

Research Article

Effect of Oral Magnesium treatment on Haematological, Biochemical profile and Liver Glycogen content in Rats

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Abstract

Oral magnesium supplementation has been advocated for its therapeutic and glucose regulatory effects. This study evaluated the haematology, serum biochemical profile and liver glycogen content in male Wistar rats orally treated with magnesium. Two studies were carried out using 50 male rats randomly divided into 2 groups of 25 rats each. Each study group was divided into 5 groups of 5 rats each as follows: Group 1 served as control, groups 2,3,4 and 5 received magnesium orally at 50mg/kg,100mg/kg,250mg/kg and 500mg/kg respectively for 28 days. Results showed no significant difference after 28 days in PCV, haemoglobin, RBC, WBC, MCV, MCHC, lymphocyte, neutrophil, monocyte, eosinophil, total protein, bilirubin, cholesterol, triglyceride, very low density lipoprotein (VLDL), AST, ALT and ALP levels while a significant increase ($P<0.05$) in platelet count, albumin level and albumin/globulin ratio was observed in magnesium treated animals at all doses used compared to controls. Globulin levels were significantly reduced ($P<0.05$) in groups 2, 4 and 5 while fibrinogen levels were significantly increased ($P<0.05$) in groups 2, 3 and 4 compared to controls. HDL levels were significantly increased in the 50mg/kg magnesium treated rats compared to control. Liver glycogen content was significantly increased ($P<0.05$) in the 100mg/kg (45.9%) and 250mg/kg (47.7%) magnesium treated rats. This study shows that oral administration of magnesium at 50,100,250 and 500mg/kg in normoglycemic rats is non-toxic, stimulates albumin, fibrinogen and platelet production and does not affect the lipid profile. At doses of 100mg/kg and 250mg/kg, oral magnesium administration may likely increase storage of glucose as glycogen in the liver.

Keywords: Magnesium supplementation, haematology, serum biochemistry, lipid profile, glycogen

INTRODUCTION

Minerals play key roles in maintaining proper body functions. They have been reported to act as co-factors in chemical reactions, support the immune system and the nervous system as well as contribute to the general growth, development and well being of the body (Shenkin, 2006). Minerals are inorganic substances that are present in all body tissues and fluids. They are reported to be necessary for the maintenance of physicochemical processes essential to life (Soetan *et al.*, 2010) and participate in energy metabolic processes in order to maintain optimal function of the cells and tissues in the body. Minerals are however not produced in the body and hence must be obtained either from food or in supplements (Shenkin, 2006).

It has been reported that magnesium is the fourth most abundant cation in the body and is known to be important in over 300 enzyme dependent pathways (Swaminathan, 2003). It is naturally present in many food products, available as dietary supplements and is present in many medications such as antacids and laxatives (Cunningham *et al.*, 2012). Reduced magnesium content in food sources (Sabatier *et al.*, 2002) and dietary magnesium deficiency has been implicated in the aetiology and progression of many disease processes (Johnson, 2001).

Various studies have reported the potential therapeutic effect of adequate magnesium intake and amelioration of symptoms in conditions like eclampsia, pre-eclampsia,

arrhythmia, severe asthma and migraine (Guerrera *et al.*, 2009). Magnesium supplementation has been reported to lower the risk of developing metabolic syndrome (He *et al.*, 2006), relieves the symptoms of dysmenorrhoea and alleviates leg cramps in pregnant women (Guerrera *et al.*, 2009). Magnesium supplementation improves insulin sensitivity, secretion and metabolism, reduces insulin stimulated glucose uptake, stabilizes blood glucose levels and improves glucose utilization (Lal *et al.* 2003, Barbagallo *et al.* 2007, Wang *et al.*, 2013).

