ratio in non-diabetic control (NC), chronic diabetic (CD) and magnesium-treated chronic diabetic (MgCD) (10 rats in each group, data were expressed as mean±SEM). *Significant difference with NC ($P<0.05$). #Significant difference with MgCD ($P<0.05$).

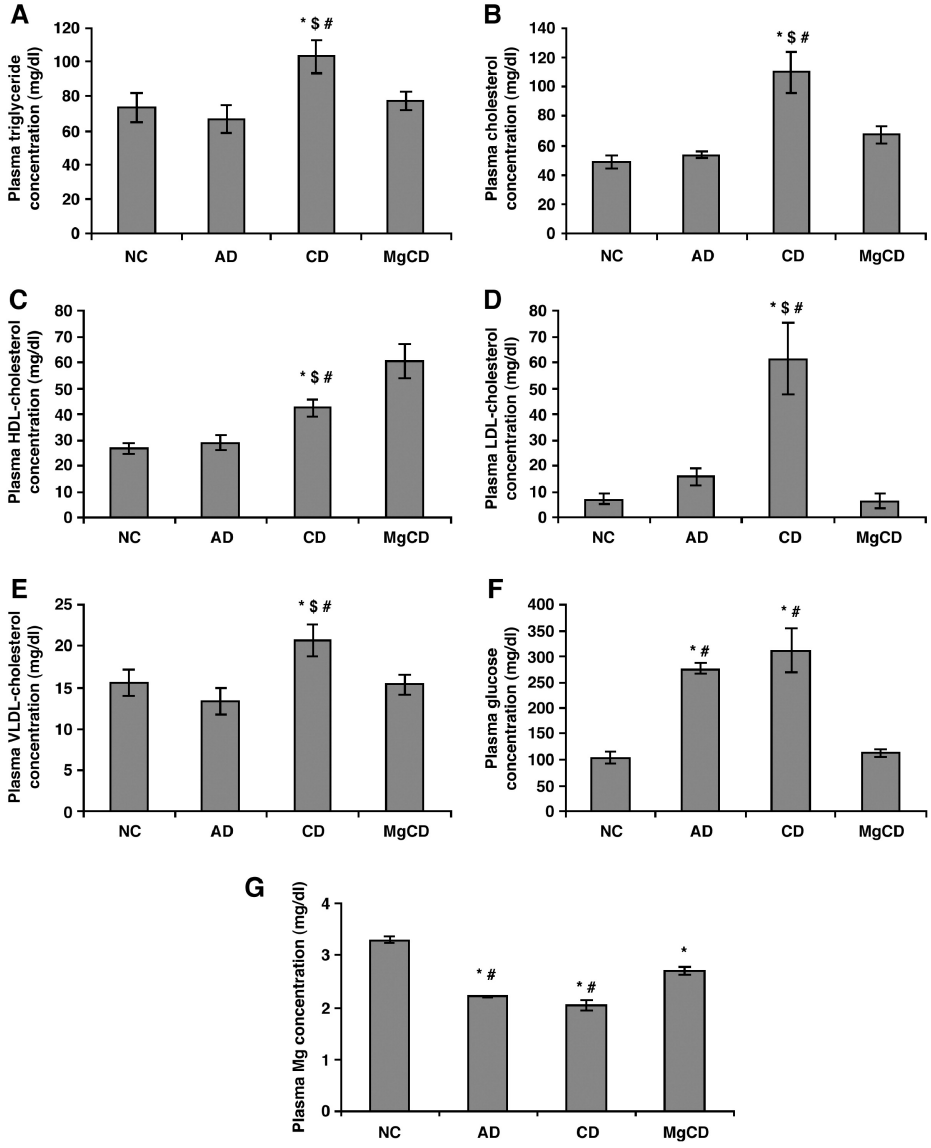

Fig. 1. Plasma triglyceride (A), cholesterol (B), HDL (C), LDL (D), VLDL (E), glucose (F) and magnesium (G) concentrations in non-diabetic control (NC), acute diabetic (AD), chronic diabetic (CD) and magnesium-treated chronic diabetic (MgCD) (10 rats in each group, data were expressed as mean±SEM). *Significant difference with NC ($P<0.05$). $Significant difference with AD ($P<0.05$). #Significant difference with MgCD ($P<0.05$).

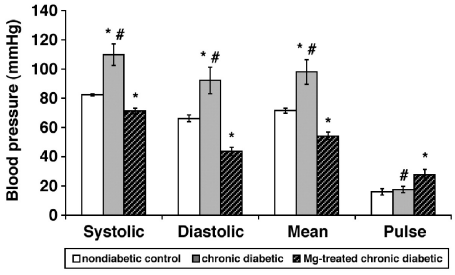

Fig. 3. Comparison of systolic, diastolic, mean and pulse pressure in non-diabetic control, chronic diabetic and magnesium-treated chronic diabetic animals (10 rats in each group. Data are expressed as mean ± SEM). *Significant difference with control ($P<0.05$). #Significant difference with magnesium-treated chronic diabetic ($P<0.05$).

Significant correlation was detected between mesenteric fat and LDL cholesterol ($P<0.05$, $r=0.526$) and between mesenteric fat and plasma cholesterol level ($P<0.05$, $r=0.498$) were observed.

