Impact of Magnesium Deficiency on Pancreatic β-Cell Function in Type 2 Diabetic Nigerians

Abdullahi Mohammed[1*], Ibrahim M. Bello[2]

1. Department of Chemical Pathology Gombe State University, Gombe, Nigeria.
2. Department of Internal Medicine Federal Teaching Hospital, Kano, Nigeria.

***Correspondence:**
Abdullahi Mohammed, Department of Chemical Pathology Gombe State University, Gombe, Nigeria.
Tel: (234) 703 769 1408
Email: drgombe@gmail.com

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Abstract

Objective: Pancreatic β-cell dysfunction is described to be present at the diagnosis of type 2 diabetes mellitus (T2DM) and progressively deteriorated with disease duration. However, its progression is variable and potentially influenced by several factors. The Magnesium (Mg) deficiency mediates insulin resistance but reports regarding its role in pancreatic β-cell dysfunction are scarce and conflicting. The aim of this study was to evaluate Mg deficiency effect on pancreatic β-cell function in T2DM patients at a specialist hospital in north eastern Nigeria.

Materials and Methods: Study subjects were categorized in to two groups according to plasma Mg levels; 34 subjects with hypomagnesemia and 45 subjects with normal magnesium levels. Fasting blood samples were analyzed for Mg, glucose and insulin. Pancreatic β-cell function was estimated as HOMA-β.

Results: Degree of pancreatic β-cell function, as measured by HOMA-β, was significantly lower among T2DM subjects with hypomagnesemia compared to the subjects with normal magnesium levels (38.1± 5.5 vs. 41.2± 6.2, *P*-value< 0.05). Lower plasma Mg was associated with decreased pancreatic β-cell function among the study subjects independent of age, BMI and duration of diabetes.

Conclusion: We concluded that among subjects with T2DM in this study, Mg deficiency might be linked with worsening of pancreatic β-cell function.

Keywords: Type 2 diabetes mellitus, Magnesium, Nigeria, Pancreatic β-cell function

Introduction

The number of people with diabetes mellitus is increasing worldwide (1). In Nigeria, the prevalence ranges from 0-2% in rural areas and 5-10% in urban settlements (2), with over 5 million diabetic patients in 2013, and more than 90% of the diagnosed cases are type 2 diabetes mellitus (T2DM) (3).

T2DM is characterized by pancreatic β-cell dysfunction and insulin resistance. T2DM is defined by hyperglycemia and develops when pancreatic β-cells fail to compensate the insulin resistance (4). More recently the role of pancreatic β-cell dysfunction in the pathogenesis and progression of T2DM has increasingly being investigated, because of its

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critical role in the prevention and treatment of the disease and its associated complications (5).

Pancreatic β-cell dysfunction is present at the diagnosis of T2DM and progressively deteriorated with disease duration (6). The progressive failure of the pancreatic β-cells to secrete enough insulin to overcome insulin resistance is associated with worsening of glycemic control and treatment failure; therefore preservation of pancreatic β-cell function is an essential component of T2DM management (5).

Magnesium (Mg) deficiency, which is common among T2DM patients (7,8) contribute development of pancreatic β-cell dysfunction according to previous studies. It was shown that among individuals with low Mg status, decrease in insulin sensitivity is not appropriately compensated by increase of pancreatic β-cell function and that administration of oral Mg supplement in non-diabetic subjects with low Mg status improves the ability of pancreatic β-cells to compensate decrease in insulin sensitivity (9-11).

We hypothesized that among Nigerian patients with T2DM, those with hypomagnesemia might have more deteriorated pancreatic β-cells function than those with normal magnesium levels. Hence, in this present study, we examined the relationship between plasma Mg levels and degree of pancreatic β-cell dysfunction among a cohort of Nigerian patients with uncomplicated T2DM at a specialist hospital in north eastern Nigeria.

