Impact of Dietary Intervention on Selected Biochemical Indices of Inflammation and Oxidative Stress in Nigerians with Metabolic Syndrome: A Pilot Study

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Author's contribution

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ABSTRACT

Aim: This study assessed the impact of dietary modification on cardiometabolic, inflammatory and oxidative stress indices in Nigerians with metabolic syndrome (MS).

Subjects and Methods: Sixty participants with MS were selected using the International Diabetes Federation criteria from a cohort participating in "Risk Assessment of Type 2 diabetes mellitus and Dementia in Nigerians with Metabolic Syndrome" study. The subjects were seen by a Dietitian and the approximate percentages of total calories from total protein, total fat, polyunsaturated fat, and carbohydrate were calculated from dietary history and pegged at 20%, 30%, 14% and 50% respectively. To ensure compliance, each participant was seen monthly (for 6 months) by the Dietitian. Glucose and lipid profile were determined using enzymatic methods. Serum activities of superoxide dismutase (SOD), catalase (CAT), Myeloperoxidase (MPO) and levels of nitric oxide (NO), malondialdehyde (MDA), hydrogen peroxide (H_2O_2), total protein and albumin were determined using spectrophotometric methods while high sensitivity C-reactive protein (hsCRP) and tumuor necrosis factor-alpha (TNF-α) were determined using ELISA. Student's t-test (paired) and Wilcoxon signed-rank test were used for statistical analysis as appropriate. P-value <0.05 was considered significant.

Results: The mean blood pressure (BP), body mass index (BMI), waist circumference (WC), hip circumference (HC), body fat, NO, hsCRP, H_2O_2, total protein and globulin were significantly reduced while the mean HDL, MDA, albumin and activities of CAT and MPO were significantly increased post-dietary modification compared with baseline.

Conclusion: Short-term dietary intervention improved cardiovascular risk, inflammation and oxidative stress indices in Nigerians with MS.

1. INTRODUCTION

Metabolic syndrome (MS) is a collection of cardiometabolic risk factors (CMF) that includes abdominal obesity, insulin resistance, hypertension and dyslipidaemia [1] associated with increased risk for developing type 2 diabetes mellitus (T2DM) and cardiovascular disease [2,3]. It has become one of the major public health challenges worldwide [4] and affects individual in industrialized [5,6] as well as developing countries [7] where poverty is prevalent [8].

More than 25% of the US population is classified as having MS and the prevalence is increasing with age [9,10,11]. In Sub-Saharan Africa, the prevalence of MS was thought to be low as there are few available data. However, emerging data showed that many African countries have a high prevalence of MS. A prevalence of 5.9% was reported in Cameroon [12] while Ghazali and Sanusi [13] and Charles-Davies et al. [7] working among different populations in Nigeria reported prevalence rates of 36.7% and 16.3% respectively. This was attributed to the rapidly growing number of sedentary population, worldwide increase in urbanization, industrialization and mechanization [14].

Visceral obesity and insulin resistance are considered the main features determining the negative cardiovascular profile in MS [3]. Among Nigerians, MS was described as a prediabetic phase marked by aberrant cardiovascular risk factors [15]. Adverse CMF were

also observed in individuals with MS and T2DM with none specifically identifying MS [8]. Overweight and obesity progress to MS through largely unclear pathophysiologic mechanisms. Female gender, hypercholesterolaemia, hypertension, increasing age, general and abdominal obesity appear to be important metabolic risk factors of CVD and not T2DM among apparently healthy traders [3,7]. Urgent need for health care strategies for effective modulation of diet, lifestyle and exercise was therefore suggested [7,15].

Cellular mechanisms that link the metabolic abnormalities of MS with the pathophysiological effects that later generate clinical disease are not yet understood. MS is often characterized by oxidative stress and proinflammatory cytokines [1,3]. Oxidative stress (OS) is thought to play a major role in aging process as well as the pathogenesis of a variety of human diseases, including atherosclerosis, diabetes and hypertension. It is a condition in which an imbalance results between the production and inactivation of reactive oxygen species. Reactive oxygen species are essential in multiple physiological systems but contribute to cellular dysfunction under conditions of oxidative stress [1].