The recommended daily allowance (RDA) of magnesium has been reported to be between 150 - 500mg/kg depending on age, gender and whether pregnant or not (Scientific Committee for Foods, 1993). However some researchers suggest that the upper limits for oral magnesium intake should not exceed 360mg/kg as side effects such as diarrhoea may manifest at high doses (Institute of Medicine, 1997). Magnesium homeostasis is largely controlled by the kidneys which excrete about 120mg of magnesium into the urine per day (Rude, 2010). Though studies suggest that magnesium supplementation is generally non-toxic provided normal kidney function is maintained (Musso, 2009), there is however a dearth of information on haematological and serum biochemical changes that may occur due to oral magnesium supplementation. In addition, the glucose stabilizing effect of magnesium is widely reported but its effect on liver glycogen content is unclear.

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The liver plays an important and crucial role in the regulation of carbohydrates metabolism and synthesis of glucose from non-carbohydrate precursors (Roden *et al*, 2003). It also plays a pivotal role in the maintenance of glucose homeostasis (Xin *et al*, 2012).

This study investigates haematological, serum biochemical, serum lipid changes and liver glycogen content in Wistar rats orally treated with magnesium at doses of 50, 100, 250 and 500mg/kg respectively.

MATERIALS AND METHODS

Animal Grouping: Fifty male Wistar rats weighing between 160 - 200gm were obtained from the Central Animal House, College of Medicine, University of Ibadan. They were housed in well aerated cages, fed on standard rat chow and allowed free access to drinking water according to the guidelines and regulations of the National Institute of Health (NIH) NIH Publication, 85 – 23, 1985). Two studies were carried out using 25 rats per study. Study A assessed haematological and biochemical parameters while study B assessed the blood lipid profile and liver glycogen content in normal and magnesium treated animals. Each study group was divided into 5 groups of 5 rats each. Group 1 served as control, groups 2, 3, 4 and 5 received magnesium (as MgSO₄) orally at 50, 100, 250 and 500mg/kg respectively for 28 days.

Blood sampling and analysis: Blood samples were obtained from the tail vein weekly (days 0, 7, 14, 21 and 28) for blood glucose evaluation and from the orbital sinus of the rats using non-heparinized capillary tubes into clean EDTA containing test tubes after 28 days of treatment. Blood glucose level was measured using the principle of glucose oxidase method as described by Trinder (1969). Blood samples obtained after 28 days post treatment was assessed for haematological, biochemical changes and liver enzymes.

Haematological Assessment: Haematological parameters were determined using standard laboratory techniques as follows: Packed cell volume (PCV) was determined by allowing whole blood to enter heparinized microhematocrit capillary tubes by capillary action, sealed at one end with plasticin and centrifuged for 3 minutes using a microhaematocrit centrifuge at 10000rpm. The separated cells were read off a hematocrit reader. Haemoglobin (Hb) concentration was assessed using Sahli's method. Red blood cell (RBC) and total white blood cell (WBC) counts were determined using the haemocytometer; the Wright's stain was used for differential WBC (lymphocytes, neutrophil, monocytes, eosinophil) count and the Ressa-Ecker method for platelet count. The Mean corpuscular haemoglobin concentration (MCHC) and Mean corpuscular volume (MCV) were thereafter calculated.

Serum Biochemical and Lipids Assessment: Blood samples (4mls) were collected from the retro-orbital sinus for biochemical analysis. The blood was allowed to stand at room temperature to obtain serum and thereafter centrifuged at 3000rpm for ten minutes to isolate the serum. Total protein and albumin concentrations were assayed using spectrophotometric methods while the globulin level was calculated. Bilirubin levels were determined using colorimetric methods and fibrinogen was assayed using heat

precipitation method. Serum cholesterol, high density lipoproteins (HDL) and triglycerides were determined using enzymatic procedures using Randox laboratory kits, Randox, United Kingdom. Very low density lipoproteins (VLDL) levels were estimated mathematically using Friedewalds equation (1972).

Liver Glycogen Assessment: The liver glycogen content was determined by reacting crude liver homogenate with anthrone reagent to form a blue-coloured solution that is compared spectrophotometrically with that formed by a known amount of glycogen (Seifter *et al*, 1950; Jermyn, 1975).

Liver Function Test: Serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and alkaline Phosphatase (ALP) were determined using Randox kits, Randox laboratories United Kingdom.

Statistical Analysis

Results obtained are expressed as mean $\pm$ SEM and the level of statistical significance was taken at $p < 0.05$ using the Student's T test.

