

INSULIN RESISTANCE IN APPARENTLY HEALTHY ADULT NIGERIANS: ASSOCIATION WITH MAGNESIUM STATUS

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ABSTRACT

Magnesium plays a critical role in glucose metabolism and evidence suggest that magnesium deficiency is associated with decreased insulin sensitivity. However, it is likely that these relationships are affected by genetic and environmental factors that can differ among different populations. The aim of this study was to determine the prevalence of insulin resistance and its association with magnesium status among apparently healthy adult Nigerians. Fasting plasma levels of magnesium, glucose and insulin were determined in 120 apparently healthy adults. Insulin resistance was calculated as HOMA-IR. Prevalence of insulin resistance was estimated and the association between plasma magnesium levels and HOMA-IR was determined. About 19.2% of the study subjects were classified as having insulin resistance. Prevalence was higher among males compared to females (21.0% vs 17.0%) and among obese compared to normal-weight subjects (26.1% vs 14.9%). Subjects with hypomagnesemia had a higher prevalence of insulin resistance compared with subjects who had normal plasma magnesium levels (50.0% vs 14.4%). Insulin resistance was inversely associated with plasma magnesium level independent of age, gender and BMI. Insulin resistance is relatively common among apparently healthy individuals in this study. Magnesium deficiency was found to be a significant predictor of insulin resistance. We recommend further studies that will investigate whether optimization of magnesium status in general population or among individuals at risk of developing type 2 diabetes will be a useful approach in lowering insulin resistance and prevent or delay the onset of type 2 diabetes mellitus in our setting.

Keywords: Magnesium; Insulin Resistance; Adult; Body mass index; Nigeria

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INTRODUCTION

Insulin resistance is defined as a state in which more insulin is required to obtain the physiological effects achieved by a lower insulin level in a healthy state [Lebovitz, 2001]. It plays a vital role in the pathogenesis of type 2 diabetes mellitus. It is the precursor or driving factor that leads to type 2 diabetes mellitus [Lebovitz, 2001]. Insulin resistance is also reported to be strongly associated with increased risk of the development of hypertension, cardiovascular disease, dyslipidemia and metabolic syndrome [Lebovitz, 2001; Paul, 2009].

The exact cause of insulin resistance is not fully understood; however, a number of mechanisms have been suggested as possible factors underlying the pathogenesis of the insulin resistance. Magnesium is the second most abundant intracellular cation and is involved in carbohydrate metabolism as a cofactor in several enzymatic reactions [Swaminathan, 2003].

Previous studies done mostly among Caucasians and African Americans, suggested that magnesium may play a significant role in enhancing/improving insulin sensitivity in healthy subjects and that maintaining optimal magnesium status may attenuate onset of type 2 diabetes mellitus in individuals at risk [Paolisso et al., 1992; Guerrero-Romero et al., 2004; Larsson, Wolk, 2007; Kao et al., 1999]. However, it is likely that these relationships are affected by genetic and environmental factors that can differ among different populations. There is limited data on the impact of magnesium deficiency on the present study was therefore designed to determine the prevalence of insulin resistance among apparently healthy individuals in our setting.

The present study was therefore designed to determine the prevalence of insulin

resistance and its relationship with magnesium status, as measured by plasma magnesium level among apparently healthy Nigerian adults.

Subjects and Methods

This was a cross-sectional analytical study including one hundred and twenty (120) apparently healthy adults volunteers (78 males and 52 females) aged greater than 18 years who gave informed consent. They were enrolled in to the study from individuals who presented to the general outpatient clinic of the Gombe State Specialist Hospital, Gombe and Federal Teaching Hospital, Gombe, Nigeria, for routine medical check-up, pre marital screening and blood donors. All study subjects are Nigerians of African descent and living in Gombe State. Subjects with diagnosed diabetes mellitus or any other illness, those who smoke or ingest alcohol, pregnant and breastfeeding mothers were excluded from the study. The study protocol was approved by the health research ethics committees of the Gombe State Ministry of Health, Gombe and Federal Teaching Hospital, Gombe.