Proinflammatory cytokines are over-expressed in obesity with progressive adipocyte enlargement, thus reducing blood supply to the adipocytes with consequent hypoxia. Hypoxia is hypothesized as the inciting aetiology of necrosis and macrophage infiltration into adipose tissue that leads to the overproduction of proinflammatory cytokines. The resultant localized inflammation in adipose tissue propagates overall systemic inflammation that is associated with the development of obesity-related co-morbidities [1]. Oxidative stress in adipocyte seems to be responsible for the sub-clinical proinflammatory state often observed in visceral obesity [16,17]. The mechanisms involved in elevation of oxidative stress and inflammation include increased production of superoxide anion via the NAD(P)H oxidase pathway which causes deregulated production of adipocytokines [18].

Appropriate diet, life style changes, weight reduction, and increased physical activity have been considered as effective lifestyle strategies to reduce the cardio-metabolic risk factors associated with MS in some populations in DR Congo [19,20]. Pharmacological and surgical interventions have also been recommended especially, in obese MS patients. The pharmacologic approach has limitation because each drug only attends to a fraction of MS without consideration for others [21]. Matfin [21] therefore, suggested a "poly-pill" therapeutic approach for MS. Studies on increased physical activity have also been hindered by the need for a stress test in order to prescribe appropriate exercise which corresponds with individual fitness. As Nigerians age with sedentary lifestyle, western diet, limited access to drugs and poverty, dietary modification may be appropriate in managing MS. To provide information in a defined population of African traders whose habitual staple foods are mainly starchy foods and vegetable based diets, this study assessed the effect of short term dietary modification on indices of inflammation and oxidative stress in individuals with metabolic syndrome.

2. MATERIALS AND METHODS

2.1 Study Design

A total of 60 apparently healthy participants aged 18-80 years without medication were purposely selected from the cohort of traders earlier reported [7]. Briefly, a total of 534 (170 males and 364 females) apparently healthy traders from a local market in Bodija, Ibadan aged 18–105 were recruited into a cohort study titled "Risk Assessment of Type 2 diabetes

mellitus and Dementia in Nigerians with Metabolic Syndrome" after written informed consent and an approval from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee. Eighty seven (87) of the subjects had MS while 447 had no MS. For this pilot study, 60 (15 males, 45 females) subjects with MS were selected from the group. All the subjects were non-diabetic, had no history of cardiovascular events and were not on any type of medication.

Diagnosis of metabolic syndrome (MS) was made using the International Diabetes Federation diagnostic criteria [22]. The criteria include central obesity; measured as waist circumference (male: ≥94 cm, female: ≥80 cm) and any two of raised triglycerides: ≥150 mg/dL (1.7 mmol/L) (or on treatment for dyslipidaemia), reduced HDL cholesterol (males: <40 mg/dL, females: <50 mg/dL (or on treatment for dyslipidaemia), raised blood pressure (≥130/≥85 mmHg) or on treatment for hypertension or raised fasting plasma glucose (FPG) (≥100 mg/dL) or previously diagnosed with type 2 diabetes mellitus. All participants with hsCRP values >10 mg/L were excluded from the study.

All the participants were seen by the Dietitian in the study at recruitment (Pre-dietary modification). Each of them was given food recipe and seen monthly to ensure compliance. The participants with MS were advised to:

a. Avoid food high in saturated and/or cholesterol (fat, meat, butter, cream), take an egg yolk per week, or equivalent in manufactured products.
b. Substitute with foods high in poly unsaturated fatty acids (e.g. sunflower seed oil, fish).
c. Eat only moderate amounts of foods containing appreciable quantities of saturated and mono unsaturated fatty acids (e.g. lean meat, palm oil).
d. Use foods containing little or no fat (skimmed milk, cereals, fruit, vegetable, sugars as desired).

The approximate percentages of total calories obtained from protein, total fat, polyunsaturated fat, and carbohydrate were calculated from dietary history and pegged at 20%, 30%, 14% and 50% respectively.

