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Association of Dietary Acid Load with Insulin Sensitivity Index among Apparently Healthy Nigerians

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Abstract
The possible role of regular consumption of diets with high acid forming potential in decreasing cellular sensitivity to insulin and its associated complications has been investigated. However, findings across different study groups are conflicting. It is likely that the association is affected by genetic and environmental factors that differ among different populations. We investigated the impact of diet-induced acidosis on the degree of insulin sensitivity among apparently healthy adult Nigerians. Assessment of dietary intake was done using a semi-quantitative food frequency questionnaire and the Nigerian Food Composition Table. Acid forming potential of our local diets were estimated as Potential Renal Acid Load (PRAL) scores. Fasting plasma glucose and insulin were measured. Degree of insulin sensitivity was calculated as Quantitative Insulin Sensitivity Check Index (QUICKI). About 35 (16.2%) of the study subjects were observed to have insulin resistance. Across the study groups, there was a statistically significant trend with higher intake of dietary acid associated with decreased insulin sensitivity (*p for trend* < 0.05). We conclude that among apparently healthy adult subjects in this study, regular consumption of diets with high acid forming potential might be linked with worsening of insulin sensitivity.

Keywords: *Dietary acid; Insulin sensitivity; Adult; Nigeria*

Introduction
Insulin resistance is associated with increased risk of pre-diabetes, type 2 diabetes mellitus, cardiovascular diseases, malignancies and other chronic metabolic disorders. It is a multi-factorial disorder influenced by both genetic and environmental factors (Lebovitz, 2001; Pankow *et al.*, *2004;* Abel *et al.*, 2012). The rapid rise in the prevalence of type 2 diabetes mellitus, in combination with earlier disease onset, especially in developing countries including Nigeria has led to increased public health concern and a more focus on the delineation of strategies that may prevent or delay its onset (Uloko *et al.,* 2018; Liu *et al.*, 2020). Recently there is mounting evidence to suggest that regular consumption of diet with high acid load increases body acidity and impairs glucose metabolism in humans by reducing cellular sensitivity to insulin and predicts type 2 diabetes mellitus (Schwalfenberg, 2012; Akter *et al.*, 2016; Lee and Shin, 2020).

The crucial role of dietary acid load in decreasing cellular sensitivity to insulin and predicting the risk of type 2 diabetes mellitus has been investigated; but findings across different study groups are inconsistent or even conflicting (Schwalfenberg, 2012; Muraki *et al.,* 2013; Fagherazzi *et al.,* 2014; Xu *et al.,* 2014; Akter *et al.,* 2016; Moghadam *et al.,* 2016; Wang *et al.,* 2016; Gæde *et al.,* 2018; Lee and Shin, 2020). It remains unclear whether differences between the cohorts of these studies, including racial origin, gender, age, or body weight status, may explain the discordant results. Studies on the effect of dietary acid load on insulin sensitivity in apparently healthy Black Africans, who have a lower insulin secretion capacity than Caucasians (Mohandas, 2018) are limited. Thus, additional evidence from studies in our setting with different dietary habits is clinically relevant to enhance the generalizability of the findings and substantiate preventive dietary recommendations and also contribute to the identification of therapeutic targets.

The aim of this present study was to evaluate the effect of regular dietary acid intake on the risk of insulin resistance in a cohort of apparently healthy Nigerian adult men and women.

Materials and Methods

Study subjects

Two hundred and sixteen (216) apparently healthy adult Nigerians, who gave informed consent, were included in this cross-sectional analytical hospital-based study and comprised of 123 males and 93 females aged greater than 18 years. All the study subjects were enrolled from among individuals who presented to the general outpatient clinic of the Gombe State Specialist Hospital, Gombe, Nigeria, for pre-marital screening, routine medical check-up and blood donors.

The subjects were categorized in to four quartiles according to their median dietary acid load scores. The study subjects were further categorized into two groups according to their degree of insulin sensitivity and include thirty-five (35) subjects who were insulin resistant (defined as QUICKI < 0.324) and one hundred and eighty-one (181) subjects with normal insulin sensitivity (QUICKI ≥ 0.324) (Udenze, 2019). All study subjects are Nigerians of African descent and living in Gombe State. We excluded subjects with diagnosed diabetes mellitus or any other illness, smokers, those who ingest alcohol, pregnant women and breastfeeding mothers from the study. The protocol of the study was approved by the health research ethics committee of the Gombe State Ministry of Health, Gombe.

