



SJMLS-4(1)-003

Magnesium Deficiency is associated with Insulin Resistance among Nigerians with Type 2 DiabetesAbdullahi Mohammed¹, Ibrahim M. Bello²Department of Chemical Pathology, Gombe State University, Gombe, Nigeria¹, Department of Internal Medicine, Federal Teaching Hospital, Gombe, Nigeria²

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Abstract

Alteration in magnesium metabolism has been implicated in the pathogenesis of the insulin resistance in type 2 diabetes mellitus and its associated complications. However, findings from previous studies across different ethnic groups are inconsistent. Determinants of insulin resistance differ in different populations because of environmental and genetic reasons. The aim of this study was to determine the relationship between plasma magnesium level and degree of insulin resistance among a group of patients with type 2 diabetes mellitus in a Specialist Hospital in North Eastern Nigeria. Fasting plasma glucose, magnesium and insulin levels were estimated in 40 type 2 diabetic subjects and 40 apparently healthy controls. Insulin resistance was calculated as HOMA-IR. Subjects with type 2 diabetes mellitus were more insulin resistant than the normal control subjects (4.1 ± 1.1 vs. 1.9 ± 0.4 , $p < 0.05$). Decreased plasma magnesium level was associated with increased insulin resistance in subjects with type 2 diabetes mellitus, independent of age and BMI ($r = -0.52$, $p < 0.05$). We conclude that subjects with type 2 diabetes mellitus in this study have lower plasma magnesium level and that lower plasma magnesium is associated with increased insulin resistance. We recommend optimization of magnesium status in type 2 diabetic patients in our setting.

Keywords: Type 2 diabetes mellitus; Magnesium; Homeostasis model assessment for insulin resistance (HOMA-IR); Nigeria

Introduction

Diabetes mellitus is a growing public health burden across the world, particularly in the developing nations (Wild *et al.*, 2004). Nigeria has the highest burden of diabetes in Africa with about 5.0 million cases. The prevalence of diabetes mellitus in Nigeria has doubled from 2.2% in 1997 to 5.0% in 2013, with more than 95% of cases being type 2 diabetes mellitus. It is a chronic debilitating condition associated with severe complications (Olufemi and Samuel, 2015; Oputa and Chinenye 2015; Ofoegbu and Chinenye 2013; Shaw *et al.*, 2010). A better understanding of the pathogenesis of type 2 diabetes mellitus will help in devising means target at its prevention, optimization of treatment and reduction of its complications.

Insulin resistance, which is defined as a state in which more insulin is required to obtain the physiological effects achieved by a lower insulin level in a normal state, plays a key role in the pathogenesis of type 2 diabetes mellitus (Lebovitz, 2001). It is the precursor or driving factor that leads to type 2 diabetes mellitus (Lebovitz, 2001). The exact cause of insulin resistance in type 2 diabetes mellitus is not fully understood, however, a number of mechanisms have been suggested as possible causes underlying the pathogenesis of insulin resistance among patients with type 2 diabetes mellitus. Alteration in magnesium metabolism has been proposed to be one of the potential mediators of the insulin resistance. In magnesium deficiency state, activation of insulin receptors, whose function is dependent on the binding of two magnesium ions, may result in decreased signal

transduction, thereby contributing to insulin resistance (Hubbard, 1997, Kandeel *et al.*, 1996). Several studies have examined the relationship between plasma magnesium levels and degree of insulin resistance in patients with type 2 diabetes mellitus. While some authors reported increased insulin resistance among type 2 diabetic patients with hypomagnesemia, others do not confirm this relationship (Siba *et al.*, 2017; Velayutharaj *et al.*, 2016; Happy and Kyrshanlang, 2015; Dae *et al.*, 2010; Lima *et al.*, 2009; Lima *et al.*, 2005; Nadler *et al.*, 1993).

Studies on the association between serum levels of magnesium and insulin resistance in type 2 diabetes mellitus among patients of African ancestry are few, and mainly done among African Americans. While determinants of insulin resistance differ in different populations because of environmental and genetic reasons, the role of magnesium deficiency in the development of insulin resistance among Black Africans living in sub Saharan Africa has not been clearly determined. This study was therefore designed to investigate the relationship between plasma magnesium level and insulin resistance in a group of Nigerian patients with type 2 diabetes mellitus at a Specialist Hospital in North Eastern Nigeria.