RESULTS

Effect of Magnesium on Haematological Indices

The effect of oral magnesium supplementation on haematological indices in male rats is shown in Table 1. There were no significant differences ($P > 0.05$) in PCV, Hemoglobin, RBC, WBC, MCV, MCHC, lymphocyte, neutrophil, monocyte and eosinophil level in magnesium treated animals at all doses when compared to the control (group 1). However significant increase ($P < 0.05$) in platelet count (17.4%, 5%, 33%, 17.2%) was observed in groups 2, 3, 4 and 5 respectively compared to the control group (Table 1).

Effect of Magnesium on Serum Biochemistry

Total protein and bilirubin levels in the magnesium treated rats were not significantly different ($P > 0.05$) from the control group. Albumin level was significantly increased ($P < 0.05$) in all magnesium treated groups compared to the control, while globulin levels were significantly reduced in groups 2, 4 and 5 compared to controls (Table 2). The albumin / globulin ratio was significantly increased ($P < 0.05$) in all treated groups compared to control while fibrinogen levels were increased by 88.7%, 77.3%, 55.3% and 11.1% in groups 2,3,4, and 5 respectively compared to controls (Table 2).

Effect of Magnesium on the Lipid profile:

There was no significant difference in the cholesterol, triglyceride and very low density lipoprotein (VLDL) levels in the magnesium treated rats compared to controls rats (Table 3). HDL levels were significantly increased in the 50mg/kg magnesium treated rats compared to control while HDL values observed in all the other magnesium treatment groups were not statistically significant compared to controls.

Effect of Magnesium on Blood Glucose level

There was no significant difference in blood glucose level in all the magnesium treated rats when compared with the control rats (Table 4).

Table 1:

Effect of oral Magnesium on Haematological Indices

Haematological indices	Control	Mg (50mg/kg)	Mg(100mg/kg)	Mg (250mg/kg)	Mg (500mg/kg)
PCV (%)	46.7±0.8	45.8±0.9	45.0±1.9	45.8±0.9	45.0±0.9
Hb (g/dl)	15.5±0.3	15.2±0.7	14.9±0.7	15.4±0.7	14.7±0.3
RBC count (10 ¹² /L)	7.5±0.1	7.5±0.2	7.2±0.3	7.6±0.2	7.4±0.1
WBC count (10 ⁹ /L)	4.3±0.5	4.7±0.6	5.1±0.9	4.8±0.5	4.3±0.6
Platelets (mm ³ /L)	73666±1757	86500±1888*	77000±1713*	98000±1184*	98000±1184*
MCV (fl)	61.8±0.9	60.2±1.1	62.3±0.3	59.8±1.1	60.5±1.3
MCHC	32.8±0.3	32.7±0.3	32.7±0.3	32.5±0.9	32.5±0.2
Lympo (%)	73.2±2.5	70.8±2.7	65.7±3.3	68.8±2.2	70.3±2.7
Neut (%)	21.0±2.6	24.2±2.8	30.0±3.2	26.5±2.7	24.8±3.4
Mono (%)	2.7±0.3	2.7±0.6	1.7±0.4	2.7±0.5	2.5±0.3
Eos (%)	3.2±0.6	3.3±0.6	2.7±0.2	2.3±0.6	3.3±0.4

Values represent Mean ± SEM. * indicate value significantly different ($P<0.05$) from control values. PCV = Packed cell volume, Hb = Hemoglobin, RBC = Red blood cell, WBC = White blood cell, MCV = Mean corpuscular volume, MCHC = Mean corpuscular haemoglobin concentration, Lympo = Lymphocytes, Neut = Neutrophil, Mono = Monocytes, Eos = Eosinophil

Table 2:

