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ORIGINAL ARTICLE

Increased Central Adiposity may not Underlie the Marked Elevation of IL-6 in Diabetes Mellitus Patients in South-West, Nigeria

Adiposité Centrale Accrue ne Pourrait pas Expliquer L'élévation Marquée D'il-6 Chez Les Patients de Diabète Sucré Dans le Sud-Ouest Du Nigéria

E. K. Oghagbon*, K. A. Jimoh†, O. Olaosebikan‡, L. Harbige§

ABSTRACT

BACKGROUND: **Chronic inflammation is linked to disorders of obesity, insulin resistance and DM2. This reflects as increase in proinflammatory cytokines including IL-6. In Nigeria, there is no study that has measured IL-6 in diabetics, in spite of having the highest number of diabetics in Africa.**

METHODS: **The twenty-eight DM2 patients and 13 controls recruited for this study had their BP, BMI, waist circumference (WC) and waist-hip-ratio (WHR) measured. They also had fasting plasma IL-6, fasting plasma glucose, total cholesterol (TC), Triglyceride (Tg), high density lipoprotein cholesterol (HDL-C), urea, creatinine, aspartate transaminases (AST), alanine transferases (ALT), total protein (TP) and albumin determined.**

RESULTS: **Mean age was 51.83 years ± 13.28, with diabetics significantly older than controls (56.61yrs. ±9.62 vs. 41.54 years ± 14.53) P < 0.05. The mean IL-6 in diabetics (194.77pg/ml ± 166.16) was significantly higher than controls' (26.29pg/ml ± 6.65) at p ≤ 0.01. No significant difference in mean BMI in diabetics and controls. But WC and WHR of diabetics (100.75cm ± 18.47; 1.01 ± 0.14) were significant higher than in controls (88.77cm ± 13.36; 0.88 ± 0.07) at p ≤ 0.05 (WC; p value 0.043) and p ≤ 0.01(WHR; p value 0.002). Among diabetics, there were significant correlations between IL-6 and Tg (p<0.01, r = 0.007**), IL-6 and LDL-C (p<0.05, r = 0.028*), IL-6 and AST (p<0.05, r = 0.041*) and IL-6 and ALT (p<0.01, r = 0.004**)**

CONCLUSION: **Elevated IL-6 in DM2 patients in South West Nigeria correlates with liver transaminases and not increased markers of central adiposity. WAJM 2014; 33(2): 130–135.**

Keywords: **IL-6, inflammation, diabetes mellitus type 2, abdominal adiposity.**

RÉSUMÉ

CONTEXTE: L'inflammation chronique est associée à des troubles de l'obésité, à l'insulino-résistance et au diabète de Type 2 (DM2). Cela se reflète comme une augmentation des cytokines pro-inflammatoires dont l'IL-6. Au Nigeria, il n'y a aucune étude qui a mesurée l'IL-6 chez les diabétiques, en dépit d'avoir le plus grand nombre de diabétiques en Afrique.

METHODES: Les vingt-huit patients DM2 et 13 contrôles recrutés pour cette étude ont eu leur BP, l'IMC, le tour de taille (TT) et taille-hanche-ratio (THR) mesurées. Ils avaient également eu un taux sanguin d' IL-6 à jeun , une glycémie à jeun, le cholestérol total (CT), les triglycérides (TG), la lipoprotéines de haute densité (LDH -C), l'urée, la créatinine, l'aspartate transaminase (ASAT), transférases alanine transférase (ALAT), protéine totale (PT) et de l'albumine sont déterminés.

RÉSULTATS: L'âge moyen était 51,83 années ± 13,28, avec des diabétiques significativement plus âgés que les témoins (56.61yrs. ± 9,62 vs 41,54 années ± 14,53) P < 0,05. La moyenne de l'IL-6 chez les diabétiques (194.77pg/ml ± 166,16) était significativement plus élevée que chez les témoins (26.29pg/ml ± 6,65) à p ≤ 0,01. Il n'y a aucune différence significative dans l'IMC moyen chez les diabétiques et les contrôles. Mais le TT et le THR des diabétiques (100.75cm ± 18,47; 1,01 ± 0,14) étaient significativement plus élevés que chez les témoins (88.77cm ± 13,36; 0,88 ± 0,07) à p ≤ 0,05 (TT, valeur p de 0,043) et p ≤ 0,01 (THR valeur p de 0,002). Parmi les diabétiques, il y avait des corrélations significatives entre l'IL-6 et TG (p < 0,01, r = 0,007 **), IL-6 et C-LDL (p < 0.05, r = 0,028 *), IL-6 et ASAT (p < 0,05, r = 0,041 *) et de l'IL-6 et ALAT (p < 0,01, r = 0,004 **).