Materials and Methods

Study subjects were 79 adult T2DM patients on treatment, with no diagnosed complications at the medical outpatient clinic of Gombe state specialist hospital, Gombe. T2DM was based on WHO diagnostic criteria (1). The study subjects were categorized in to two groups according to their plasma Mg levels and include thirty four (34) subjects who were found to have hypomagnesemia (defined as plasma Mg less than 0.75mmol/L) and forty five (45) subjects with normal magnesium level (plasma magnesium 0.75-0.95 mmol/L) (12). All study subjects were Nigerians of African descent and living in Gombe state. Exclusion criteria were: evidence of secondary diabetes mellitus, clinical and/or biochemical evidence of any other pre-existing illness, pregnancy, breastfeeding or use oral contraceptives, insulin dependence, current insulin therapy and other medications known to interfere with insulin and/or Mg metabolism.

We further excluded those who smokes or alcohol use. Informed consent for participation in the study was obtained from each of the study subjects.

All the study subjects were evaluated in the morning following 10-12 hours overnight fasting.

History and demographic information were obtained and anthropometric measurements were done in light clothing without shoes. Height was measured to the nearest centimeter and weight was measured to the nearest 0.1 kilogram. Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared and expressed as kg/m^2.

Fasting venous blood samples were drawn in a heparin bottles and centrifuged immediately for 15 minutes. Plasma were collected and frozen in aliquots at -20 ^{0}C until analysis. Plasma Mg was measured using a colorimetric assay kit (Agappe Diagnostics Limited, India). Plasma insulin was analyzed using an enzyme linked immunosorbent assay (ELISA) kit (Monobind Inc. USA). Plasma 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.

Marker of pancreatic β-cell function was determined by the homeostasis model assessment-beta (HOMA-β) index

HOMA-β= (20× fasting plasma insulin (μU/mL))/ (fasting plasma glucose (mmol/L) - 3.5) (13).

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Statistical analysis

All analyses were conducted using statistical package for social sciences (SPSS) Version 20.0. All *P*-values (two-sided) of less than 0.05 were considered statistically significant. Measures of central tendency and dispersion were used to summarize quantitative variables. Differences between group means were determined using T-test. The distributions of fasting insulin and HOMA-β were not normally distributed in the Kolmogorow-Smirnov test and therefore logarithmic transformation was used to improve their normalization. Partial correlation and multiple linear regression analysis were used to determine association between plasma Mg and HOMA-β and to adjust for age, BMI and duration of diabetes (confounders).

Ethical considerations

The study protocol was approved by the Health Research Ethics committee of the Gombe State Ministry of Health, Gombe, Nigeria (MOH/ADM/S/658/VOL.11/55).

Results

Baseline characteristics of the study subjects are presented in Table 1. The study included 34 T2DM subjects with hypomagnesemia (19 men and 15 women) and 45 T2DM subjects with normal plasma Mg (28 men and 17 women). The study subjects with hypomagnesemia were older and more obese than subjects with normal magnesium level (51.9 (± 4.9) vs. 42.4 (± 7.0) years, *P*-value< 0.05) and (25.4 (± 2.0) vs. 23.4 (± 1.7) kg/m^2, *P*-value: 0.0001) respectively. Mean duration of disease was not significantly different between two groups (*P*-value: 0.852).

Biochemical parameters of the study subjects were shown in Table 2. Mean plasma Mg level in the hypomagnesaemia group was 0.66 mmol/ L, while in the normal magnesium level group was 0.86 mmol/ L (*P*-value: 0.0001). Subjects with hypomagnesemia had similar mean fasting plasma glucose with subjects in the normal magnesium level group, (9.0 (± 0.9) vs. 8.8 (± 0.8) mmol/L, *P*-value: 0.138).

Degree of pancreatic β-cells function as measured by HOMA-β was observed to be significantly lower in subjects with hypomagnesemia than in subjects with normal plasma magnesium level (38.1 (± 5.5) vs. 41.2 (± 6.2), *P*-value: 0.024) (Table 2 and Figure 1).

