EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 11
96-102
Year: 2017

HIGH SENSITIVITY C-REACTIVE PROTEIN AND PLASMA LIPIDS IN TYPE 2DIABETIC PATIENTS IN ENUGU, NIGERIA.

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Article Received on 09/09/2017 **Article Revised on 30/09/2017** **Article Accepted on 20/10/2017**

ABSTRACT

Background: Type II Diabetes is a worldwide health problem. It exerts a heavy economic burden on the society and is associated with microvascular and macrovascular complications. **Objective:** This study on high sensitivity C-reactive protein (hs-CRP) and plasma lipids in type II diabetic patients was carried out to have a baseline data of hs-CRP and plasma lipids in type II diabetics and its relation to glycaemic control. **Methods:** In this cross-sectional study 150 known type II diabetics and 100 age-matched non diabetics without inflammatory conditions were used as controls. Fasting plasma glucose, lipids and hs-CRP were assayed, Body mass index was calculated by using the Quetelet formula [weight (Kg)/height (m^2)]. Values presented as mean ± 2standard deviations. Student's t test and Chi-square tests were used to compare the means and proportion between two groups respectively. Pearson correlation was utilised in comparing the relationship between the hs-CRP and other parameters. **Results:** In the diabetics the following plasma parameters were significantly higher ($p<0.05$) than in the non-diabetic controls. In mmol/L, glucose 5.44± 1.19(4.88±1.41), TC 6.03±1.16(5.01±1.39), LDL Cholesterol 5.28±1.43(3.90±1.27), TG1.12±0.58(0.81±0.29); hs-CRP 0.12±0.10mg/dl(0.07±0.04), BMI29.04±5.72Kg/m^2(23.62±5.22) There was a significant decrease in HDL Cholesterol in diabetics than in the non-diabetic controls, 1.38±0.25mmol/L (1.47±0.38). Pearson's Correlation Coefficient for hs-CRP and BMI is 0.119($p>0.05$ and was not significant). **Conclusion:** Data shows that there are significant increases in the parameters measured in all the diabetic subjects except in HDL-cholesterol where there is significant reduction when compared with the control ($P<0.05$). There is no significant correlation between the hsC-reactive protein and BMI ($P>0.05$). The results concluded that total Cholesterol, triglyceride, low density lipoprotein cholesterol and hs–CRP have strong associations with type 2 diabetes mellitus, the significance of these associations was discussed.

KEYWORD: Diabetes mellitus, high sensitivity C-reactive protein, plasma lipids, glucose.

INTRODUCTION

Type II diabetes mellitus is a world wide health problem, and is steadily increasing in incidence. In 2010, the world prevalence of diabetes mellitus among adults (aged 20 – 79years) was estimated at 6.4%, (affecting about 285 million adults), and it is estimated to increase to 7.7% by 2030. It is expected that between 2010 and 2030, there will be a 69% increase in the numbers of adults with diabetes in developing countries.[1] In 2004 the Diabetes Association of Nigeria (DAN) estimated the diabetic population in Nigeria at 10 million.[2]

Type II diabetes mellitus was estimated to affect about 15 million Americans[3], and in Nigeria there was an overall prevalence of 2.2% with a higher proportion of people with the condition living in the towns and cities compared with the rural areas.[4] Type II, Diabetes Mellitus was commonest in approximately 90% of all the diabetic patients and in individuals above 40 years.[5]

The progressive increase in the prevalence rates of diabetes is associated with lifestyle, overweight, and obesity, physical inactivity, alcohol consumption, dietary changes and cigarette smoking – factors that are potentially modifiable.

Type II Diabetes Mellitus is associated with increased risk of stroke, peripheral arterial disease and coronary artery disease because of the resultant macro-vascular and micro vascular complications (diabetic nephropathy, neuropathy and retinopathy) that occur in the disease. Data from numerous clinical studies showed that the incidence of the clinical syndrome arising from the vascular disease is mainly related to the duration and the severity of hyperglycaemia.