CONCLUSION: L'élévation de l'IL-6 chez les patients de DM2 dans sud ouest Nigeria corrèle avec les transaminases hépatiques et non pas avec une augmentation des marqueurs de l'adiposité centrale. **WAJM 2014; 33 (2): 130–135.**

Mots clés: IL-6, l'inflammation, le diabète sucré de type 2, l'adiposité abdominale

Departments of *Chemical Pathology, College of Health Sciences, Benue State University, Makurdi, Nigeria. Email: efosaoghagbon@yahoo.com †Chemical Pathology, Federal Medicine Centre, Ido-Ekiti, Ekiti State, Nigeria. Email: jim_kayode@yahoo.co.uk ‡Chemical Pathology, Federal Medicine Centre, Bida, Niger State, Nigeria. Email: laoshpapa@yahoo.com §The School of Science, University of Greenwich, Medway Campus, Central Avenue, Chatham Maritime, Kent ME4 4TB, UK. Email: L.S.Harbige@gre.ac.uk

Correspondence: **Dr. E. K. Oghagbon,** Department of Chemical Pathology, College of Health Sciences, Benue State University, Makurdi, Nigeria

Abbreviations: ALT, Alanine Transferases; **AST,** Aspartate Transaminases; **HDL-C,** High Density Lipoprotein Cholesterol; **OHA,** Oral Hypoglycaemic Agents; **TC,** Total Cholesterol; **Tg,** Triglyceride; **TP,** Total Protein; **WC,** Waist Circumference; **WHR,** Waist-Hip-Ratio

INTRODUCTION

In 1993, it was reported that inflammation is associated with metabolic disorders such as obesity, insulin resistance and diabetes mellitus type 2 (DM2),[1] and this was later observed to involve the body's innate immune system[2] consisting of sentinel trouble-shooting cells such as macrophages, endothelial and dendritic cells. The functions of these cells include recognising and neutralising environmental threats through the action of pattern-recognition receptors (PRRs) and release of proinflammatory cytokines.[3]

Proinflammatory cytokines such as IL6 among others has been associated with obesity, insulin resistance and diabetes mellitus.[4–9] Commonly measured cytokine markers in DM2 patients are CRP, IL-6 and TNF-alpha/TNF-a-receptor 2.[8–11] It is known that these three cytokine markers tend to relate together in that CRP which is primarily synthesised in the liver is regulated mainly by TNF-alpha and IL-6.[12]

Various studies have consistently shown elevated CRP and TNF-alpha in diabetes mellitus patients[8–11,13–15] with a tendency for these cytokines to express some ethnic variations.[10,14,15]

In this present study, we chose to investigate the levels of IL-6 in Nigerian type 2 diabetics, especially as it appears to be consistently elevated and independently associated with diabetes mellitus.[10–15]

This study became necessary given the increasing prevalence of DM2 in developing countries including sub-Saharan Africa.[16,17] Nigeria in particular has the highest number of diabetes mellitus patients in Africa[18] and the disease prevalence has been on the rise, yet there is no study that has measured such an important inflammatory marker; IL6, in Nigerian diabetics. Since the 1960s, the prevalence of diabetes mellitus in different populations in Nigeria rose from less than 1%[19] to about 6.8%.[20] It is hoped that this study could reveal some peculiar associated risk factors in Nigeria diabetics that could be exploited in reducing the rising prevalence of the disease and therefore help in addressing the high mortality/morbidity from the disease among Nigerians.[21]

MATERIALS AND METHOD

Forty one subjects were recruited for this study out of which 23 were type II diabetics attending the Diabetic Clinic of Federal Medical Centre, Ekiti State, Nigeria. The eighteen control subjects were non-diabetic patients who were seen at the General Out-patient Clinics of the same hospital. The inclusion criteria for the diabetic subjects were attendance at the diabetic clinic and fasting plasma glucose of more than 7mmol/L on more than two occasions after two weeks of initial testing.

