



### Plasma Lipid Peroxidation and Total Antioxidant Status among Dyslipidaemic and Hypertensive Nigerians with High Risk of Coronary Heart Disease

*Plasma Lipid Peroxidation et Total Antioxydant Status Dyslipidaemic entre Nigériens et d'hypertension avec un risque élevé de maladie coronarienne*

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#### ABSTRACT

**BACKGROUND:** The oxidative modification hypothesis of atherosclerosis predicts that low density lipoprotein-cholesterol (LDL-C) oxidation is an early event in atherosclerosis and that oxidized LDL-C contributes to atherogenesis

**OBJECTIVE:** To determine a link, if any, between the plasma lipid peroxidation and total antioxidant status (TAS) among dyslipidemic and hypertensive Nigerian patients with high risk of coronary heart disease.

**METHODS:** The study groups comprised 58 hypertensive adult Nigerians whose fasting plasma total cholesterol (TC) levels were > 5.5mmol/L and with high risk coronary heart disease (CHD) lipid fraction i.e. 'the ratio of high density lipoprotein cholesterol to total cholesterol' (HDL-C/TC) < 0.13 were selected for the study. The control groups comprised 58 non hypertensive adult Nigerians with (HDL-C/TC) >0.30.

**RESULTS:** The mean± SD TAS level(1.02 ± 0.15 mmol/L trolox) for males and (0.99 ± 0.17 mmol/L) for females were significantly reduced (p< 0.05) compared to the controls; however(MDA) level(5.15 ± 0.82 mmol/ml) for males and (5.06 ± 0.73mmol/ml) for females were significantly increased (p< 0.01) compared to the controls. The mean ± SD plasma TC and LDL-C malonyl level (5.87 ±0.23mmol/L and 4.65 ±0.34 mmol/L) were significantly increased (p<0.01) in males hypertensive compared to the control. An inverse correlation between the TAS/TC(r= -0.53, p< 0.001) and TAS/LDL-C(r= -0.50, p< 0.001), however a direct correlation between the MDA/TC(r= 0.51, p< 0.001) and MDA/LDL-C(r= 0.48, p< 0.01) for males hypertensive were found. In female subjects the mean± SD plasma TC (5.95 ±0.13mmol/L) and LDL-C (4.45 ±1.04 mmol/L) were significantly increased (p< 0.05) and (p< 0.01) respectively compared to the controls. Also in hypertensive females inverse correlation between the TAS/TC(r= -0.59, p< 0.001) and TAS/LDL-C(r= -.41, p< 0.01), and a direct correlation between the MDA/TC(r= .48, p< 0.01) and MDA/LDL-C(r= 0.31, p< 0.05) were found.

**CONCLUSION:** Since dyslipidaemia, hypertension and lipid peroxidation were directly relate to the severity of atherosclerosis, elimination of free radicals in the plasma before the peripheral tissues can take them up might reduce atherosclerosis. In view of our present findings, a management strategy aimed at simultaneously reducing lipid peroxidation and increasing total antioxidant status in dyslipidemic patients may be of benefit. *WAJM 2009; 28(2): 87-91.*

**Keywords:** Coronary heart disease, hypertension, cholesterol, lipid peroxidation, total antioxidant.

#### RÉSUMÉ

**CONTEXTE:** La modification hypothèse oxydative de l'athérosclérose prédit que des lipoprotéines de faible densité-cholestérol (LDL-C), l'oxydation est un événement précoce dans l'athérosclérose et que l'oxydation du LDL-C contribue à l'athérogenèse.

**Objectif:** déterminer un lien éventuel entre le plasma et de la peroxydation lipidique total antioxydant status (TAS) et les dyslipidemic nigérien patients hypertendus à haut risque de maladie coronarienne.

**MÉTHODES:** Les groupes d'étude comprenait 58 hypertendus adultes Nigériens dont le plasma à jeun de cholestérol total (CT) ont été > 5.5mmol/L et avec un risque élevé de maladie coronarienne (CHD) niveau c'est-à-dire la fraction «le taux de cholestérol des lipoprotéines de haute densité pour le cholestérol total» (HDL-C/TC) <0,13 ont été retenus pour l'étude. Les groupes de contrôle comprenant 58 adultes hypertendus non avec les Nigériens (HDL-C/TC) > 0,30.