Materials and method

This is a cross sectional analytical study conducted at the medical outpatient clinic of Gombe State Specialist Hospital, Gombe, Nigeria. We studied forty (40) type 2 diabetic subjects on treatment with no complications who gave informed consent. Forty (40) apparently healthy volunteers with no personal or family history of diabetes mellitus were included as controls. Diagnosis of diabetes mellitus was based on WHO diagnostic criteria (World Health Organization, 2016). While patients were classified as having type 2 diabetes mellitus based on clinical ground of non-dependence on insulin therapy for survival. All study subjects are Nigerians of African descent and living in Gombe State. We excluded subjects who had clinical or biochemical evidence of any other pre-existing illness; those who had evidence of secondary diabetes mellitus and those who were pregnant, breastfeeding or using oral

contraceptives. We further excluded those who smokes or ingests alcohol. Insulin dependence, current insulin therapy and other medications known to interfere with insulin and/or magnesium metabolism were also part of the exclusion criteria.

The study protocol was approved by the Health Research Ethics committee of the Gombe State Ministry of Health, Gombe, Nigeria.

The study subjects were evaluated in the morning following 10-12 hours overnight fasting. History and physical examination were performed in each of the study subjects at the time of blood sample collection. Information on age, gender and duration of disease were recorded. Height was taken with subjects standing erect without shoes or headgear and rounded to the nearest centimetre. Weight of the study subjects were measured with only undergarment and rounded to the nearest 0.1 kilogram. Body mass index was calculated as weight in kilogram divided by height in meters squared and expressed as kg/m^2 .

Sample collection

Venous blood samples were collected following 10-12 hours overnight fasting. Blood was collected in heparin bottles and centrifuged immediately for 15 minutes. Plasma were collected and frozen in aliquots at -20°C until analysed.

Laboratory analysis

Plasma magnesium was measured using a colorimetric assay kit (Agappe Diagnostics Limited, India). Insulin was analyzed using an Enzyme linked immunosorbent assay (ELISA) kit (Monobind Inc. USA). Glucose was measured using glucose oxidase method (Agappe Diagnostics Limited, India). All laboratory analyses were done at the Chemical Pathology laboratory of Gombe State University/Federal Teaching Hospital, Gombe.

Calculation of indices

Insulin resistance was calculated as Homeostatic Model Assessment-IR (HOMA-IR). $\text{HOMA-IR} = \text{Fasting plasma insulin (FPI)} \times \text{Fasting plasma glucose (FPG)} / 22.5$ (Matthews *et al.*, 1985) with FPI in mIU/mL and FPG in mmol/L .

Statistical analysis

Statistical package for social sciences (SPSS) version 20.0 was used for statistical analysis. Data are presented using measures of central tendency and dispersion. Kolmogorow-Smirnov test was used to test for normality of distribution of data. A logarithmic transformation was used to improve the normality of distribution of plasma magnesium and HOMA-IR. We compare mean differences of plasma magnesium and HOMA-IR between groups using t-test. Association between plasma magnesium and HOMA-IR was examined using partial correlation and linear regression analyses. All p-values were two-sided and considered significant if less than 0.05.

Results

Demographic parameters of the study subjects are presented in Table 1. Study subjects with type 2 diabetes mellitus were older (52.1 ± 5.0 years vs. 40.9 ± 5.5 years, $p < 0.05$) and have greater body mass index ($28.0 \pm 3.7\text{kg/m}^2$ vs. $23.3 \pm 3.6\text{kg/m}^2$, $p < 0.05$) than subjects in the control group. About 35% of subjects in the type 2 diabetes mellitus group were females, whereas only 20% of the control subjects were females. Mean duration of type 2 diabetes mellitus was 5.4 years.

Biochemical data of the study subjects are shown

in Table 2. Subjects with type 2 diabetes mellitus had significantly lower plasma magnesium levels compared with subjects in the control group ($0.74 \pm 0.10\text{mmol/L}$ vs. $0.89 \pm 0.23\text{mmol/L}$, $p < 0.05$). Degree of insulin resistance, as measured by HOMA-IR, was observed to be significantly higher in subjects with type 2 diabetes mellitus than in the controls (4.1 ± 1.1 vs. 1.9 ± 0.4 , $p < 0.05$).

The relationship between plasma magnesium and degree of insulin resistance was examined (Table 3 and Figure 1). There was a negative correlation between plasma magnesium levels and insulin resistance as measured by HOMA-IR among subjects with type 2 diabetes mellitus adjusted for age, body mass index and duration of diabetes mellitus ($r = -0.52$, $p < 0.05$). Linear regression analysis was used to determine the contribution of plasma magnesium level to HOMA-IR in subjects with type 2 diabetes mellitus. The adjusted R-square was 0.19, indicating that 19% of the variance in insulin resistance among the subjects with type 2 diabetes mellitus can be attributed to the plasma level of magnesium. Plasma magnesium was found to be a significant predictor of insulin resistance among the study subjects with type 2 diabetes mellitus.