After inclusion in the study, all the subjects had their blood pressure (systolic blood pressure; SBP, diastolic blood pressure; DBP) measured, body mass index (BMI; kg/m^2) was determined from weight (kilogram) and height (metres), waist circumference (WC) and waist-hip-ratio (WHR) were also recorded.

Venous blood samples were taken on the morning after an overnight fast of 10–16 hours. Blood sample was taken for measurement of plasma levels of fasting plasma glucose, total cholesterol (TC), Triglyceride (Tg), high density lipoprotein cholesterol (HDL-C), urea, creatinine, aspartate transaminases (AST), alanine transferases (ALT), total protein (TP), albumin and IL-6. Low density lipoprotein cholesterol (LDL-C) was determined from Freldwald fomula as long as the level of plasma Tg was not more than 400mg/dl.

To measure IL-6 in plasma of the subjects, we made use of R&D IL-6 DuoSet ELISA Development kit and the manufacturer's instructions were followed in assaying for IL-6 in our subjects' samples.

The absorption of the final solutions in each of the ELISA well was determined by a microplate reader (Mikroscan) set to 450 nm and the mean value was determined for each study subject and standard sample. A standard curve was determined by plotting the mean absorbance for each standard on the y-axis against the concentration on the x-axis and then drawing a best fit curve through the points on the graph. Calculation of the actual concentration of IL-6 in pg/ml was deduced from formula obtained from a regression analysis of the curve.

RESULTS

The study comprised of 41 subjects out of whom 28 were diabetics and 13 non-diabetic controls. Among the diabetics, 10 (35.7%) were males and 18 (64.3%) males. The mean age of the whole population was 51.83 years ± 13.28, but the mean age for diabetics was 56.61 years ± 9.62. The diabetics were significantly older than controls (41.54 years ± 14.53) $P < 0.05$

In the diabetics, twenty (20) of them were put on oral hypoglycaemic agents (OHA), three (3) on insulin and three (3) on both agents (OHA and Insulin). Two of these patients were recently diagnosed and yet to be commenced on drugs at the time of the study. Among the diabetics and controls, there was no significant difference in the means of the variables when they grouped according to their gender. This supposes that the gender of the subjects did not affect mean values of the variables.

In the diabetic population, twenty (71.4%) were on oral hypoglycaemic agents, three on insulin (10.7%) and three were on a combination of insulin and oral hypoglycaemic agents (10.7%). The other two (7.1%) were on dietary manipulations.

There was a significant difference ($p < 0.001$) in IL-6 values between controls (26.29 pg/ml ± 6.25) and diabetics (194.77pg/ml ± 166.16).The mean waist circumference (WC) for diabetics (100.75 cm ± 18.47) and controls (88.77 cm ± 13.36), and waist-hip-ratio for diabetics (1.01 ± 0.14) and controls (0.88 ± 0.07), showed significant differences (p value; 0.043 and 0.002 respectively). However, there was no significant difference ($p = 0.871$) in mean BMI between diabetics (26.99kg/m2 ± 5.34) and controls (27.29kg/m2 ± 5.61).

We did not find any significant difference in the mean values for of the other analytes measured in diabetics versus controls. ($P \leq 0.05$).This was in spite of the fact that values were higher in diabetics than controls, except for albumin and HDL-C. The small number of subjects enrolled in the study may be responsible for this.

Among diabetics and controls, there was no sex impact on the mean values of the analytes measured. ($p \leq 0.05$).