Diabetes mellitus causes dyslipidaemia, the activity of lipoprotein lipase is decreased, hence very low density lipoprotein (VLDL) accumulate in the plasma following increase synthesis by the liver as a result of enhanced

lipolysis. The rate of cholesterol synthesis is also increased, with an associated increase in plasma low density lipoprotein (LDL) concentrations. Consequently, patients with diabetes may show high plasma triglyceride, raised cholesterol and low HDL cholesterol concentrations.[6]

Overweight (body mass index (BMI) = 25.0 to 29.9 kg/m^2) and particularly obesity (BMI = 30.0kg/m^2 and more) may be associated with dyslipidaemia, diabetes or insulin resistance and elevated levels of C-reactive protein and fibrinogen.[7]

High sensitivity C-reactive protein (hs-CRP) has been shown to be a strong predictor of type 2 diabetes mellitus and has been considered in diabetic risk assessment.[8,9,10] Other risk factors such as age, family history of diabetes mellitus, fasting insulin, body mass index (BMI), total cholesterol, high density cholesterol, triglyceride, systolic blood pressure and physical activity are used in the assessment.[8,9] More recently, markers of inflammation including interleukin-6(IL-6), sialic acid, fibrinogen and hs-CRP have been studied for their association with type 2 diabetes mellitus.[11,12,13] Of these, hs-CRP a non-specific marker of inflammation has consistently been shown to be a strong predictor of type 2 diabetes mellitus.[3,12,13] This study therefore intends to examine the plasma hs-CRP and lipid levels in both diabetic and non-diabetic subjects in Enugu, Nigeria with a view to establishing a relationship between them and glycaemic control. The study will also provide baseline data for these parameters in type 2 diabetics and non-diabetics.

SUBJECTS AND METHODS

This cross-sectional study was carried out at the department of chemical pathology and internal medicine of the University of Nigeria Teaching Hospital, Enugu. Ethical Clearance was obtained from the Ethical Committee of the University of Nigeria Teaching Hospital. Informed consent was obtained from patients before commencement of study. A total of 250 subjects were recruited. They were divided into:- 150 known type 2 diabetics and 100 age-matched healthy non diabetics, served as controls.

The controls were recruited from subjects attending general out patient clinics for routine check-up and are not diabetic.

Subjects must met the World Health Organization criteria for diagnosis of diabetes mellitus using fasting plasma glucose of $\geq$ 7.0mmol/L (126mg/dl) with at least one diabetic symptom or previous diagnosis of diabetes mellitus and attending the diabetic clinic and maybe on hypoglycaemic medication. They were adequately briefed about the tests to be performed and written informed consent obtained. Tests were conducted at no cost to both the patients and the control subjects. The following investigations were performed on each subject: fasting plasma glucose, total cholesterol (TC), triglyceride (TG), High Density lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol and high sensitivity C-reactive protein (hs-CRP).

Excluded were subjects with ulcer e.g. gastric ulcer, leg ulcer, infective diseases, rheumatoid arthritis, systemic lupus erythematosis, chronic respiratory diseases such as active tuberculosis, chronic bronchitis, emphysema, asthma; cardiac diseases such as angina pectoris, smokers, because effect on inflammatory markers and oral contraceptives because of the effect of oestrogen on plasma lipids.

Sample collection and processing

Samples were collected after overnight fasting. The blood was collected into EDTA bottles for plasma lipid estimation, plain tubes for plasma hsCRP and fluoride oxalate bottles for glucose estimation.