Data collection

Each of the study subjects was assessed in the morning following 10-12 hours of overnight fasting. Basic demographic data and self-reported information on dietary intake were obtained and recorded. Body height, measured to the nearest centimeter, and body weight, measured to the nearest 0.1kg, were obtained with each subject standing erect without shoes or headgear. Body mass index was calculated as weight in kilogram (kg) divided by height in meters squared (m^2) and expressed as kg/m^2. Systolic and diastolic blood pressures were taken at rest in a sitting position using a mercury sphygmomanometer.

Dietary assessment

Assessment of dietary intake was based on a semi-quantitative food frequency questionnaire (FFQ). The FFQ was administered to each of the subjects and included all the local food items as identified by their local names. Subjects were asked to recall all foods and drinks they had consumed over the past week and to estimate portion size and frequency of consumption. Food items that are not initially part of the FFQ but are consumed by a study subject were added to the list. For seasonal foods and foods not consumed by a subject during the past week but were part of their usual diet, monthly consumption frequencies were determined and converted to weekly consumption frequencies. The consumption frequencies were then converted to daily and the portion sizes were converted to grams using household measures. We used the Nigerian food composition table to determine the energy and nutrient content of all the food items.

Estimation of Dietary Acid Load

Dietary acid intake was estimated using the Potential Renal Acid Load (PRAL) score; The PRAL score was calculated based on nutrient intakes using the following equation (Remer, 2003):
PRAL (mEq/day) = [0.4888 × Dietary Protein (g/day)] + [0.0366 × Dietary Phosphorus (mg/day)] – [0.0205 × Dietary Potassium (mg/day)] – [0.0125 × Dietary Calcium (mg/day)] – [0.0263 × Dietary Magnesium (mg/day)].

Laboratory analysis

Fasting venous blood samples from each of the subjects were collected into lithium heparin bottles. Each blood sample was immediately centrifuged for 15 minutes and the separated plasma was stored in aliquots at -20^{0}C until analysis. Plasma Insulin was 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 Insulin Sensitivity Index

The quantitative insulin-sensitivity check index (QUICKI) was calculated using the following equation (Katz *et al, 2000);*

QUICKI = 1 / [Log (Fasting Plasma Insulin/) + Log (Fasting Plasma Glucose)].

Fasting Plasma Insulin in µU/mL

Fasting Plasma Glucose in mg/dL

Definition of Insulin Resistance

Insulin Resistance was defined as QUICKI values < 0.324 (Udenze, 2019).

Statistical analysis

Statistical analysis of data was done using Statistical package for social sciences (SPSS) version 20.0. Shapiro-Wilk test was 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 the study variables between the groups were compared using t-test and ANOVA. Partial correlation analysis was used to determine relationship between the PRAL score and the QUICKI and to adjust for confounders. All p-values were two-sided and considered significant if less than 0.05.

Results

The basic characteristics study subjects were given in Table 1. A total of two hundred and sixteen (216) subjects; including 123 males (56.9%) and 93 females (43.1%), with an overall mean age and BMI of 26.2 ± 5.3 years and 24.5 ± 4.4 kg/m^2 respectively, were included in the study. No significant differences were observed in the age and BMI statuses across the male and female subjects (26.3 ± 5.6 vs. 26.0 ± 5.0 years) and (24.9 ± 4.4 vs. 24.0 ± 4.5 kg/m^2) respectively ($p > 0.05$). The median level of potential renal acid load (PRAL) score was significantly higher among the female subjects than the male subjects (+10.4mEq/day vs. +9.0mEq/day ($p < 0.05$).

The subjects were categorized in to four quartiles according to their PRAL scores (Table 2). The median dietary PRAL scores in the first (Q1), second (Q2), third (Q3) and fourth (Q4) quartiles were -22.5mEq/day, +6.5mEq/day, +12.0mEq/day and 41.5mEq/day respectively. The distributions of the subjects in terms of age and body mass index were not significantly different across the quartiles of the PRAL scores (*p for all* > *0.05*). Higher dietary acid intake was statistically significantly associated with lower intakes of energy and potassium and higher intakes of magnesium, calcium, protein and phosphorus (*p for all* < *0.05*).

Prevalence of insulin resistance among the study subjects were presented in Table 3. About 35 (16.2%) of the study subjects were observed to have insulin resistance, with higher prevalence among male than female subjects (22.6% vs. 11.4%).

Higher intake of dietary acid was significantly associated with decreased insulin sensitivity regardless of gender and independent of age, energy intake and body mass index as shown in Table 4 and Figure 1. Across the quartiles, there was a statistically significant trend with higher intake of dietary acid associated with decreased insulin sensitivity (*p for trend* < *0.05*).