Table 1: Demographic parameters of the study subjects

Variables	Type 2 DM (M ± SD)	Controls (M ± SD)	p-value
Sample size (n)	40	40	-
Age (years)	52.1 ± 5.0	40.9 ± 5.5	0.000
Gender ratio (M/F)	26/14	32/8	-
Duration of type 2 DM (years)	5.4	-	-
Body Mass Index BMI (kg/m^2)	28.0 ± 3.7	23.3 ± 3.6	0.000
Systolic blood pressure (mmHg)	116.0 ± 10.0	117.8 ± 6.2	0.334
Diastolic blood pressure (mmHg)	77.5 ± 5.9	79.0 ± 3.8	0.179

Key: M= Mean; SD= Standard deviation; DM= Diabetes mellitus

Table 2: Biochemical parameters of the study subjects

Variable	Type 2 DM (M ± SD)	Controls (M ± SD)	p-value
Sample size(n)	40	40	
Fasting plasma glucose(mmol/L)	9.0 ± 0.9	5.3 ± 0.7	0.000
Fasting plasma insulin(μU/mL)	10.2 ± 2.8	8.1 ± 2.2	0.000
Plasma magnesium (mmol/L)	0.74 ± 0.10	0.89 ± 0.23	0.000
HOMA-IR	4.1 ± 1.1	1.9 ± 0.4	0.000

Key: M= Mean; S= Standard deviation; HOMA-IR= homeostasis model assessment-insulin resistance; DM= Diabetes mellitus

Table 3: Correlation of plasma magnesium with anthropometric and biochemical factors

Variable	Type 2 DM patients		Controls	
	R	p-value	r	p-value
Age (years)	0.10	0.707	-0.58	0.000
Duration of DM (years)	-0.11	0.518	-	-
BMI (kg/m ²)	-0.04	0.795	-0.82	0.000
Fasting plasma insulin(μU/ml)	-0.45	0.004	-0.002	0.992
HOMA-IR	-0.52	0.001	-0.15	0.357

Key: HOMA-IR= homeostasis model assessment-insulin resistance; BMI= body mass index; r= correlation coefficient; DM= Diabetes mellitus

Table 4: Multiple linear regression analysis with Log HOMA-IR as a dependent variable

Independent variables	Type 2 DM (n=40) R ² = 0.19		
	β-value	SE	p-value
Constant	0.42	0.211	0.055
Age	0.02	0.004	0.928
Duration of DM	-0.02	0.014	0.911
BMI	0.02	0.005	0.923
Log Plasma Mg	-0.52	0.305	0.001

Key: HOMA-IR= homeostasis model assessment-insulin resistance; β = regression coefficient; SE= standard error; BMI= body mass index; DM= diabetes mellitus; Mg= magnesium

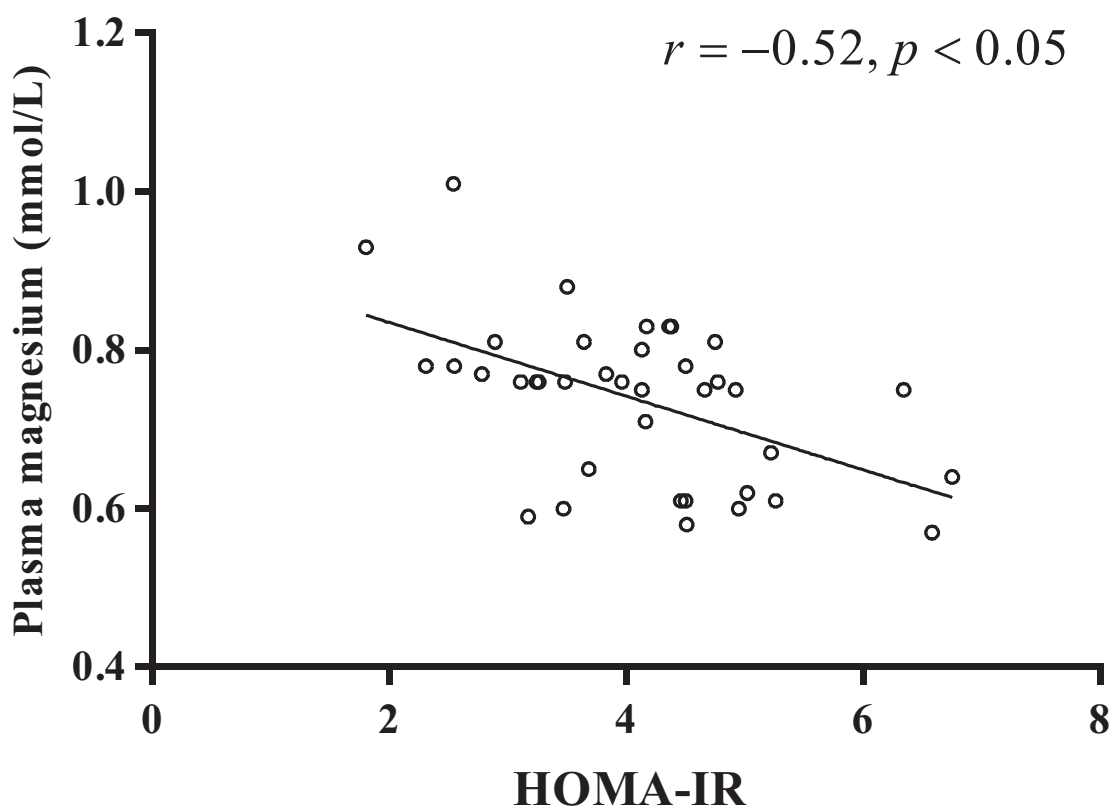


Figure 1: Correlation between plasma magnesium levels and HOMA-IR in subjects with type 2 diabetes mellitus.