Effect of oral Magnesium on serum Biochemical Indices

Biochemical indices	Control	Mg (50mg/kg)	Mg(100mg/kg)	Mg (250mg/kg)	Mg (500mg/kg)
Total Protein (g/dl)	7.2±0.09	7.6±0.17	7.4±0.12	7.3±0.14	7.1±0.07
Albumin (g/dl)	3.3±0.05	4.7±0.09*	4.3±0.21*	3.9±0.14*	3.6±0.06*
Globulin (g/dl)	4.0±0.11	3.4±0.16*	3.8±0.04	3.3±0.24*	3.5±0.11*
A/ G ratio	0.8±0.04	1.3±0.07*	1.1±0.03*	1.2±0.08*	1.0±0.04*
Fibrinogen (mg/dl)	150.0±22.4	283±30.73*	266.7±22.35*	233.3±29.44*	166.7±23.33
Bilirubin (mg/dl)	0.30±0.03	0.30±0.05	0.40±0.03	0.30±0.04	0.30±0.03

Values represent Mean ± SEM. * indicate value significantly different ($P<0.05$) from control values. A.G ratio = Albumin: Globulin ratio.

Table 3:

Lipid Profile in Control and Magnesium treated rats

Doses of Magnesium	CHOL (mg/dl)	HDL(mg/dl)	TG (mg/dl)	VLDL (mg/dl)
Group 1 (Control)	52.93±4.08	52.39±2.04	34.19±2.40	6.84±0.48
Group 2 Mg(50mg/kg) treated	59.40±3.67	67.82±2.17*	29.98±4.35	6.00±0.86
Group 3 Mg(100mg/kg) treated	45.71±9.86	54.31±2.49	31.86±4.41	6.37±0.88
Group 4 Mg(250mg/kg) treated	50.66±4.03	49.41±3.03	32.54±0.37	6.51±0.08
Group 5 Mg(500mg/kg) treated	46.26±2.69	49.37±3.60	43.45±7.42	8.69±1.48

The values are Mean ± Standard Error of Mean. * indicates values that are significantly different from control values ($P<0.05$). CHO = Total Cholesterol, HDL = High Density Lipoprotein, TG = Triglyceride, VLDL = very Low Density Lipoproteins (VLDL)

Table 4:

Effect of oral Magnesium on Fasting blood glucose level (mg/dl)

	Fasting Blood Glucose Level (mg/dl)				
	Day 0	Week 1	Week 2	Week 3	Week 4
Group 1 (Control)	80±5.31	91±1.4	89±3.1	88±3.0	76±1.3
Group 2 Mg(50mg/kg) treated	85±4.45	91±5.6	80±2.9	89±1.0	84±1.6
Group 3 Mg(100mg/kg) treated	80±4.36	92±3.8	92±2.8	80±2.8	85±3.9
Group 4 Mg(250mg/kg) treated	89±1.67	94±3.1	83±3.0	77±1.8	92±1.8
Group 5 Mg(500mg/kg) treated	83±1.54	88±3.2	82±1.7	82±1.7	73±1.3

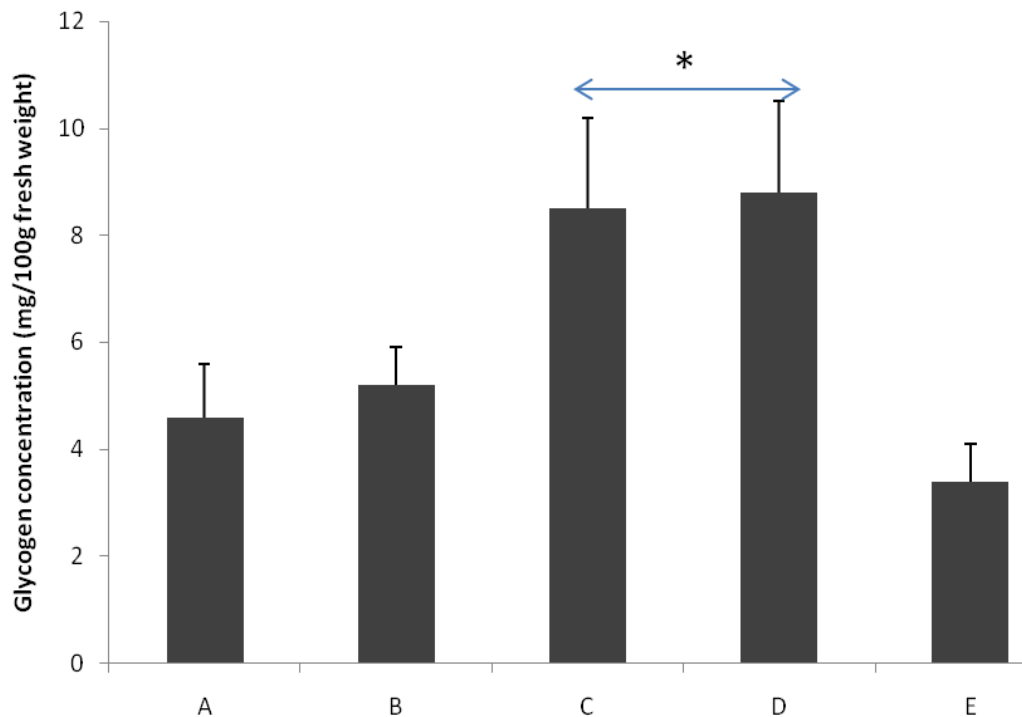
The values are mean± Standard Error of Mean.