**RÉSULTATS:** La moyenne ± TAS niveau (1,02 ± 0,15 mmol/L trolox) pour les hommes et de (0,99 ± 0,17 mmol/L) pour les femmes a été sensiblement réduit (p < 0,05) par rapport aux contrôles, mais (MDA) niveau (5,15 ± 0,82 mmol/ml) pour les hommes et de (5,06 ± 0,73mmol/ml) pour les femmes étaient significativement augmenté (p < 0,01) par rapport aux contrôles. La moyenne ± TC plasma et du LDL-C malonyl niveau (5,87 ± 0,23mmol/L et 4,65 ± 0,34 mmol/L) ont augmenté de manière significative (p < 0,01) chez les hommes hypertendus par rapport au témoin. Une corrélation inverse entre le TAS / TC (r = -0,53, p < 0,001) et le TAS / LDL-C (r = -0,50, p < 0,001), cependant une corrélation directe entre le MDA / TC (r = 0,51, p < 0,001) et MDA / LDL-C (r = 0,48, p < 0,01) chez les hommes hypertendus ont été trouvés. Dans les sujets de sexe féminin à la moyenne ± écart-type plasma TC (5,95 ± 0,13mmol/L) et le LDL-C (4,45 ± 1,04 mmol/L) ont augmenté de manière significative (p < 0,05) et (p < 0,01) respectivement par rapport aux contrôles. Toujours dans l'hypertension femelles corrélation inverse entre le TAS / TC (r = -0,59, p < 0,001) et le TAS / LDL-C (r = -. 41, p < 0,01), et une corrélation directe entre le MDA / TC (r = .48, p < 0,01) et MDA / LDL-C (r = 0,31, p < 0,05) ont été trouvés.

**CONCLUSION:** Depuis une dyslipidémie, d'hypertension et de la peroxydation lipidique ont été directement liées à la gravité de l'athérosclérose, l'élimination des radicaux libres dans le plasma avant que les tissus périphériques peuvent prendre leur place pourrait permettre de réduire l'athérosclérose. Compte tenu de nos résultats, une stratégie de gestion visant à la fois de réduire la peroxydation des lipides et l'augmentation totale dans le statut antioxydant dyslipidemic patients mai être bénéfique. *WAJM 2009; 28(2): 87-91.*

**Mots-clés:** maladie coronarienne, l'hypertension, le cholestérol, la peroxydation lipidique, le total des antioxydants.

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**Abbreviations:** CHD, Coronary Heart Disease; HDLC, High Density; LDL-C, Low Density Lipoprotein-Cholesterol; MDA, Malonyldialdehyde; TAS, Total Antioxidant Status; TC, Total Cholesterol.

## INTRODUCTION

The activities of free radicals in many age-related diseases have long been of interest, and there is substantial evidence linking diabetes, cancer, and atherosclerosis to free radical-induced alterations.<sup>1,2</sup> With regard to atherosclerosis, evidence for a free radical contribution to the disease was advanced by Parthasarathy and co-workers who proposed the oxidative modification hypothesis for atherosclerosis.<sup>3</sup>

Although the aetiology of atherosclerosis has been the subject of intense research for the last several decades, our understanding of the role of the major risk factors, such as lipoprotein, in the development of atherosclerotic lesions was quite limited until recently.<sup>3</sup> The mechanism by which increased low-density lipoproteins-cholesterol (LDL-C) levels cause increased fatty deposits on the cells lining the arterial wall, thereby forming the earliest lesion of the fatty streak, has been of major interest.<sup>4</sup> Recent investigations have produced cogent evidence that oxidatively modified LDLs play a major role in the formation of the fatty streaks.<sup>4</sup> A major clue to the identity of the missing link was uncovered by several recent studies on the uptake of oxidized LDLs by monocytes and macrophages, which eventually convert to lipid-laden foam cells.<sup>4,5</sup> Steinberg *et al.* demonstrated that modification of LDL molecules takes place only in the presence of metals and can be suppressed by antioxidants, strongly implicating the involvement of free radical-mediated peroxidative reactions.<sup>7</sup> Triau *et al.* showed that incubating oxidized LDLs with endothelial cells stimulates production of prostaglandins, thus making oxidatively modified LDL more active than native LDL in promoting