Table 1: Demographic and biochemical parameters of the study subjects

Variables	All	Males (m ± SD)	Females (m ± SD)	*p*-value
Sample size (n)	216	123	93	-
Age (years)	26.2 ± 5.3	26.3 ± 5.6	26.0 ± 5.0	0.646
Weight (kg)	63.3 ±14.0	64.7 ± 14.1	61.5 ± 13.6	0.097
Height (cm)	160.2 ± 7.4	160.6 ± 7.5	159.7 ± 7.3	0.373
BMI (kg/m^2)	24.5 ± 4.4	24.9 ± 4.4	24.0 ± 4.5	0.144
Systolic BP (mmHg)	118 ± 5.2	118 ± 5.0	118 ± 5.5	0.591
Diastolic BP (mmHg)	78.5 ± 3.8	78.5 ± 4.1	78.6 ± 3.5	0.780
PRAL (mEq/day) *	+ 9.1	+9.0	+10.4	0.00#
FPG (mmol/L)	4.3 ± 0.7	4.2 ± 0.7	4.3 ± 0.6	0.241
Fasting Plasma Insulin (mIU/mL)	10.2 ± 5.3	9.4 ± 5.2	11.2 ± 5.4	0.011
QUICKI	0.359 ± 0.04	0.366 ± 0.04	0.351 ± 0.03	0.005

Key:
m, mean
SD, standard deviation
FPG, fasting plasma glucose
BP, blood pressure
BMI, body mass index
PRAL, potential renal acid load
QUICKI, quantitative insulin sensitivity check index
**Median values*
#Kruskal-Wallis test
Data are presented as m ± SD.

Table 2: Energy and Nutrient Intake of the Study Subjects across the PRAL Quartiles

	Dietary PRAL Scores				
	Q1	**Q2**	**Q3**	**Q4**	***p*-value**
Energy (kcal/day)	2398 ± 305	2429 ± 255	2199 ± 380	1808 ± 528	0.000
Protein (g/day)	76.4 ± 21.3	89.1 ± 7.4	90.6 ± 6.1	105.8 ± 21.2	0.000
Calcium (mg/day)	460 ± 188	549 ± 141	550 ± 128	558 ± 134	0.002
Phosphorus (mg/day)	838 ± 216	965 ± 80	982 ± 66	1135 ± 215	0.000
Potassium (mg/day)	3447 ± 750	3385 ± 670	2771 ± 582	2754 ± 596	0.000
Magnesium (mg/day)	1376 ± 186	1043 ± 545	594 ± 637	233 ± 204	0.000
PRAL (mEq/day) *	-22.5	+6.5	+12.0	+41.5	0.000#
QUICKI	0.337 ± 0.02	0.360 ± 0.03	0.360 ± 0.04	0.381 ± 0.05	0.000

Key:
m, Mean
SD, Standard deviation
PG, plasma glucose
BP, blood pressure
PRAL, potential renal acid load
Data are ratio or mean ± SD.
**Median values*
#Kruskal-Wallis test

Table 3: Prevalence of Insulin resistance in relation to gender and body mass index

BMI	Insulin resistance: number (%)		
	All (n=120)	Males(n=67)	Females(n=53)
BMI < 25kg/m^2	21/121 (17.4%)	7/62 (11.3%)	14/59 (23.7%)
BMI $\geq$ 25kg/m^2	14/95 (14.7%)	7/61 (11.5%)	7/34 (20.6%)
Total	35/216 (16.2%)	14/123 (11.4%)	21/93 (22.6%)

Key: *BMI, body mass index*

Table 4: Correlation of QUICKI with the dietary PRAL scores

Variables	All (n=216)	
	r	*p-value*
Age (years)	-0.10	0.39
BMI (kg/m^2)	0.06	0.39
PRAL score (mEq/day)	-0.17	0.01

Key:
BMI, body mass index
r, correlation coefficient
PRAL, potential renal acid load