2.2 Sample Collection

10 ml of venous blood sample was asceptically obtained by venepuncture from the participants after an overnight fast (10-14 h). 4 ml was dispensed into potassium ethylene diamine tetra acetic acid (K3EDTA) tube for the determination of lipid profile (total cholesterol, triglyceride and high density lipoprotein-cholesterol). 2 ml was dispensed into fluoride oxalate tube for FPG estimation, while 4 ml was dispensed into plain tubes for the estimation of markers of inflammation and oxidative stress. All samples were centrifuged at 500 g for 5 min after which plasma/serum were aspirated in small aliquots into clean vials and stored at -20ºC until analyses were done.

2.3 Cardiometabolic Risk Factors

2.3.1 Anthropometric and blood pressure measurements

Body weight, height, BMI, WC and hip circumferences (HC), WHR, WHT, PBF and BP (systolic and diastolic) were obtained from the participants by standard methods as described elsewhere [7,15].

2.3.2 Lipid and fasting plasma glucose

Plasma TG, TC, HDL and FPG were estimated by enzymatic methods while LDL was calculated using Friedwald et al. [23] formula. Ratios of LDL to HDL, TC to HDL, TG to HDL were also calculated.

2.4 Inflammatory Factors

Serum levels of highly sensitive C-reactive protein (hsCRP) and tumor necrosis factor-alpha (TNF-α) were determined using ELISA (MP Biomedicals, Ohio and Boster Biological Technology, USA respectively). Serum level of albumin was estimated using the Bromocresol Green (BCG) method as described by Doumas et al. [24]. The total protein level was estimated using Biuret's method as described by Gornal et al. [25] while globulin was calculated as the difference between total protein and albumin.

2.5 Oxidative Stress Factors

Myeloperoxidase (MPO) activity was determined using the method of Bergmeyer [26]. Nitric oxide (NO) estimation was done using Griess reagent as described by Green et al. [27]. Serum level of malondialdehyde (MDA) was determined using the method of Adam-Vizi and Seregi [28], while serum hydrogen peroxide (H_2O_2) level was estimated using Wolff's method [29]. Catalase (CAT) activity was determined using the method of Sinha [30] and serum superoxide dismutase (SOD) activity was determined using the method of Misra and Fridovich [31].

2.6 Statistical Analysis

Differences between pre-dietary modification and post-dietary modification values were determined using paired Student's t-test or Wilcoxon signed-rank test as appropriate. *P* value less than 0.05 was considered as significant.

3. RESULTS

Table 1 shows the levels of CMF, inflammatory and oxidative stress indices in all the participants before dietary modification. Table 2 shows comparison of mean levels of CMF, inflammatory and oxidative stress indices and their percentage changes in participants with MS, pre and post dietary modification. Only 49 MS subjects were seen after the 6-month of dietary modification as 11 subjects did not report exactly at 6-month. The mean baseline values for all parameters for the 49 MS subjects seen after six months were not significantly different from the corresponding values in the 60 subjects who were seen at the first visit (data not shown). Significant reductions were observed in all the CMF levels except glucose, TC, LDL and TG while a significant increase was observed in HDL only (p<0.05) post dietary modification. Amongst these, HDL had the most extensive change of 34.3%, while ratios of TG to HDL, LDL to HDL and TC to HDL had percentage changes of 28, 33.3 and 20.0 respectively. All inflammatory indices changed significantly after post dietary modification except TNF-α (p<0.05). The percentage reductions in globulin, hsCRP and total protein were 33.3, 33.3 and 7.8 respectively; while the percentage increase in albumin was 7.5. Although the difference between pre- and post -dietary modification level of TNF-α was not significant (p>0.05), its percentage reduction after dietary modification was 49.92. All oxidative stress factors except catalase were significantly different between pre- and post- dietary

modification. Increases were observed in MPO, SOD, and MDA with percentage changes of 16.7, 20 and 33.3 respectively. Reductions were observed in NO and H_2O_2 with percentage changes of 19.3 and 10.0 respectively.