Methods of Analysis

Plasma glucose was measured using the glucose oxidase method[14], the plasma total cholesterol was analysed using the direct enzymatic method[15] and plasma triglyceride using the enzymatic method.[16] HDL-C was estimated in the plasma supernatant after precipitating β-apoprotein containing lipoproteins using the precipitation technique.[17] LDL-C was determined by using the Friedewald's formula[18] LDL – C= Total chol – (HDL chol + TG/2.2) mmol/L Sera was analysed for hs-CRP using the enzyme – linked immunosorbent assay technique.[19] The high sensitivity C-reactive protein (hsCRP) ELISA is based on the principle of a solid phase enzyme-linked immunosorbent assay. The assay system utilises a unique monoclonal antibody directed against a distinct antigenic determinant on the hs-CRP molecule. This mouse monoclonal anti CRP antibody was used for solid phase immobilisation (on the microtitre wells). A goat anti-CRP antibody was in the antibody enzymes (horseradish peroxidase) conjugate solution. The test sample was allowed to react simultaneously with the two antibodies, resulting in the CRP molecule being sandwiched between the solid phase and enzyme – linked antibodies. After 45 minutes incubation at room temperature (20-25^{0}C) the wells were washed with water to remove unbound labeled antibodies. A tetramethylbenzine (TMB) reagent was added and incubated for 20 minutes, resulting in the development of a blue colour. The colour development was stopped with the addition of IN HCL changing the colour to yellow. The concentration of hs-CRP in the sample is directly proportional to the absorbance of the test sample. Absorbance was measured spectrophotometrically at 450nm. The mean absorbance values for each of reference standards, controls and samples were calculated. A standard curve was plotted using the mean absorbance obtained from each reference standard against its concentration in mg/L on graph paper, with absorbance on the vertical (Y) axis and concentration on the horizontal (X) axis. The concentration of

corresponding hs-CRP (mg/L) was determined from the standard curve using the mean absorbance value for each sample.

The kit is produced by Diagnostic Automation Inc, 23961 Craftsman Road, suit E/F Calabasas, CA, 91302, U.S.A. Cat No. 1668z.

Data Handling and Analysis

Data obtained from the study was grouped and analysed by tables and graphic representations.The mean values of plasma lipids, hs-CRP and plasma glucose in the type 2 diabetics was compared with those of the control group. The percentage of those subjects who were diabetic with high plasma lipid was determined and also, the percentage of those subjects who were diabetic with high hs-CRP was determined using the SPSS II statistical package.

The student's t-test and Chi-square tests were used to determine the significant difference in lipid profile and hs-CRP in diabetics and controls.Also Pearson correlation study was used to obtain the values of hs-CRP and lipids in both diabetic and non- diabetic subjects.

RESULTS

The results of the different test are summarized in tables i, ii, iii, iv, v. The ages of the 150 diabetic subjects and 100 controls used in this study, ranged from 41–72years and 42–73years with mean and standard deviation of 54.6±8.4years and 53.1±7.8years respectively (Table i). There was no significant difference in the socio-demographic characteristics such as age, education, occupational status, gender and locality between diabetics and the control (P>0.05).

In the diabetics the following parameters were significantly higher (p<0.05) than in the non-diabetic controls: BMI, glucose, TC, LDL Cholesterol, TG and hs-CRP(Table ii). In mmol/L, the mean plasma glucose for diabetics was 5.44± 1.19 while control was 4.88±1.41, plasma TC for diabetics was 6.03±1.16 while the controls had 5.01±1.39, the diabetics had LDL Cholesterol 5.28±1.43 while the controls was 3.90±1.27, the mean plasma TG for diabetics was 1.12±0.58 while the controls was 0.81±0.29; plasma hs-CRP for diabetics was 0.12±0.10mg/dl and controls was 0.07±0.04mg/dl, BMI for diabetics was 29.04 ±5.72Kg/m^2 and the controls was 23.62±5.22Kg/m^2.There was a significant decrease (p<0.05) in HDL Cholesterol in diabetics than in the non-diabetic controls, 1.38±0.25mmol/L and 1.47±0.38mmol/L respectively (Table ii).

Among the male gender, the mean plasma glucose, total cholesterol, LDL cholesterol; mean triglyceride; mean hs-CRP BMI are significantly higher (p<0.05) in male diabetics than male controls. The mean HDL cholesterol for male diabetics is 1.53±0.21mmol/L, while the controls had 1.59±0.31mmol/L. This is not significant (P>0.05) and thus, the male diabetic subjects did not have lower mean HDL than that of the male controls (Table iii).

The following parameters are significantly higher (p<0.05) in female diabetics than female controls; BMI, Total Cholesterol, LDL cholesterol, triglyceride and hs-CRP while plasma glucose and HDL Cholesterol were not significantly higher in female diabetics than female controls (Table iv). The mean plasma glucose level in female diabetics was 5.62±1.26mmol/L while the controls had 5.04±1.83mmol/L. The diabetic subjects had mean HDL cholesterol of 1.23±0.29mmol/L, while the controls had 1.34±0.44mmol/L.