3.3. Blood pressure evaluation

In chronic diabetic control animals systolic, diastolic and mean arterial pressures were significantly elevated comparing to non-diabetic control groups. Magnesium administration returned systolic blood pressure to the normal levels. Decreases in diastolic pressure and mean arterial pressure (MAP) were significantly lower in Mg-treated chronic diabetic animals than non-diabetic controls. The pulse pressure in Mg-treated chronic diabetic group was significantly also elevated (Fig. 3).

4. Discussion

In the present study the effect of oral magnesium sulfate on atherogenic risk factors such as serum lipid profile and blood pressure was examined. Approximately one-third of patients with type 1 diabetes develop a variety of complications (Djurhuus et al., 2001). The reason for these complications is not entirely known, but insufficient metabolic control is a major factor (Djurhuus et al., 1999). Clinical atherosclerotic disease is positively associated with total and LDL cholesterol and inversely associated with HDL cholesterol (Jensen et al., 2002).

Magnesium is a necessary cofactor for many enzymes such as those involved in lipid metabolism. Magnesium is one of the nutritional minerals that play a crucial role in the regulation of carbohydrate and lipid metabolism (Anetor et al., 2002). Magnesium deficiency has been described in 30% of all patients with type 1 diabetes (Djurhuus et al., 1999). Mg-deficiency enhances catecholamine secretion which result in an increase in lipolysis and blood plasma magnesium has been shown to decrease when lipolysis is increased. Enhancement in lipolysis and subsequent elevation of plasma free fatty acids levels may lead to an increase in hepatic VLDL and triglycerides synthesis and secretion and elevated plasma triglyceride concentration (Rayssiguier et al., 1992). The hepato-biliary pathway is the main rout for removal of cholesterol from the body. Bile flow is significantly lower in Mg-deficient rats than in controls and the cholesterol concentration in bile is decreased (Rayssiguier et al., 1992). But reports regarding the effect of magnesium on lipid profile in diabetic patients are controversial. Lal et al. (2003) showed that Mg supplementation has a beneficial effect on the lipid profile of diabetic patients with no significant effect on blood glucose levels (Lal et al., 2003). On the other hand, de Valk et al. (1998) showed that Mg has no effect on glycemic control and plasma lipids (de Valk et al., 1998).

Our results showed that magnesium sulfate could decrease triglycerides, cholesterol and LDL cholesterol and also increased HDL cholesterol. The decrease in serum triglycerides was associated with the change in serum total Mg concentration. Other supporting evidence is accumulating for the role of magnesium in the modulation of serum lipids and lipids uptake in macrophages (Altura and Altura, 1991).

In this study diabetes induction caused mesenteric fat/ body weight ratio to increase, but administration of magnesium sulfate for eight weeks prevented increase in this ratio. Liu et al. (2003) showed that mesenteric fat thickness had better associations with some of the cardiovascular risk factors. It may potentially be a useful tool to evaluate regional distribution of obesity in the assessment of cardiovascular risk (Liu et al., 2005). In this study we also showed that there is a significant correlation between mesenteric fat and LDL cholesterol ($P<0.05$, $r=0.526$) and also we observed significant correlation between mesenteric fat and plasma cholesterol level ($P<0.05$, $r=0.498$).

Hypertension is one of the vascular complications associated with diabetes mellitus (Ozcelikay et al., 2000). Although the etiology of vascular disorder in diabetes is not fully understood, it has been suggested that alteration in the sensitivity or reactivity of vascular smooth muscle to neurotransmitters and circulating hormones may cause or contribute to diabetic hypertension (Abe et al., 2003). Laurant and Touyz (2000) showed that increase in plasma endothelin I due to magnesium deficiency and a direct effect of magnesium deficiency on vascular smooth muscle is involved in the elevation of vascular tone. Elevated vascular tone can contribute to increased blood pressure. We have observed that systolic and diastolic blood pressure and mean arterial blood pressure in Mg-treated chronic diabetic rats are lower than in chronic diabetic animals, yet systolic and diastolic blood pressure in Mg-treated chronic diabetic rats are even lower than in non-diabetic control. In our previous studies (Soltani et al., 2005a,b) we showed that the administration of magnesium can decrease mesenteric vascular bed sensitivity to phenylephrine and decrease Ca/Mg ratio. We also showed that magnesium decreases collagen thickness, intima/media thickness and the lumen/media ratio in aorta (Soltani et al., 2005a,b). This suggests that the administration of magnesium can decrease blood pressure and prevent vascular morphological changes and decrease in vascular sensitivity to neurotransmitter.

In the present study plasma magnesium levels after Mg administration increased but it didn't reach the same plasma level as in control group. Although plasma magnesium levels failed to reach the normal value, it appeared to prevent diabetes complications. Intracellular magnesium shift may explain the above observation. This is in agreement with our previous studies (Soltani et al., 2005a,b) and the hypothesis proposed by

Paolisso and Barbagallo (1997) suggesting that intracellular magnesium may play a key role in glucose uptake and vascular tone. In brief, we have observed that magnesium administration can improve lipid profile, decrease mesenteric fat, and also decrease systolic and diastolic blood pressure suggesting that magnesium sulfate administration decreases cardiovascular risk factors. Our results support the hypothesis that magnesium plays a part in the management of diabetes and the prevention of its vascular complications in streptozocin-induced diabetic rats and that it may be useful in the treatment of hyperlipidaemia in diabetic case. However, more studies are needed to confirm the role of magnesium in lipid metabolism control.

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