Table 1. Cardiometabolic, oxidative stress and inflammatory factors before dietary modification in participants with metabolic syndrome

	MS (n = 60)
Cardiometabolic Factors	
Age (years)	54±11
Height (m)	2±0
Body Weight (kg)	76±15
BMI (kg/m2)	29±4
Waist circumference (cm)	102±10
Hip circumference (cm)	106±9
Waist-Hip ratio	1±0
Waist-Height ratio	63±6
Body fat (%)	38±8
Systolic BP (mmHg)	152±28
Diastolic BP (mmHg)	93±14
FPG (mg/dL)	94±35
TC (mg/dL)	143±42
TG (mg/dL)	77±32
HDL (mg/dL)	35±11
LDL (mg/dL)	92±40
LDL-HDL ratio	3±1
TG-HDL ratio	2±2
TC-HDL ratio	4±2
Inflammatory Factors	
TNF-α (pg/mL)	625 (313-728)
hsCRP (mg/L)	3 (2-5)
Protein (g/L)	64±6
Albumin (g/L)	40±7
Globulin (g/L)	24±10
Oxidative Stress Factors	
NO (µmole)	115±40
MPO (U/mL)	1±0
SOD (%inhibition)	-20±7
CAT (µmole/mg protein)	6±1
MDA (x10-6U/mg protein)	1±0
H2O2 (µmole)	4±1

values are in mean ± standard deviation or median (interquartile range), BP=blood pressure, BMI=body mass index, FPG = fasting plasma glucose, TC=total cholesterol, TG=triglyceride, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TNF- α=tumour necrosis factor-alpha, hsCRP=high sensitivity C reactive protein, NO=nitric oxide, MPO=myeloproxidase, SOD=superoxide dismutase, CAT=catalase, MDA=malondialdehyde, H_2O_2=hydrogen peroxide, n=number of participants, MS=metabolic Syndrome

Table 2. Changes in metabolic, oxidative stress and inflammatory indices in participants with metabolic syndrome after 6 months of dietary modification

Index	Pre- Dietary Modification (n=49)	Post-Dietary Modificaton (n=49)	p-value	Absolute change (%)
Cardiometabolic Risk Factors				
Body Weight (kg)	73±12	70±11	*0.000	3 (4.1)a
BMI (kg/m2)	28±4	27±4	*0.017	1 (3.57)a
WC (cm)	100±9	96±7	*0.000	4 (4.0)a
HC (cm)	106±10	103±7	*0.011	3 (2.8)a
Waist-Hip ratio	1±0	0.9±0	*0.028	0.1 (10)a
Waist-Height ratio	62±5	60±4	*0.000	2 (3.2)a
Body fat (%)	39±7	37±8	*0.046	2 (5.1)a
SBP (mmHg)	153±27	143±23	*0.001	10 (6.5)a
DBP (mmHg)	93±2	87±13	*0.006	6 (6.5)a
FPG (mg/dL)	94±37	89±15	0.343	5 (5.3)
TC (mg/dL)	147±42	158±41	0.140	11 (7.5)
TG (mg/dL)	78±34	75±36	0.754	3 (3.8)
HDL (mg/dL)	35±12	47±16	*0.000	12 (34.3)b
LDL (mg/dL)	97±40	98±40	0.854	1 (1.0)
LDL-HDL ratio	3±2	2±2	*0.033	1 (33.3)a
TC-HDL ratio	5±2	4±2	*0.013	1 (20.0) a
TG-HDL ratio	2.5±2	1.8±1	*0.018	0.7 (28)a
Inflammatory Factors				
TNF-α (pg/mL)	625 (313-864)	313 (313-625)	0.063	312 (49.92)
hsCRP (mg/L)	3 (1-6)	2 (1-4)	*0.049	1 (33.3)a
Total Protein (g/L)	64±6	59±3	*0.000	5 (7.8)a
Albumin (g/L)	40±7	43±5	*0.023	3 (7.5)b
Globulin (g/L)	24±9	16±5	*0.000	8 (33.3)a
Oxidative Stress Factors				
NO (µmole)	119±43	96±13	*0.001	23 (19.3)a
MPO (U/mL)	0.6±0	0.7±0	*0.009	0.1 (16.7)b
SOD (%inhibition)	-20±7	-24±10	*0.018	4 (20.0)b
CAT (µmole/mg pr)	6.3±1	6.4±1	0.549	0.1 (1.6)
MDA (x10-6U/mg pr)	0.6±0	0.8±0	*0.008	0.2 (33.3)b
H2O2 (µmole)	4.0±1	3.6±1	*0.001	0.4 (10.0)a