platelet aggregation.<sup>8,9</sup> These stimulating effects of oxidatively modified LDL seem to be specific to the oxidation because neither native LDL nor acetylated LDL affected prostaglandin synthesis.<sup>8</sup> Recently, Morel *et al.* showed that oxidatively damaged low-density lipoproteins found in streptozotocin-induced diabetic rats were cytotoxic to cultured fibroblasts.<sup>9</sup> The addition of antioxidants such as vitamin E or probucol, which also lowers cholesterol, attenuated the extent of the toxicity.<sup>9</sup> The therapeutic efficacy of antioxidant treatment of atherosclerosis has not been pursued vigorously, but there are some indications that LDL isolated from patients treated for hypercholesterolemia with probucol or vitamin E is more resistant to oxidative alterations induced by metal ions.<sup>10</sup> Experiments with the Watanabe rabbit, which lacks LDL receptors, found that probucol decreases the rate of atherosclerotic progression by acting as an antioxidant.<sup>11</sup>

The above finding was confirmed in humans, which provides strong evidence for a causal relationship between free radicals, lipid peroxidation, and atherosclerosis.<sup>12</sup> These investigators demonstrated a close association between the susceptibility to LDL oxidation and coronary atherosclerosis in male subjects. Other studies further support the relationship between lipid peroxidation and oxidative processes as being important factors in atherogenesis.<sup>13</sup> The protective efficiency of antioxidants in hypercholesterolemic patients would depend on the balance between free radicals and the availability of antioxidants themselves.<sup>14</sup> However the relationship between hypertension and dyslipidemia has also been demonstrated by various investigators

from Nigeria, it has been established that dyslipidemia and hypertension are independent risk factors of coronary heart disease.<sup>15,16</sup>

Hence the present study was undertaken to evaluate a correlation between malonyldialdehyde (MDA), which is a marker of lipid peroxidation and total antioxidant status in plasma of dyslipidemic and hypertensive adult Nigerians with high risk of Coronary Heart Disease

## SUBJECTS, MATERIALS AND METHODS

The study was carried out at the Ladoké Akintola University of Technology Teaching Hospital, Osogbo between the months of January 2005 and March 2006. The study population comprised 58 hypertensive patients (Systolic blood pressure = 140 mmHg and diastolic = 90 mmHg), whose plasma total cholesterol level was = 5.5 mmol/L and between the ages of 30–70 years who were not on any drugs with high risk coronary heart disease (CHD) lipid fraction, that is the ratio of high density lipoprotein cholesterol to total cholesterol (HDL-C/TC) = 0.13 were selected for the study. The study was approved by the college and hospital ethics committee. Patients who were diabetics, have any form of cancer, renal pathology, liver disease, lung disease, neurodegenerative disease, inflammatory disease, infectious disease and cardiovascular disease were excluded from the study. Formal consent was obtained from the patients after explaining to them the benefit of the study before commencing the study. Fifty-eight consenting healthy subjects between the ages of 30–70 years whose plasma cholesterol is = 3.5 mmol/L, with (HDL-C/TC) = 0.30 was used as controls.

**Table 1: Age and Anthropometric Data for Subjects and Controls**

Characteristic	Male		p value	Female		p value
	Control (n = 30)	Subjects (n = 30)		Controls (n = 28)	Subjects (n = 28)	
Age	51.50 ± 7.20	50.90 ± 5.70	(1.1963)	54.15 ± 4.50	55.72 ± 2.67	(1.7109)
Weight (kg)	63.42 ± 7.70	70.15 ± 8.52	(0.0417)*	58.84 ± 6.07	69.15 ± 7.21	(0.0381)*
Height (m)	1.62 ± 0.08	1.60 ± 1.10	(1.5208)	1.59 ± 0.52	1.56 ± 0.12	(1.2912)
BMI	24.20 ± 1.81	27.79 ± 0.70	(0.0487)*	20.89 ± 2.15	28.46 ± 1.09	(0.0399)*

Results are mean ± SD, Significant level,  $p < 0.05$ .