Table 1: Descriptive Characteristics of the General Population

Variables	Mean	SD ±
Age	51.83	13.28
Systolic blood pressure	124.88	15.39
Diastolic blood pressure	80.22	9.21
Body mass index (kg/m^2)	27.09	5.36
Waist circumference (cm)	96.95	17.77
Waist hip ratio	0.97	0.13
Fasting plasma glucose(mmol/L)	6.72	2.70
ALT (mIU/L)	11.24	3.99
AST (mIU/L)	25.12	13.62
Total Protein (g/L)	73.08	11.59
Albumin (g/L)	48.42	6.71
Urea (mmol/L)	2.94	1.30
Creatinine (μmol/L)	61.26	43.77
Triglyceride (mmol/L)	1.45	0.90
Total cholesterol (mmol/L)	3.70	0.90
HDL-C (mmol/L)	1.00	0.38
LDL-C (mmol/L)	2.05	1.02
IL-6 (pg/ml)	125.06	166.29

Table 2: Sex Distribution among the Study Populations

Gender	Whole Study Population (%)	Diabetics (%)	Controls (%)
Males	15 (36.6)	10 (35.7)	5 (38.5)
Females	26 (63.4)	18 (64.3)	8 (61.5)
Total	**41 (100)**	**28 (100)**	**13 (100)**

Table 3: Comparison of Means of Variables between Diabetics and Controls

Variables	Diabetics ± SD (N=28)	Controls ± SD (N=13)	Significance (2 –Tailed)
Age	56.61 ± 9.62	41.54 ± 14.55	0.000
Systolic blood pressure	125.71 ± 14.25	123.08 ± 18.09	0.616
Diastolic blood pressure	79.07 ± 8.70	82.69 ± 10.13	0.246
Body mass index (kg/m2)	26.99 ± 5.34	27.29 ± 5.61	0.871
Waist circumference (cm)	100.75 ± 18.47	88.77 ± 13.36	0.043
Waist hip ratio	1.01 0.14	0.88 ± 0.07	0.002
Fasting plasma glucose (mmol/L)	7.78 ± 2.62	4.43 ± 0.82	0.000
ALT (mIU/L)	11.43 ± 4.31	10.85 ± 3.34	0.669
AST (mIU/L)	27.43 ± 15.32	20.15 ± 7.15	0.113
Total Protein (g/L)	71.85 ± 10.14	75.74 ± 14.33	0.390
Albumin (g/L)	47.18 ± 6.60	51.09 ± 6.39	0.083
Urea (mmol/L)	3.17 ± 1.12	2.43 ± 1.53	0.086
Creatinine (μmol/L)	62.94 ± 50.94	58.02 ± 26.44	0.748
Triglyceride (mmol/L)	1.55 ± 0.98	1.24 ± 0.69	0.311
Total cholesterol (mmol/L)	3.86 ± 0.72	3.34 ± 1.15	0.087
HDL-C (mmol/L)	0.95 ± 0.40	1.11 ± 0.33	0.228
LDL-C (mmol/L)	2.21 ± 0.89	1.68 ± 1.21	0.120
IL-6 (pg/ml)	194.77 ± 166.16	26.29 ± 6.65.	0.001

Table 4: Correlations among the Diabetic Population

Variables	Correlation
IL-6 vs Tg	P = 0.007 (0.568)
IL-6 vs LDL-C	P = 0.028 (–0.455)
IL-6 vs AST	P = 0.041 (0.376)
IL-6 vs ALT	P = 0.004 (0.514)

Correlation Analyses

Among subjects with diabetes mellitus, we found significant correlations between IL-6 and Tg ($p<0.01$, $r = 0.007$**), IL-6 and LDL-C ($p<0.05$, $r = 0.028$*), IL-6 and AST ($p<0.05$, $r = 0.041$*) and IL-6 and ALT ($p<0.01$, $r = 0.004$**)

When we combined the groups (patients and controls) there were more significant correlation relationships; IL-6 correlated with WHR ($p<<0.01$, $r = 0.006$**), Tg ($p<0.01$, $r = 0.002$**), AST ($p<0.01$, $r = 0.003$**), ALT ($p<0.01$, $r = 0.004$**), FBS ($p<0.01$, $r = 0.007$**). There was no significant correlation between IL-6 and BMI ($p<0.05$, $r = 0.441$) and WC ($p<0.05$, $r = 0.325$).

DISCUSSION

The significant age difference between diabetics and controls in this study is not surprising. This is because diabetes mellitus is commonly a disease of older hospital patients (mean age < 50 years) in Nigeria[22–24] and other developing countries.[25] Since insulin resistance and glucose intolerance are present for up to a decade or more before the advent of frank diabetes mellitus, it will be important to commence, efforts aimed at preventing or slowing diabetes in Nigerians, early.