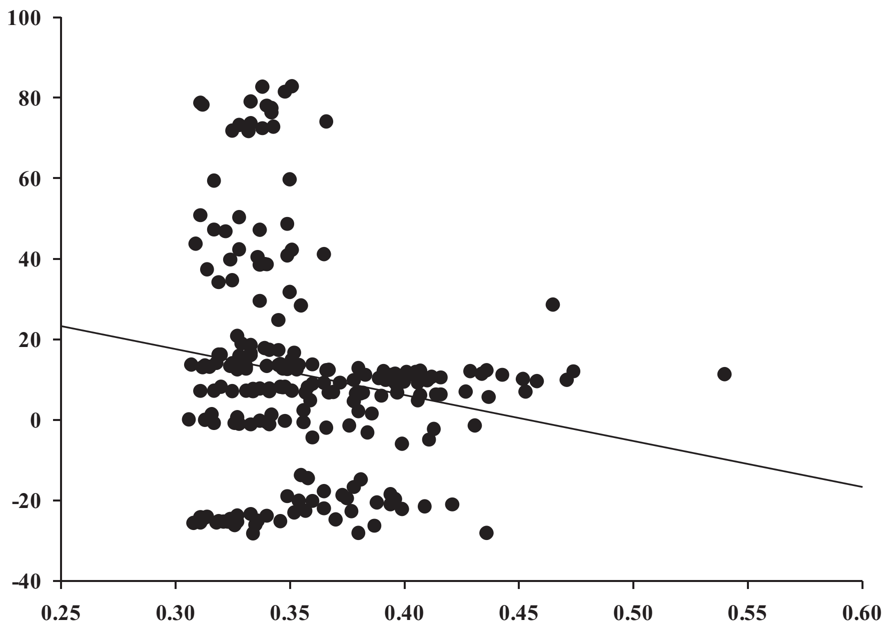

Figure 1: Correlation of Dietary PRAL Score with Insulin Sensitivity Index (QUICKI) among the study subjects. PRAL, potential renal acid load

Discussion

In the present study we examined the impact of the dietary acid load on degree of insulin sensitivity in a group of apparently healthy adult Nigerians. We found that consumption of foods with high acid-forming potential, as determined by high PRAL scores, was significantly associated with decreased insulin sensitivity among apparently healthy individuals. The overall prevalence of insulin resistance among the study subjects was observed to be 16.2%.

Our findings are in agreement with those from other investigators that reported positive relationship between consumption of diets with high acid load and risks of insulin resistance (Akter *et al.,* 2016; Moghadam *et al*., 2016; Gæde *et al.,* 2018). Furthermore, it was reported that regular consumption of food items with high alkalizing potential as fruits and vegetables is associated with decreased risk of type 2 diabetes mellitus (Schwalfenberg, 2012; Muraki *et al.,* 2013; Wang *et al.,* 2016).

However, in contrast to our findings, no significant association was found between dietary acid load scores and insulin sensitivity in a prospective study conducted among Swedish elderly men (Xu *et al,* 2014). Heterogeneity of the study subjects, including differences in dietary patterns, socio-demographic characteristics, mean ages, gender proportion and body weight status might partially explain the discrepancies in the findings from the previous studies. Studies involving predominantly elderly subjects reported no significant associations.

Mechanisms by which diet induced acidosis could contribute to the decreased cellular sensitivity to insulin have been proposed. Decreased in blood pH could disrupt the binding of insulin to its receptors, by decreasing the binding affinity of insulin to the insulin receptors, thereby inhibiting the early step in the insulin signaling pathway; resulting in the possible decreased cellular glucose uptake and insulin resistance (Igarashi *et al.,*1993; Hayata *et al*., 2014 Baldini and Avnet, *2018*). Also, sustained elevation of circulating cortisol, whose secretion from the adrenal cortex is stimulated by the acid retention, may decrease cellular sensitivity to insulin (Esche *et al.*, 2016; Kamba *et al.,* 2016). Circulating level of adiponectin, an insulin sensitizing adipocytokine, is lower in a state of chronic acidosis because of the inhibitory effect of acidosis on the adiponectin gene expression (Disthabanchong *et al.*, 2010). The resulting hypoadiponectinemia has been suggested to be positively associated with insulin resistance (Hanley *et al.,* 2003; Yamamoto *et al.,* 2004; Ziemke and Mantzoros, 2009).

Limitations

1. The study is cross-sectional in nature; therefore, we cannot be certain of causality.
2. It was an observational study; and therefore, residual confounders are still possible and could influence the relationships.
3. Quantitative insulin sensitivity check index (QUICKI) was used to assess the degree of insulin resistance, rather than the gold standard hyperglycemic clamp technique.
4. The study subjects were predominantly young and from Fulani ethnic group living in Gombe State, so the findings may not be generalizable to other ethnic groups living in other geographical regions with different dietary habits.

Conclusion

In summary, consumption of a diet loaded with high acid forming potential food items was associated with a decreased cellular sensitivity to insulin in a group of apparently healthy adult Nigerians in this study. We recommend further prospective studies to validate the findings. Interventional studies modifying the dietary acid intake are especially recommended to confirm the impacts on acid base balance and insulin sensitivity as well as its role in the initiation and progression of type 2 diabetes mellitus in our setting.

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Conflict of interest: Nil

Ethics approval
The Health Research Ethics Committee of the Gombe State Ministry of Health, Gombe, Nigeria approved the study protocol.

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