*values are in mean ± standard deviation or median (interquartile range),*significant at p < 0.05 (2-tailed), BP=blood pressure, BMI=body mass index, WC=waist circumference, HC=Hip circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure, FPG = fasting plasma glucose, TC=total cholesterol, TG=triglyceride, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TNF- α=tumour necrosis factor-alpha, hsCRP=high sensitivity C reactive protein, NO=nitric oxide, MPO=myeloproxidase, SOD=superoxide dismutase, CAT=catalase, MDA=malondialdehyde, H_2O_2=hydrogen peroxide, n=number of participants, a = reduced change, b= increased change, pr = protein*

4. DISCUSSION

Low grade inflammation has been implicated in obesity and in the development of co-morbidities such as the metabolic syndrome, T2DM and cardiovascular disease [32].

Significant improvement six months post dietary modification were observed in the cardiometabolic risk factors (p<0.05) except FPG with mild percentage reduction of 5.3. Lifestyle change and weight loss are considered the most important initial steps in treating metabolic syndrome [33]. The Whitehall II prospective cohort study reported that dietary modification for 5 years reversed the risks associated with MS [34]. Similar observations were made in our study as HDL had the most positive change of 34.3% while TG to HDL, LDL to HDL, TC to HDL ratios had the percentage changes of 28, 33.3 and 20.0 respectively.

Increased concentration of TNF-α is associated with insulin resistance, which is associated with and probably in part caused by inflammation as insulin itself has acute anti-inflammatory properties [32]. A 12-week dietary carbohydrate diet of high postprandial insulin response exacerbated inflammation compared with low postprandial insulin response as assessed by cytokine concentrations in serum and gene expression in subcutaneous abdominal fat in individuals with the metabolic syndrome [32]. In our study, all inflammatory indices changed significantly 6 months post dietary modification except TNF-α (p<0.05). The percentage reductions in globulin, hsCRP and total protein were 33.3, 33.3 and 7.8 respectively; while the percentage increase in albumin was 7.5. Although the difference between pre- and post - dietary modification level of TNF-α was not significant (p>0.05), its percentage reduction after dietary modification was 49.92. Decreased circulating level of TNF-α is associated with decreased weight loss. It has been suggested that TNF-α induces adipocytes apoptosis and promotes insulin resistance by the inhibition of the insulin receptor substrate 1 signaling pathway [3]. Reduction of adiposity measures were observed in this present study post dietary modification. However, further investigation is still required to understand the role of disturbed protein homeostasis in the pathogenesis of MS.

Significant reduction in hsCRP level observed in MS subjects post dietary modification in our study is similar to reports in MS subjects placed on dietary modification in other studies [35,36,37]. This observation could be attributed to a host of factors including increased receptor mediated CRP uptake, reduced pro-inflammatory markers and decreased glycaemic load [38]. Increased albumin and reduced globulin production may be sequel to reduced inflammation.