Table 2: Comparison of Biological Parameters of Subjects and Controls

Biochemical parameter	Male		p value	Female		p value
	Controls (n = 30)	Subjects (n = 30)		Controls (n = 28)	Subjects (n = 28)	
Systolic BP (mmHg)	124.60 ± 8.91	149.6 ± 11.60	(0.0495)	110.45 ± 5.42	157.21 ± 13.45	(0.0471)
Diastolic BP (mmHg)	72.10 ± 9.70	97.34 ± 4.27	(0.0431)	79.73 ± 6.81	98.65 ± 7.15	(0.0483)
Triglyceride (mmol/L)	1.65 ± 0.54	2.97 ± 0.80	(0.0391)	1.47 ± 0.81	2.75 ± 1.06	(0.0317)
Total Cholesterol (mmol/L)	3.83 ± 0.17	5.87 ± 0.23	(0.0061)	4.01 ± 1.01	5.95 ± 0.13	(0.0419)
LDL Cholesterol (mmol/L)	1.55 ± 0.12	4.65 ± 0.34	(0.0037)	1.85 ± 0.16	4.45 ± 1.04	(0.0070)
HDL Cholesterol (mmol/L)	1.95 ± 0.21	0.63 ± 0.17	(0.0025)	1.87 ± 0.75	0.60 ± 0.52	(0.029)
HDL.C/TC	0.51 ± 0.02	0.10 ± 0.03	(0.0021)	0.47 ± 0.05	0.10 ± 0.01	(0.0024)
MDA (nmol/ml)	3.68 ± 0.60	5.15 ± 0.82	(0.0069)	2.87 ± 0.47	5.06 ± 0.73	(0.0051)
TAS. (mmol/L trolox equivalent)	1.86 ± 0.31	1.02 ± 0.15	(0.0379)	1.79 ± 0.59	0.99 ± 0.17	(0.0213)

After an overnight fast, 10ml of venous blood was collected at the antecubital fossa in sitting position without stasis into lithium heparinized bottle. Plasma was obtained after centrifugation at 3500r.p.m for 10 minutes and immediately stored at -20°C until they were analysed.

Total plasma cholesterol and triglycerides were determined enzymatically using kits from Randox laboratory Ireland UK.<sup>17,18</sup> HDL (high-density lipoprotein) – cholesterol was measured (when triglycerides were <4 mmol/L) after low-density lipoproteins, very low density lipoprotein (LDL, VLDL) and chylomicron fractions were precipitated quantitatively by addition of phosphotungstic acid in the presence of magnesium ions. After centrifugation, the cholesterol concentration in the HDL (high density lipoprotein) fraction, which remained in the supernatant, was analyzed.<sup>19</sup> Quality control was ensured by the use of control materials from Randox laboratory and Human Company of Germany. LDL-cholesterol was calculated using Friedwald formula (LDL Cholesterol=Total Cholesterol – (Triglyceride/5 + HDL Cholesterol)).<sup>20</sup> The cardiovascular risk ratio was calculated from the values of lipids profile obtained.<sup>21</sup>

Measurement of secondary products of lipid peroxidation such as malonyldialdehyde (MDA) was employed to assess oxidative stress in this study. Malonyldialdehyde (MDA) was estimated according to the method of Satoh.<sup>22</sup> Measurement of total antioxidant status in the plasma was performed using a commercial kit from Randox Laboratories (Randox Laboratories Ltd, Diamond Road, Crumlin, Co. Antrim, Ireland).<sup>23</sup> The assay was calibrated using 6-hydroxy-2, 5, 8-tetra-methylchroman-2-carboxylic acid (trolox). The results were expressed as mmo/L of trolox equivalent.

**Statistical analysis:** All values were entered into EPI INFO (version 6.4a database). Values are expressed as mean ± SD, the statistical significance of the mean differences between groups was assessed by Student's t-test. Method of correlation analysis (PEARSON) was also used to determine the degree of association between variable of interest. Value of p < 0.05 was taken as a measure statistical significance.