Table 4

Effect of oral Magnesium on Liver enzymes

Liver Enzymes	Control	Mg (50mg/kg)	Mg(100mg/kg)	Mg (250mg/kg)	Mg (500mg/kg)
AST (U/I)	41.2±0.9	42.7±1.3	41.0±1.0	43.8±0.9	43.0±1.2
ALT (U/I)	29.2±1.1	30.8±1.1	31.0±1.5	31.8±0.7	30.5±0.6
ALP (U/L)	80.3±3.2	87.8±3.5	86.3±9.3	87.2±4.2	85.8±4.8

Values are Mean ± SEM. AST = Aspartate aminotransferase, ALT = alanine aminotransferase and ALP = Alkaline Phosphatase.

**Fig. 1**

Liver Glycogen concentration in Control and Magnesium treated rats. Values are Mean ± SEM. * indicates values that are significantly different ($P < 0.05$) from control values. A = Control, B = Magnesium 50mg/kg treated, C = Magnesium 100mg/kg treated, D = Magnesium 250mg/kg treated, E = Magnesium 500mg/kg treated

Effect of Magnesium on Liver Glycogen content

There was significant increase in the 100mg/kg (45.9%) and 250mg/kg (47.7%) magnesium treated rats while 50mg/kg and 500mg/kg magnesium treated rats showed no significant difference compared to control rats (Fig 1).

Effect of Magnesium on Liver Enzymes

There were no significant differences ($P > 0.05$) in AST, ALT and ALP levels in all magnesium treatment groups compared to control (Table 5).

DISCUSSION

Haematologic and serum biochemical indices are important tools in evaluating the health status of an individual. Changes in normal values of these indices are usually indicative of a pathophysiological process in the body (NseAbasi *et al.*, 2014). In this study, oral magnesium supplementation at 50, 100, 250 and 500mg/kg showed no significant effect on PCV, Haemoglobin, RBC, WBC, MCV, MCHC, lymphocyte, neutrophil, monocyte and eosinophil level suggesting that magnesium supplementation at these doses do not alter haematological indices. The principal function of platelets is

to prevent bleeding and in this study, an increase in platelet count was observed in the magnesium treated animals; this is in accordance with Rishi *et al.*, (1990) who reported an increase in platelet level after oral magnesium supplementation. It is therefore likely that oral magnesium supplementation at the doses used might have potentiated platelet production.

Plasma proteins are known to perform important function in the body ranging from blood buffering, transport of different substances and acting as protein reservoirs for the body. Assessment of these proteins has been reported to provide early signal of potentially deleterious changes in a stressed animal (Vasile *et al.*, 2009). This study showed no significant change in total protein concentration in the treated animals thus suggesting that treatment at the doses used was non-stressful and non-inflammatory in the rats. However, differential protein analysis showed an increase in albumin level in all magnesium treated rats compared to control.