There is significant positive correlation (r = 0.175, 0.244, 0.268, 0.276, P<0.05) between BMI and plasma glucose, TC, LDL and TG in diabetic subjects (Table v). There is significant positive correlation (r = 0.175, 0.248, 0.205, P<0.05) between plasma glucose and BMI, TC, and LDL; but there is negative significant correlation between plasma glucose and HDL (r = -0.123, P<0.05) in diabetic subjects (Table v). Also, there is significant positive correlation (r = 0.965, 0.665, and 0.203, P<0.05) between plasma glucose and LDL, TG and hs-CRP respectively in the controls (Table vi). There is significant positive correlation (r = 0.244, 0.248, 0.872, 0.404, P<0.05) between total cholesterol and BMI, plasma glucose, LDL, and TG respectively in diabetic subjects (Table v). Also, there is significant positive correlation (r = 0.719, 0.965, 0.665, and 0.203, P<0.05) between total cholesterol and Plasma glucose, LDL, TG and hs-CRP respectively in the controls (Table vi). There is significant negative correlation (r = -0.234, -0.297, P<0.05) between plasma glucose and LDL respectively in diabetic subjects (Table v). There is no significant correlation between the hs-CRP and BMI (P>0.05).

Table i: Distribution of the socio-demographic characteristics of the diabetics and controls according to age group, gender, occupational status, educational status and locality.

Socio-demographic Characteristics	Diabetics (n = 150)	Controls (n = 100)	Chi-square	P-value
Age Group (years)				
41 – 50	61 (40.7%)	46 (46.0%)	3.25	0.197
51 – 60	42 (28.0%)	33 (33.0%)		
Above 60	47 (31.3%)	21 (21.0%)		
Gender				
Male	71 (47.3%)	57 (57.0%)	2.24	0.134
Female	79 (52.7%)	43 (43.0%)		
Occupational Status				
Employed	99 (66.0%)	74 (74.0%)	1.80	0.180
Not employed	51 (34.0%)	26 (26.0%)		
Educational Status				
Educated	92 (61.3%)	69 (69.0%)	1.54	0.215
Not educated	58 (29.7%)	31 (31.0%)		
Locality				
Urban	79 (52.7%)	63 (63.0%)	2.61	0.106
Rural	71 (47.3%)	37 (37.0%)		

*P < 0.05 Significant.
*P ≥ 0.05 Not significant.

Table ii: Comparison of mean BMI, Plasma glucose, TC, HDL-C, LDL-C, Tg and hs CRP in diabetic subjects and controls using student's t-test.

Parameters	Group		P-value	Comment
	Diabetics (n=150)	Controls (n=100)		
BMI (kg/m^2)	29.04±5.72	23.62±5.22	0.000	Significant
Plasma Glucose (mmol/L)	5.44±1.19	4.88±1.41	0.000	Significant
Total Cholesterol (mmol/L)	6.03±1.16	5.01±1.39	0.000	Significant
HDL Cholesterol (mmol/L)	1.38±0.25	1.47±0.38	0.025	Significant
LDL Cholesterol (mmol/L)	5.28±1.43	3.90±1.27	0.000	Significant
Triglyceride (mmol/L)	1.12±0.58	0.81±0.29	0.000	Significant
hs C-Reactive Protein (mg/dl)	0.12±0.10	0.07±0.04	0.000	Significant

*Significant at P <0.05.

Table iii: Comparison of mean BMI, Plasma glucose, TC, HDL-C, LDL-C, Tg and hs CRP in diabetics and controls using student's t-test in males.

Parameters	Group		P-value	Comment
	Diabetics (n=71)	Controls (n=57)		
BMI (kg/m^2)	29.13±5.96	22.79±5.01	0.000	Significant
Plasma Glucose (mmol/L)	5.27±1.11	4.72±0.99	0.004	Significant
Total Cholesterol (mmol/L)	5.71±1.13	5.23±1.44	0.000	Significant
HDL Cholesterol (mmol/L)	1.53±0.21	1.59±0.31	0.196	Not significant
LDL Cholesterol (mmol/L)	4.22±1.44	3.25±1.28	0.000	Significant
Triglyceride (mmol/L)	1.06±0.29	0.95±0.38	0.003	Significant
hs C-Reactive Protein (mg/dl)	0.11±0.09	0.08±0.03	0.000	Significant

*Significant at P <0.05.