In several studies, oxidative stress occurred more frequently in people with metabolic syndrome than among those without MS [18,39,40,41]. Matsuzawa-Nagata et al. [42] showed that reactive oxygen species (ROS) overproduction in the adipose tissue and liver preceded the onset of insulin resistance induced by a high-fat diet. Furukawa et al. [18] observed good correlation between obesity and systemic oxidative stress. Additionally, they observed a higher expression of reduced nicotine adenyl dinucleotide phosphate (NADPH) oxidase that is accompanied by a decrease of antioxidant enzymes. Leptin, a hormone produced by adipocytes acts on hypothalamic centre to regulate food intake and energy expenditure and contributes to the OS of MS. It stimulates ROS production such as H_2O_2 and hydroxyl radical directly. Leptin also reduces the activity of paraoxonase-1 (PON-1), an enzyme that protects against LDL oxidation [43]. An earlier study by our group observed that increased leptin levels in both MS and T2DM groups, reflected adiposity and might be a compensatory mechanism for maintenance of weight/fat loss and blood pressure [8]. In this study, all measured oxidative stress factors except catalase were significantly different between pre and post dietary modification. Increases were observed in MPO, SOD and MDA with percentage changes of 16.7, 20.0 and 33.3 respectively. Reductions were observed in NO and H_2O_2 with percentage changes of 19.3 and 10.0 respectively. Glucose and fatty acid independent sources of oxidative stress such as NADPH oxidase and xanthine oxidase

convert molecular oxygen into superoxide anion which is dismutated by SOD to yield hydrogen peroxide. The hydrogen peroxide is detoxified by catalase or glutathione peroxidase to form water. Therefore, increased NADPH activity, or reduced SOD or glutathione activity, culminate in increased ROS production. The activities of these enzymes have been reported to be low in obese individual [18,44]. Catalase deficiency has been associated with oxidative DNA damage and development of type 2 diabetes [45,46,47].

In our present study, SOD activities increased significantly with a percentage change of 20.0 post dietary modification in participants with MS ($p < 0.05$). Isogawa et al. [48] reported a negative correlation between SOD activity and TG concentration as well as BMI, FPG and both systolic and diastolic blood pressure.

The reduced H_2O_2 level post dietary intervention indicates reduced production of oxidants resulting in decreased oxidative stress and confirms earlier findings in other studies [37,49]. Elevated MPO activity might indicate continuous destruction of already hypertrophied and necrotic adipocytes in other to restore the adipose tissue to pre-MS stage. MPO has been associated with direct utilization of NO [50,51]. This could be responsible for our observed decreased level of NO post-dietary modification. The observed elevated level of MDA could be a reflection of increased release of lipid peroxides from the adipocytes and foam cells which could be induced by elevated MPO activity as observed in this study. This on-going restructuring of the adipose tissue might be responsible for the observed elevated activity of SOD which might be required to dismutate ROS released during the destruction of necrotic adipocytes. Metabolic overload evokes several stress reactions, such as oxidative, inflammatory, organelle and cell hypertrophy stresses, generating vicious cycles that amplify each other leading to dysfunction. Adipocyte hypertrophy facilitates cell rupture and evokes an inflammatory reaction. Inability of adipose tissue development to engulf all incoming fat leads to fat deposition in other organs, mainly in the liver, with marked consequences on insulin resistance. The accompanying oxidative stress due to excessive ingestion of fat and/or other macronutrients without concomitant ingestion of antioxidant-rich foods/beverages, may contribute to the inflammatory markers attributed to obesity [52]. Our observations suggest that inflammatory and oxidative stress mechanisms are important in the pathogenesis of MS and relate to some components of the metabolic syndrome. Short term dietary intervention of six months resulted in significant loss of adiposity and greatly improved cardiovascular risk, inflammatory and oxidative stress factors without significant reduction in FPG levels.

5. CONCLUSION

Cardio-metabolic risk factors, inflammatory and oxidative mechanisms underlie metabolic syndrome. Improvement in most of the factors as a result of short dietary intervention of 6 months was observed. Monitored dietary modification could be a viable therapeutic regime against the chronic inflammation and oxidative stress associated with metabolic syndrome. Screening of communities for cardiometabolic, inflammatory and oxidative stress indices as well as modulation of diet of affected individuals to prevent diseases associated with MS is advocated especially in Nigeria, with poor economy. Since fasting plasma glucose was not markedly affected by 6 months post dietary intervention, studies for longer periods will shed more light on the mechanism involved.

ETHICAL CONSIDERATION AND INFORMED CONSENT

This study was approved by the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Review Committee. Also, written informed consent was obtained from each subject.

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COMPETING INTEREST

Authors have declared that no competing interests exist.

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