Key: HOMA-IR= homeostasis model assessment-insulin resistance

Discussion

We examined the correlation between plasma level of magnesium and degree of insulin resistance among a group of Nigerian patients with type 2 diabetes mellitus. In the present study we reported that decreased plasma level of magnesium is significantly associated with increased insulin resistance among subjects with type 2 diabetes mellitus. This association remained significant even after adjustment for age, body mass index and duration of disease.

Similar finding among type 2 diabetic patients has been reported in previous studies, where hypomagnesemia was shown to be associated with increased insulin resistance in patients with type 2 diabetes mellitus (Siba *et al.*, 2017; Velayutharaj *et al.*, 2016; Happy and Kyrshanlang, 2015; Lima *et al.*, 2009). Also, in support of the results of this study Dae *et al.* (2010) showed that low dietary magnesium among apparently healthy adults are associated

with higher risk of developing type 2 diabetes mellitus. Furthermore, similar results were found in a study involving apparently healthy subjects, where induced hypomagnesemia reduced insulin secretion and action (Nadler *et al.*, 1993).

However, the findings of Lima *et al.* (2005) did not show significant association between plasma magnesium levels and HOMA-IR in a cohort of type 2 diabetic subjects. Their negative findings might be explained by the limited sample size (27 type 2 DM subjects) and the relatively younger study subjects (mean age of 33 years for the type 2 DM subjects), with poorly controlled disease.

Hypomagnesaemia could contribute to the development of insulin resistance in subjects with type 2 diabetes mellitus, as the physiological function tyrosine kinase receptors

family, for which, insulin receptors belong, depends on the binding of two magnesium ions (Hubbard, 1997). Following the activation of insulin receptors, a complex intracellular signalling cascade is activated and mediated through proteins of the insulin receptor substrate (Taniguchi *et al.*, 2006). In hypomagnesaemia, activation of insulin receptors can cause a decrease in signal transduction, which contributes to insulin resistance (Reis *et al.*, 2000, Suarez *et al.*, 1995). It has also been proposed that increased expression of inflammatory mediators and reactive oxygen species in magnesium deficiency may contribute to insulin resistance (de Luca *et al.*, 2008, Guerrero-Romero and Rodríguez-Morán, 2006). Previous studies reported that serum magnesium level is inversely related to circulating levels of C-reactive protein, suggesting that hypomagnesaemia is related to the onset of low-grade chronic inflammation, which is associated with insulin resistance (Kim *et al.*, 2010; Rodríguez-Morán and Guerrero-Romero, 2008; Song *et al.*, 2007; Rumawas *et al.*, 2006; Guerrero-Romero and Rodríguez-Morán, 2002). Therefore, magnesium deficiency may be implicated in the pathogenesis of insulin resistance via the deterioration of the enzymatic pathways involved in cellular transport of glucose and utilization, as well as by the triggering of low-grade chronic inflammation (Barbagallo and Dominguez, 2007).

Limitations

Total plasma magnesium, rather than intracellular magnesium, a more sensitive indicator of magnesium status, was measured. Also, HOMA-IR is only a surrogate marker of insulin resistance based on fasting insulin and glucose levels. The degree to which these might have influenced the findings of this study requires further investigation.

Conclusion

We conclude that among subjects with type 2 diabetes mellitus in this study lower plasma magnesium level is associated with increased insulin resistance. We recommend further studies to investigate whether increasing dietary consumption of foods with high magnesium content and/or magnesium supplementation will

be a useful approach in improving insulin sensitivity and thus improved metabolic control among type 2 diabetic patients with magnesium deficiency in our setting.

Acknowledgement

We would like to thank staff of the Department of Health Records, Federal Teaching Hospital, Gombe for their help in acquiring the data. We are also grateful to all the study participants. There was no external funding source. The study was funded by personal financial contributions from the authors.

Conflict of interest: Nil

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Citation: Abdullahi Mohammed, Ibrahim M. Bello. Magnesium Deficiency is associated with Insulin Resistance among Nigerians with Type 2 Diabetes. *Sokoto Journal of Medical Laboratory Science*;4(1): 21 - 27.

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