Table iv: Comparison of meanBMI, Plasma glucose, TC, HDL-C, LDL-C, Tg and hsCRP in diabetics and controls using student's t-test in females.

Parameters	Group		P-value	Comment
	Diabetics (n=79)	Controls (n=43)		
BMI (kg/m^2)	28.94±5.47	24.42±5.43	0.000	Significant
Plasma Glucose (mmol/L)	5.62±1.26	5.04±1.83	0.064	Not significant
Total Cholesterol (mmol/L)	6.34±1.18	4.78±1.34	0.000	Significant
HDL Cholesterol (mmol/L)	1.23±0.29	1.34±0.44	0.136	Not significant
LDL Cholesterol (mmol/L)	6.34±1.41	4.55±1.27	0.000	Significant
Triglyceride (mmol/L)	1.26±0.38	0.66±0.19	0.000	Significant
hs C-Reactive Protein (mg/dl)	0.12±0.10	0.06±0.04	0.000	Significant

*Significant at P <0.05

Table v: Correlations of the parameters in diabetics.

		BMI	Plasma Glucose	TC	HDL	LDL	TG	hsCRP
BMI	Pearson Correlation	1.000	.175*	.244**	-.112	.268**	.276**	-.128
	P-value		.032	.003	.171	.001	.001	.119
	N	150.000	150	150	150	150	150	150
Plasma Glucose	Pearson Correlation	.175*	1.000	.248**	-.234**	.205*	.279**	-.059
	P-value	.032		.002	.004	.012	.001	.473
	N	150	150.000	150	150	150	150	150
TC	Pearson Correlation	.244**	.248**	1.000	-.123	.872**	.404**	-.078
	P-value	.003	.002		.134	.000	.000	.344
	N	150	150	150.000	150	150	150	150
HDL	Pearson Correlation	-.112	-.234**	-.123	1.000	-.297**	-.067	-.007
	P-value	.171	.004	.134		.000	.413	.934
	N	150	150	150	150.000	150	150	150
LDL	Pearson Correlation	.268**	.205*	.872**	-.297**	1.000	.359**	-.109
	P-value	.001	.012	.000	.000		.000	.184
	N	150	150	150	150	150.000	150	150
TG	Pearson Correlation	.276**	.279**	.404**	-.067	.359**	1.000	.030
	P-value	.001	.001	.000	.413	.000		.715
	N	150	150	150	150	150	150.000	150
hs CRP	Pearson Correlation	-.128	-.059	-.078	-.007	-.109	.030	1.000
	P-value	.119	.473	.344	.934	.184	.715	
	N	150	150	150	150	150	150	150.000

Table vi: Correlations of the parameters in controls.

		BMI	Plasma Glucose	TC	HDL	LDL	TG	hsCRP
BMI	Pearson Correlation	1.000	.006	.008	.148	-.043	.112	-.043
	P-value		.954	.940	.142	.674	.269	.671
	N	100.000	100	100	100	100	100	100
Plasma Glucose	Pearson Correlation	.006	1.000	.719**	.120	.683**	.471**	.022
	P-value	.954		.000	.235	.000	.000	.829
	N	100	100.000	100	100	100	100	100
TC	Pearson Correlation	.008	.719**	1.000	.147	.965**	.665**	.203*
	P-value	.940	.000		.144	.000	.000	.042
	N	100	100	100.000	100	100	100	100
HDL	Pearson Correlation	.148	.120	.147	1.000	-.098	-.122	-.120
	P-value	.142	.235	.144		.334	.227	.235
	N	100	100	100	100.000	100	100	100
LDL	Pearson Correlation	-.043	.683**	.965**	-.098	1.000	.670**	.259**
	P-value	.674	.000	.000	.334		.000	.009
	N	100	100	100	100	100.000	100	100
TG	Pearson Correlation	.112	.471**	.665**	-.122	.670**	1.000	.043