History and physical examination were performed in each of the study subjects at the time of blood sample collection. Information on age, sex and past medical history were obtained from each subject and recorded.

Standing height was measured to the nearest centimeter using a stadiometer. Body weight was measured to the nearest 0.1 kilogram. Measurement of height and weight were done with the study subjects in light clothing without head gear or shoes. Body mass index was calculated as a ratio of weight in kilogram and height in meters squared and expressed as kg/m².

Laboratory Analysis

Fasting venous blood samples were collected in the morning following 10-12 hours overnight fasting into heparin bottles. Blood samples were immediately centrifuged for 15 minutes for Sierra Leone Journal of Biomedical Research assayed using a commercially available human insulin 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). $HOMA-IR = \text{Fasting plasma insulin (FPI)} \times \text{Fasting plasma glucose (FPG)} / 22.5$ [Wallace, FPI in milliU/mL and FPG in mmol/L

Definitions

Hypomagnesaemia was defined as plasma magnesium level < 0.75 mmol/L [Costello, 2016]. Insulin Resistance was defined as HOMA IR values > 2.0 [Oli, 2009].

Statistical Analysis

Statistical package for social sciences (SPSS) version 20.0 was used for statistical analysis. Kolmogorow-Smirnov Shapiro-Wilk tests were used to test for normality of distribution of data and logarithmic transformation was used to improve the normality of distribution of skewed data. Quantitative variables were presented using proportions and measures of central tendency and dispersion. Mean differences of plasma magnesium and HOMA-IR between groups were compared using t-test. Partial correlation and linear regression analyses were used to determine relationship between plasma magnesium levels and HOMA-IR and to adjust for confounders. All p-values

were two-sided and considered significant if less than 0.05.

RESULTS

Demographic and biochemical characteristics of the study subjects are presented in Table 1. The mean age of the study subjects, which were predominantly males (55.8%), was 37.2 ± 3.5 years and the mean BMI was 26.1 ± 3.3 kg/m². There were no significant differences in the age and BMI levels between males and females subjects (39.1 ± 4.1 vs. 34.8 ± 3.2 years, $p > 0.05$) and (26.5 ± 3.1 vs. 25.6 ± 2.4 kg/m², $p > 0.05$) respectively.

Prevalence of insulin resistance among the study subjects were presented in Tables 2 and 3. About 19.2% of the study subjects were found to have insulin resistance. Prevalence of insulin resistance was higher among male than female subjects (21.0% vs. 17.0%) and in obese subjects compared with normal weight subjects (26.1% vs. 14.9%). Prevalence of insulin resistance was also determined according to plasma magnesium level. Subjects with hypomagnesemia had higher prevalence of insulin resistance than subjects with normal plasma magnesium levels in both genders and regardless of body weight status (Tables 2 and 3).

Table 1: Demographic and biochemical parameters of the study subjects

Variables	All	Males (m ± SD)	Females (m ± SD)	p-value
Sample size (n)	120	67	53	
Age (years)	25.8 ± 5.4	26.0 ± 5.4	265.7 ± 5.4	0.744
Sex ratio (male/female)	67/53	-	-	-
BMI (kg/m ²)	24.8 ± 3.7	25.5 ± 4.0	23.9 ± 3.2	0.018
PBG (mmol/L)	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.7	0.969
Plasma Magnesium (mmol/L)	0.83 ± 0.13	0.84 ± 0.15	0.81 ± 0.09	0.179
Fasting Insulin (µIU/L)	0.83 ± 0.13	0.84 ± 0.15	0.81 ± 0.09	0.744
HOMA-IR	1.83 ± 0.18	1.83 ± 0.20	1.83 ± 0.15	0.873

m, Mean; SD, Standard deviation; DM, Diabetes mellitus; HOMA-IR, homeostasis model assessment-insulin resistance; BP, blood pressure; BMI, body mass index

Table 2: Prevalence of Insulin resistance in relation to BMI and plasma magnesium level