Moe *et al.*, (2005) reported that 55% of Magnesium in the blood is free (ionized), 30% bound to proteins (primary albumin) and 15% is combined to anions. Hence, it is likely that the increased albumin content observed in the magnesium treated animals may be due to an increase in magnesium absorption in the gut which would require more albumin for

adequate transport in blood. Differential protein analysis also showed no change in globulin level in the treated animals suggesting that oral administration of magnesium at the doses used did not affect the functions of globulin in the circulatory system which include immune response, clot formation and protein transport.

Fibrinogen, a soluble glycoprotein found in plasma, is known to play a significant role in blood clot formation. Elevated fibrinogen levels can be seen in conditions such as in inflammation, tissue damage/trauma and infections (Monroe 2010). This study showed an increase in fibrinogen values in the magnesium treated rats however, values obtained were still within the normal physiological range of 150 – 400mg/dl (Johnson-Delaney, 1996). This suggests that oral magnesium treatment at the doses used did not activate any pro-inflammatory mechanisms. In addition to this, bilirubin and liver enzymes values obtained in this study indicate that oral magnesium supplementation at the doses used was non-toxic to red blood cells and hepatocytes.

Blood lipids (total cholesterol, high density lipoproteins (HDL), triglyceride, low density lipoproteins (LDL) and very low density lipoproteins (VLDL) are often assessed clinically to diagnose predispositions to disease processes such as diabetes mellitus and cardiovascular diseases. This study showed no change in lipid profile in treated animals except for the 50mg/kg treated rats that showed an increase in HDL level compared to controls. This is at variance with other studies that report reductions in total cholesterol, LDL, triglyceride levels and an increase in HDL in magnesium treated subjects (Corica *et al.*, 1994, Lal *et al.*, 2003). It should however be noted that these other studies reported the effect of oral magnesium supplementation in different pathological conditions such as diabetes mellitus, hypertension, diabetic retinopathy and the metabolic syndrome. This study on the lipid profile after oral magnesium supplementation is however consistent with Marken *et al.*, (1989) and Mooren *et al.*, (2011) who reported no change in lipid profile after oral magnesium supplementation in normal subject.

Magnesium supplementation has been widely reported to stabilize blood glucose level in diabetes mellitus (Song *et al.*, 2006). It is also known to exert hypoglycaemic effects and increase insulin sensitivity in cells (Barbagallo and Dominguez, 2007). In normal subjects, it has been reported to reduce insulin resistance at the tissue and cellular level (Mooren *et al.*, 2011). In this study, blood glucose level remained relatively stable in the treated rats suggesting that oral magnesium treatment has no effect on blood glucose level in normo-glycemic rats.

The liver plays a central and crucial role in the regulation of carbohydrates metabolism and synthesis of glucose from non-carbohydrates precursors (Roden *et al.*, 2003). It is known to also play a pivotal role in the maintenance of glucose homeostasis by adapting to the bodies energetic needs leading to the release of glucose in times of hypoglycaemia and facilitating the uptake of excess glucose from the blood stream in the hyperglycaemic state (Roden *et al.*, 2003). Magnesium has been reported to be vital in the conversion of glycogen to glucose for use as energy (Noronha and Matuschak, 2002). This study reports an increase in liver glycogen content in rats orally treated with magnesium at 100mg/kg and 250mg/kg suggesting that at this doses magnesium may not only be important in cellular glucose utilization (Noronha and Matuschak, 2002) but may also facilitate the storage of glucose as glycogen in the liver. This is in accordance with the

study of Barbagallo and Dominguez (2007) who reported that magnesium potentiates the actions of insulin one of which includes increasing the storage of glucose as glycogen in the liver. Interestingly, magnesium treatment at 500mg/kg caused an insignificant reduction in liver glycogen compared to controls; the reason for this is presently unknown and is currently under investigation in our laboratory.

In conclusion, oral administration of magnesium at 50,100,250 and 500mg/kg is not toxic to blood and liver cells as haematological and biochemical indices are within normal range and liver enzyme activities were also comparable to control. Magnesium at the doses used, stimulates albumin and fibrinogen production, does not affect the lipid profile and causes an increase in platelet count. At 100mg/kg and 250mg/kg, oral magnesium administration most likely increases storage of glucose as glycogen in the liver.

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