## RESULTS

The study was carried out with equal numbers of subjects (n=58) and controls

(n=58), males were 30 and females 28 giving a male: female ratio of 1:0.9. The anthropometric data for the subjects and controls are presented in Table 1. The mean ages ±SD of the subjects and controls was not significantly different in both sexes. However, the body mass index was significantly higher (27.79 ± 0.70 kg/m<sup>2</sup>) in male and (28.46 ± 1.09 kg/m<sup>2</sup>) in female subjects compared to the controls: (24.20 ± 1.81 kg/m<sup>2</sup>) in males and (20.89 ± 2.15 kg/m<sup>2</sup>) in females, P < 0.05.

The mean ± SD (TAS) level (1.02 ± 0.15 mmol/L trolox) for male subjects and (0.99 ± 0.17 mmol/L trolox) for female subjects were significantly reduced (p < 0.05) compared to the controls, however MDA levels (5.15 ± 0.82 mmol/ml) for male subjects and (5.06 ± 0.73 mmol/ml) for female subjects were significantly increased (p < 0.01) compared to the controls. The mean ± SD plasma TC and LDL-C level (5.87 ± 0.23 mmol/L and 4.65 ± 0.34 mmol/L) were significantly increased (p < 0.01) in male hypertensive compared to the control. An inverse correlation between the TAS/TC (r = -0.53, p < 0.001) and TAS/LDL-C (r = -0.50, p < 0.001), however a direct correlation between the MDA/TC (r = 0.51, p < 0.001) and MDA/LDL-C (r = 0.48, p < 0.01) for

**Table 3: Correlation coefficients of coronary heart disease risk factors vs lipid peroxidation (MDA) and total antioxidant status (TAS)**

	Male (n = 30)				Female (n = 28)			
	MDA		TAS		MDA		TAS	
	"r"-value	(p value)	"r"-value	p value	"r"-value	(p value)	"r"-value	p value
Triglyceride (mmol/L)	0.34	(0.0325)	-0.35	(0.0311)	0.29	(0.0391)	-0.37	(0.0208)
Total Cholesterol (mmol/L)	0.51	(0.0008)	-0.53	(0.0006)	0.48	(0.0042)	-0.59	(0.0002)
LDL Cholesterol (mmol/L)	0.48	(0.0043)	-0.50	(0.0009)	0.36	(0.0304)	-0.41	(0.0054)
HDL Cholesterol (mmol/L)	-0.41	(0.0053)	0.43	(0.0049)	-0.45	(0.0053)	0.48	(0.0042)
HDL/TC	-0.39	(0.0189)	0.27	(0.0405)	-0.31	(0.0331)	0.45	(0.0052)
Systolic BP (mmHg)	0.24	(0.0419)	-0.37	(0.0209)	0.31	(0.0330)	-0.29	(0.0392)
Diastolic BP (mmHg)	0.21	(0.0451)	-0.25	(0.0410)	0.19	(0.0508)	-0.23	(0.0447)

male hypertensive was found. In female subjects the mean  $\pm$  SD plasma TC ( $5.95 \pm 0.13$  mmol/L) and LDL-C ( $4.45 \pm 1.04$  mmol/L) were significantly increased ( $p < 0.05$ ) and ( $p < 0.01$ ) respectively compared to the control. Also in female hypertensive an inverse correlation between the TAS/TC ( $r = -0.59$ ,  $p < 0.001$ ) and TAS/LDL-C ( $r = -0.41$ ,  $p < 0.01$ ), however a direct correlation between the MDA/TC ( $r = 0.48$ ,  $p < 0.01$ ) and MDA/LDL-C ( $r = 0.31$ ,  $p < 0.05$ ) was found.

HDL Cholesterol showed an inverse correlation with MDA ( $r = -0.41$ ,  $p < 0.01$ ) and ( $r = -0.45$ ,  $p < 0.01$ ) respectively in male and in female hypertensive subjects. However a direct correlation between HDL-C/MDA ( $r = 0.43$ ,  $p < 0.01$ ) and ( $r = 0.48$ ,  $p < 0.01$ ) respectively in male and in female hypertensive subjects.

Both male and female hypertensive subjects with high risk coronary heart disease (CHD) lipid fraction, had an inverse correlation with MDA ( $r = -0.39$ ,  $p < 0.05$ ) and ( $r = -0.31$ ,  $p < 0.05$ ) respectively. However a direct correlation with TAS ( $r = 0.27$ ,  $p < 0.05$ ) and ( $r = 0.45$ ,  $p < 0.01$ ) respectively for male and female hypertensive subjects.