Magnesium status	Insulin resistance: number (%)		
	All (n=120)	BMI < 25kg/m ²	BMI > 25kg/m ²
Hypomagnesemia	8/16 (50.0%)	3/8 (37.5%)	5/8 (62.5%)
Normomagnesemia	15/104 (14.4%)	8/66 (12.1%)	7/38 (18.4%)
Total	23/120 (19.2%)	11/74 (14.9%)	12/46 (26.1%)

Table 3: Prevalence of Insulin resistance in relation to gender and plasma magnesium level

Magnesium status	Insulin resistance: number (%)		
	All (n=120)	BMI < 25kg/m ²	BMI > 25kg/m ²
Hypomagnesemia	8/16 (50.0%)	4/7 (57.1%)	4/9 (44.4%)
Normomagnesemia	15/104 (14.4%)	10/60 (16.7%)	5/44 (11.4%)
Total	23/120 (19.2%)	14/67 (21.0%)	9/53 (17.0%)

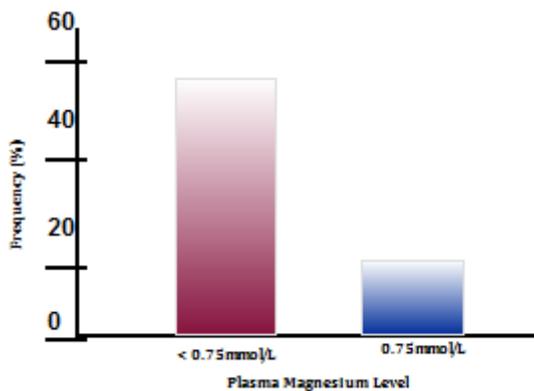


Figure 1: Frequency of insulin resistance among the hypomagnesemic and normomagnesemic study groups.

The relationship between plasma magnesium and degree of insulin resistance in the study subjects was examined (Table 4 and Figure 2.). A significant inverse relationship, independent of age and BMI, was found between plasma magnesium levels and HOMA-IR ($r = -0.55, p < 0.05$) in all the study subjects. When the study subjects were categorized into males and females, the inverse relationships between plasma magnesium levels and HOMA-IR was observed to be stronger in male subjects.

Table 4: Correlation of HOMA-IR with anthropometric and biochemical factors

Variables	All (n=120)		Males (n=67)		Females (n=53)	
	r	pValue	r	pValue	r	pValue
Age (Years)	0.42	0.000	0.47	0.000	0.35	0.009
BMI Kg/M ²	0.18	0.044	0.20	0.109	0.44	0.001
Plasma Magnesium (mmol/L)	-0.55	0.000	-0.60	0.000	-0.43	0.002

HOMA-IR, homeostasis model assessment-insulin resistance
 BMI, body mass index
 r, correlation coefficient
 DM, Diabetes mellitus
 HOMA-IR, homeostasis model assessment-insulin resistance
 BP, blood pressure
 BMI, body mass index

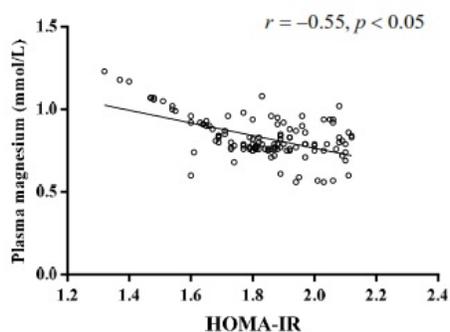


Figure 2: Correlation of plasma magnesium level and HOMA-IR among the study subjects.

DISCUSSION

We studied the prevalence of insulin resistance and its association with magnesium status, as measured by plasma magnesium level in a group of apparently healthy adult Nigerians. In this present study, we reported 19.2% as the overall prevalence of insulin resistance among the study subjects. The prevalence was observed to be higher among male than female subjects and in overweight compared to normal weight subjects regardless of gender. We also observed that magnesium deficiency is significantly associated with increased frequency of insulin resistance among the study subjects irrespective of gender and body weight status. Reports on prevalence of insulin resistance among general population vary widely ranging from 17% to 61% [Bermudez *et al.*, 2016; Friedrich *et al.*,

2012; Do *et al.*, 2010; Huguette *et al.*, 2010; Young *et al.*, 2016]. The wide range/disparity might be explained by heterogeneity of the study population, definition of insulin resistance and methods of assay of insulin used in the various studies. Studies conducted among lean and young individuals generally reported lower prevalence.