Statistically significant direct association was observed between plasma Mg level and HOMA-β regardless of gender and independent of age, BMI and duration of diabetes mellitus (Table 3 and Figure 2.).

The relative contribution of plasma Mg to HOMA-β in the study subjects was examined using multiple linear regression analysis. The adjusted R-square was 0.20, indicating that 20% of the variance in HOMA-β among the study subjects can be attributed to the plasma

Table 1. Demographic and biochemical parameters of patients according to plasma Mg

Variable	Hypomagnesemia (mean ± SD)	Normal magnesium (mean ± SD)	*P*-value
Sample size (n)	34	45	
Age (years)	51.9 (± 4.9)	42.4 (± 7.0)	0.000
Sex ratio (M/F)	19/15	28.17	-
Duration of type 2 DM (years)	5.3 (± 1.5)	5.4 (± 1.4)	0.852
Body mass index (kg/m^2)	28.0 (± 3.6)	23.7 (± 3.7)	0.000
Systolic BP (mmHg)	117.0 (± 9.0)	117.0 (± 8.6)	0.947
Diastolic BP (mmHg)	78.0 (± 5.4)	78.4 (± 4.7)	0.661
Fasting PG (mmol/L)	9.0 (± 0.9)	8.8 (± 0.8)	0.354
Fasting plasma insulin (µU/mL)	10.3 (± 1.4)	10.8 (± 1.3)	0.138
Plasma magnesium (mmol/L)	0.66 (± 0.07)	0.86 (± 0.11)	0.000
HOMA-β	38.1 (± 5.5)	41.2 (± 6.2)	0.024

SD, Standard deviation
DM, Diabetes mellitus
BP, blood pressure
PG, plasma glucose
HOMA-β, homeostasis model assessment-β

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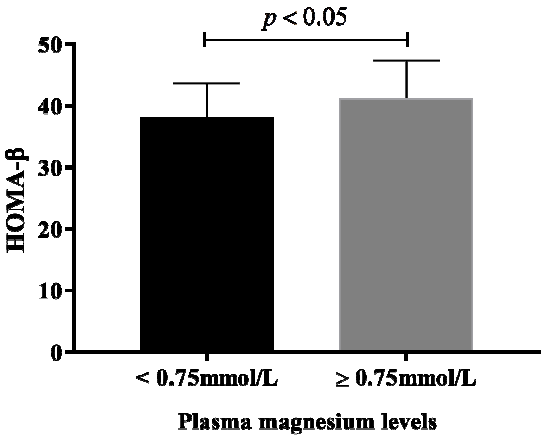

Figure 1. HOMA-β among the two study groups (mean ± SD)

Table 2. Correlation of HOMA-β with anthropometric and biochemical factors

Variable	All study subjects (n= 79)	
	r	*P*-value
Age (years)	-0.14	0.205
Duration of DM (years)	0.20	0.083
BMI (kg/m^2)	0.04	0.752
Plasma magnesium (mmol/L)	0.41	0.000

HOMA-β, homeostasis model assessment-β
BMI, body mass index
r, correlation coefficient
DM, Diabetes mellitus

level of magnesium. Plasma magnesium was found to be a significant predictor of pancreatic β-cells function, as measured by HOMA-β among T2DM.

Discussion

In this present study, we studied the degree of pancreatic β-cell dysfunction, as measured by HOMA-β and its potential relationship with Mg status, as measured by plasma Mg level in a group of T2DM patients at a specialist hospital in north eastern Nigeria. We found that HOMA-β was lower among T2DM subjects with hypomagnesemia than patients with normal plasma Mg levels. We also observed that decreased plasma Mg level is associated with increased degree of pancreatic β-cells dysfunction, as measured by HOMA-β, among the study subjects independent of age, duration of disease and BMI.