## DISCUSSION

Atherosclerosis is a major source of morbidity and mortality in the developed world, currently a problem of the developed world; however it is gradually becoming one of the major health

problems in third world countries like Nigeria, especially among the upper class due to the influence of foreign culture.<sup>24</sup> In this study, we observed that hypertensive and dyslipidemia patients with high risk CHD have increased body weight and BMI in both sexes when compared to the controls. We also observed a significant increased in the plasma MDA level which serves as the marker of lipid peroxidation in these category patients. This finding is similar to the study of Prasad and Kalra;<sup>25</sup> they reported an increased in the blood MDA concentration in rabbits with a high cholesterol diet. We also observed a direct correlation between plasma concentration of MDA and plasma concentration of triglyceride, total cholesterol, LDL-cholesterol, systolic BP and diastolic BP and on the other hand an inverse correlation with HDL cholesterol and HDL- Chol/TC ratios in both sexes. These finding is similar to the finding of Das S et al among hypercholesterolemia patients of Asian origin.<sup>26</sup>

The total antioxidant status in the plasma of patients in this study with dyslipidemia was significantly reduced in both sexes in comparison with the control subjects; sex did not show a particular pattern in this case. Plasma TAS have inverse correlation with plasma concentration of triglyceride, total cholesterol, LDL-cholesterol, systolic BP and diastolic BP and on the other hand

direct correlation with HDL cholesterol and HDL Chol/TC ratios in both sexes. In healthy condition a balance exists between free-radical generation and antioxidant defense system which prevents occurrence of diseases.<sup>1,2</sup> Our finding in this study shows that dyslipidemia would shift the balance in favour of free-radical generation, which may lead to oxidative tissue damage and thus sets the stage for atherosclerosis. Since dyslipidemia and lipid peroxidation both directly relate to the severity of atherosclerosis,<sup>3</sup> elimination of free radicals in the plasma before they can be taken up by the peripheral tissues might reduce the process of atherosclerosis in these categories of patients.

Enstrom *et al.* in their study showed an inverse relationship between vitamin C intake and overall cardiovascular mortality in a population study involving 11,348 adults.<sup>27</sup>

Similarly, Schwertner *et al.* shown in their study on 877 men that serum bilirubin, an endogenous antioxidant had an inverse relationship with serum cholesterol, cigarettes smoked/day, systolic BP, serum triglyceride and fasting glucose.<sup>28</sup> Based on our discussion oxidative stress, arising as a result of an imbalance between free radical production and antioxidant deficiencies, is associated with damage to a wide range of molecular species, which includes lipids and lipoproteins. Dyslipidemia is

universally accepted as a major risk factor for atherosclerosis,<sup>12</sup> but at any given concentration of plasma cholesterol, there is variability in the occurrence of cardiovascular events, as it has been shown that the oxidative modification of LDL might be a crucially important step in the development of atherosclerotic plaque.<sup>7</sup> Studies have shown that antioxidant supplementation in healthy subjects or CAD patients can reduce levels of free radical damage produced and protect LDL-cholesterol against oxidation.<sup>27</sup> Large scale epidemiological studies have shown that low intake of antioxidants is associated with increased cardiovascular risk.<sup>29</sup>

Limitations of our study lie in the weakness of parameters used for measurement of oxidative stress. TBARS is not the best available marker of lipid peroxidation and we have not included measures of red-cell antioxidant enzymes. Another weakness is the lack of data on dietary intake of our subjects during the study period. Nevertheless, accepting these limitations, our results show a reduction in plasma TAS and increase in MDA in hypertensive and dyslipidemic patients with high risk coronary heart disease.

## CONCLUSION

Since dyslipidemia, hypertension and lipid peroxidation were directly related to the severity of atherosclerosis, elimination of free radicals in the plasma before they can be taken up by the peripheral tissues might reduce or eliminate development atherosclerosis in these category of patients. In view of our present findings, a management strategy aimed at simultaneous controlling lipid peroxidation and increasing total antioxidant status in patients with dyslipidemic may be beneficial.

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