Our result of higher prevalence of insulin resistance among males compared to females was similar to reports from studies conducted by Friedrich *et al.* [Friedrich *et al.*, 2012] and Do *et al.* [Do *et al.*, 2010]. Obese subjects were also observed to have higher prevalence of insulin resistance than normal weight subjects regardless of gender. The same finding was reported by Bermudez *et al.* [Bermudez *et al.*, 2016].

In the present study we reported a significantly higher frequency of insulin resistance among subjects with hypomagnesemia compared to subjects with normal plasma magnesium levels and that decreased plasma levels of magnesium is significantly associated with increased insulin resistance among the study subjects independent of age, gender and body mass index.

Similar findings have been reported in many previous studies, where hypomagnesemia was shown to be associated with increased insulin resistance [Guerrero-Romero, Rodríguez-Morán, 2013; Humphries *et al.*, 1999; Huerta *et al.*, 2005; Rosolova *et al.*, 2000; Resnick *et al.*, 1990].

Also in support of the results of this study Nadler *et al.* showed that induced hypomagnesemia is associated with decreased insulin secretion and action [Nadler *et al.*, 1993]. In addition it was found that low dietary magnesium intake among apparently healthy adults are associated with higher risk of developing type 2 diabetes mellitus [Kao *et al.*, 1999; Lopez-Ridaura *et al.*, 2004]. Although Cahill F *et al.* reported that high dietary magnesium intake is associated with low insulin

resistance, they did not find significant relationship between serum magnesium and insulin resistance [Cahill *et al.*, 2013]. The inconsistencies in the reports from the various studies might be due to the variation in sample size and experimental conditions. Heterogeneity of the study subjects, such as

differences in age, gender proportion, BMI and health status, and differences in the assay methods used in analysis of plasma magnesium and insulin levels might also contribute to the discrepancies. Several mechanisms by which magnesium deficiency could contribute to the development of insulin resistance have been proposed. Magnesium is required for autophosphorylation of insulin receptor. Binding of two magnesium ions to the tyrosine kinase domain of the insulin receptor enhances the tyrosine kinase activity by increasing the affinity of the receptor to ATP [Gommers *et al.*, 2016]. In magnesium deficiency state therefore, there is decreased insulin receptor phosphorylation, and therefore decreased insulin sensitivity [Gommers *et al.*, 2016]. Increased expression of inflammatory markers and reactive oxygen species in individuals with magnesium deficiency has also been proposed to contribute to the insulin resistance in magnesium deficiency states [Guerrero-Romero, Rodríguez-Morán, 2006].

LIMITATIONS

HOMA-IR is only surrogate marker of insulin resistance based on fasting insulin and glucose levels and plasma magnesium, rather than intracellular magnesium, a more sensitive indicator of magnesium status, was measured. The extent to which these might have affected the outcome of this study needs to be further investigated. Because of the cross-sectional nature of this study, we cannot be certain of a causal/temporal relationship between magnesium and insulin resistance. The study subjects were mainly from Fulani ethnic group, so the findings may not be applicable to other ethnic groups.

CONCLUSION

We conclude that among apparently healthy adult individuals in this study, insulin resistance is relatively common and lower plasma magnesium is associated with increased insulin resistance as measured by HOMA-IR. This finding may require replication from studies involving larger sample size and various ethnic groups. We recommend further studies that will investigate whether increasing dietary consumption of foods rich in magnesium, such as whole grains and green vegetables and/or magnesium supplementation in general population or among individuals at risk

of developing type 2 diabetes will be a useful approach in lowering insulin resistance and preventing (and/or delay) type 2 diabetes mellitus in our setting. We also recommend large scale study that will establish an evidence-based local reference interval that will allow more accurate assessment of the prevalence of insulinresistance among our local population.

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