	P-value	.269	.000	.000	.227	.000		.674
	N	100	100	100	100	100	100.000	100
Hs-CRP	Pearson Correlation	-.043	.022	.203*	-.120	.259**	.043	1.000
	P-value	.671	.829	.042	.235	.009	.674	
	N	100	100	100	100	100	100	100.000

DISCUSSION

This study on high sensitivity C – reactive protein and plasma lipids in type 2 diabetic patients in Enugu area, Nigeria showed that there was no significant difference in the socio-demographical factors (gender, occupational status, education and locality) of the diabetic subjects and the controls. However, the study by Azimi-Nezhad *et al* (2008)[20] in Iran on the prevalence of type 2 diabetes mellitus in Iran and its relationship with gender, urbanisation, education, marital status and occupation differed from the findings in Nigeria.

The mean body mass index was significantly higher in diabetic subjects than the controls; also between male diabetic subjects and male controls, and female diabetic subjects and female controls ($P<0.05$). This was confirmed by the study done by Ni Mhurchu *et al*, (2006)[21] and NHANES (2005)[22] whose reports indicated that most adults with diagnosed diabetes were overweight or obese – prevalence of overweight or obesity was 85.2% and the prevalence of obesity was 54.8%. Cosin Aguilar *et al* (2007)[23] from his study stated that the obese patients showed higher prevalence of diabetes.

The diabetic subjects had higher significant mean plasma glucose, low density lipoprotein cholesterol, total cholesterol and triglyceride and a reduced high density lipoprotein than the controls.

This study agrees with the previous reports by Izezuo *et al.*[24] on comparative analysis of lipid profiles among patients with type 2 diabetes mellitus, hypertension and concurrent type 2 diabetes, and hypertension: a view of metabolic syndrome that plasma lipid concentrations are higher among Nigerian hypertensive and diabetics than controls. This is equally consistent with previous studies done by Aduba *et al.*[25] Nyakor *et al*,[26] however found lower serum lipid and lipoprotein levels in Ghanaians with diabetes mellitus and hypertension. The levels of cholesterol and lipoprotein obtained in Ghanaians with hypertension and diabetes mellitus were similar to those of their age-matched healthy controls. These results suggest a reduced risk of coronary artery disease from the atherogenic effects of cholesterol in Ghanaians with diabetes mellitus and `hypertension.

The diabetic subjects had mean HDL cholesterol significantly lower than that of the controls. In this study, there was significant negative correlation between plasma glucose and HDL respectively in diabetic subjects. This is similar to a study by Paisey *et al*[27] that showed low HDL cholesterol levels in type 2 diabetics.

The diabetic subjects had hs-CRP significantly higher than those of the controls. Even among the diabetics those who had abnormal plasma glucose had significantly higher hs-CRP than those who had normal plasma glucose. Studies on western populations have shown low grade systemic inflammation to be one of the mechanisms by which known risk factors such as obesity, smoking and hypertension promote the development of diabetes mellitus (Pradhan *et al*. 2001; Hu *et al* 2004).[3,10] Several studies have earlier shown that hs-CRP (a biomarker of inflammation) predicts diabetes in western populations (Nakanishi *et al*.2003, Hu *et al*.2004 and Pradhan *et al*. 2001).[3,9,10] The result obtained in this study is similar to the earlier works that emphasized the prediction of incident Type 2 diabetes by hs-CRP level. (David and Paul (2007).[28]

Among the diabetic subjects, the male and female had no significant difference in the hs-CRP but the opposite was the case in the control group where the males had a significant increase of hs-CRP than the female ($p<0.05$).

In this study there is no significant correlation between the high sensitivity C-reactive protein and BMI ($P>0.05$) but study carried out by Li CZ, *et al* 2004)[29] showed that hs-CRP was positively related to BMI.

This study has shown that in Type 2 diabetes, there is elevated triglyceride and low density lipoprotein cholesterol but reduced high density lipoprotein cholesterol than in the controls. These are in consonance with other previous studies. Plasma hs-CRP is higher in diabetic subjects than in the controls. In conclusion, this study showed that hs-CRP has a strong association with diabetes in Enugu, Nigeria.

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