Similar finding was reported in a study carried out among non-diabetic subjects, where it was observed that individuals with Mg deficiency have decreased pancreatic β-cell function compared to individuals who have normal plasma Mg level (9). Furthermore, Simental-Mendía et al. showed that decreased insulin sensitivity is not appropriately compensated by increase of pancreatic β-cell function among individuals with low Mg status and in addition it was reported that administration of oral Mg supplement in non-diabetic subjects with low Mg status improves the capacity of pancreatic β-cells to compensate decrease in insulin sensitivity (10,11).

On the contrary, Randell et al, reported a negative relationship between plasma magnesium level and pancreatic β-cell function, as determined by HOMA-β, among Canadian non-diabetic subjects (14).

Mg plays an essential role in the secretion of insulin by the pancreatic β-cells. Increased blood glucose level and subsequent uptake of the glucose by the β-cells via GLUT2 is the first step that stimulates insulin secretion.

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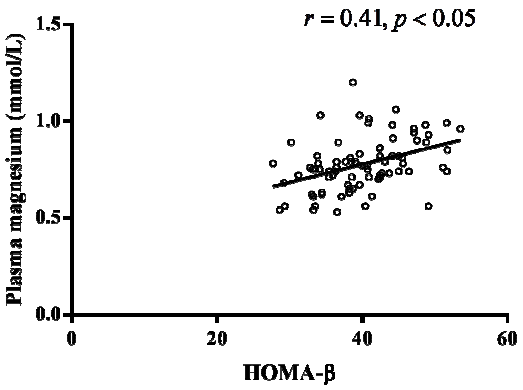

Figure 2. Correlation of plasma Mg level and HOMA-β among the study subjects.
HOMA-β, homeostasis model assessment-β

Table 3. Multiple linear regression analysis with HOMA-β as a dependent variable

Independent variables	All study subjects (n= 79) R^2= 0.20		
	β-value	SE	*P*-value
Constant	6.40	9.5	0.504
Age	0.10	0.10	0.423
BMI	0.20	0.16	0.104
Duration of DM	0.23	0.44	0.032
Log plasma Mg	0.53	5.5	0.000

HOMA-β, homeostasis model assessment-β
β, regression coefficient
SE, standard error
BMI, body mass index
DM, diabetes mellitus
Mg, magnesium

The intracellular glucose is further metabolized through a series of enzymatic reactions with resultant generation of energy in form of ATP. The ATP then binds to intracellular Mg and induces closure of ATP-sensitive K channels, resulting in depolarization of the β-cell membrane. The depolarization leads to opening of voltage-gated Ca^{2+} channels and subsequent entry of Ca^{2+} ions in to the cells. This triggers the release of insulin from the secretory vesicles via exocytosis in to the circulation (15). Mg is required as a cofactor for a number of enzymes involved in the glucose metabolism (16), and therefore, its deficiency decreases ATP production. Mg deficiency and decreased ATP generation both inhibit the synthesis of Mg-ATP, with the resultant activation of the K channels and therefore suppression of insulin secretion (15,16). Mg is involved in cell division and synthesis of proteins including insulin (17). Therefore decreased insulin synthesis and pancreatic β-cell mass might contribute to the decrease in insulin secretion observed in Mg deficiency.

Limitations

HOMA-β as a surrogate measure of insulin secretion was used to assess pancreatic β-cells function rather than the gold standard methods that precisely measures insulin secretion. This may underestimate the degree of pancreatic β-cell dysfunction. Total plasma Mg, rather than intracellular Mg, a more sensitive indicator of Mg status, was measured. This study is cross sectional in nature and therefore association does not mean causation.

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Conclusions

We conclude that among T2DM patients in this study, Mg deficiency is associated with lower insulin secretion ability, as measured by HOMA-β. As decreased insulin secretion is one of the factors contributing to deterioration of glycemic control in T2DM, we recommend routine check of Mg status and prompt treatment if deficiency is detected among patients with T2DM in our setting.

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Conflict of interest

All authors declare there were no conflicts of interest.

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