This study did not find any significance difference in BMI, SBP, DBP, TC and Tg in the diabetics compared to non-diabetic controls, a result similar to what others have recorded. In a 2011 study in Iran, there was no significant difference in mean values of variables listed above, except for HDL-C and LDL-C.[26]

The waist circumference and waist hip ratio, but not BMI, showed the impact of difference in body size and shape between diabetics and controls. This was particularly demonstrated by WHR, thus supporting the relevance of abdominal

adiposity in insulin resistance and diabetes mellitus. Furthermore, central adiposity-related indicators (WC, WHR and WC/WHR) have been found to correlate better, than those assessing body mass indexes, with plasma proinflammatory markers such as IL-6.[27]

In humans, IL-6 is secreted by both adipose and non-adipose stroma cells, with a significant portion secreted by adipose tissue. This secretion is mainly from white adipose tissues and visceral adipocytes.[28,29] The marked difference in the levels of IL-6 in diabetics and controls among our patients did not show any correlation with indices of central adiposity (WC and WHR). This lack of correlation was also found some other studies[30,31] but not in all.[32,33]

Various studies have shown increase in IL-6 levels in diabetic subjects[34–37] and this high cytokine level is reported tobe contributory to the development of complications in diabetes.[38–40] It has been reported that, proinflammatory cytokines such as IL-6, TNFa and CRP are elevated in patients before they become overtly diabetic,[41,42] thus adding to the importance of tracking cytokines before and after development of diabetes mellitus. Increased level of IL-6 in these subjects could be related to noted abdominal fat mass in relation to controls as evident by their mean WC and WHR. This has been found in other works which reveals high levels of IL-6 with increasing abdominal adiposity.[43–45] We are unable to categorically say observed high IL-6 is due to central adiposity due to the lack of correlation between the two factors.

The elevated levels of IL-6 in insulin resistant state could contribute to progression from glucose intolerance to frank diabetes by increasing expression of suppressor of cytokine signalling 3 (SOCS-3), impaired phosphorylation of IRS-1 and PkB/Akt[46] and down regulation of GLUT-4.[47]

One opinion is that high level of IL-6 in subjects with abdominal obesity may be responsible for observed increased energy expenditure through induction of lipolysis and elevated fatty acid oxidation.[48,49] Even for similar body fat, it has been noted that subjects with higher level of IL-6 shows higher omental lipolysis, again supporting a key forthe cytokine in adipocyte metabolism.[50] This may account for the observed negative correlation between IL-6 and abdominal obesity, in one study.[49,51] In the present study, we did not find any significant correlation between abdominal adiposity (WC and WHR) and IL-6 among the diabetic subjects, but in the controls. We therefore thought that elevated IL-6 in our patients maybe coming from a non-natural adipose storage site.

This seeming discrepancy may be affected by the multiple sources of IL-6 in the body. It is known that up to 25% of systemic IL-6 comes from subcutaneous adipose tissue, where it still can alter glucose and lipid metabolism.[52,53]

Given the significant correlation between IL-6 with AST and ALT we suspect that elevated IL-6 in our patients may have hepatic origin. It is known that liver pathology such as non-alcoholic liver disease (NALD) is a common finding in DM patients, especially in the presence of high level of IL-6.[54] An earlier study showed a similar relationship between IL-6 and hepatic transaminases in insulin resistant patients. This study noted that there was also increased Caspase-generated cytokeratin-18 (CK-18), a marker of hepatic cell apoptosis, in patients with high IL-6 and elevated transaminases.[55] The assault on the liver by DM2 maybe worsened in the presence of visceral adiposity as a result of increased intra-abdominal adipocytes lipolysis and resultant lipo-hepatic toxicity.[56]

In spite of the non-significant differences in means of lipid parameters in diabetics versus controls, there was a significant correlation between IL-6 and Tg, and IL-6 and LDL-C. The suggestion from this is that there is a possible increase of IL-6 by abnormal lipid levels, or the elevated IL-6 due to insulin resistance and diabetes state affects the levels of lipids. Apart from this study, others have shown a correlation between IL-6 and LDL-C[40,55] It is possible that the lack of significant difference between subjects with diabetes mellitus and controls, maybe linked to the lipid lowering ability of IL-6.[57] However, it should be noted that high level of IL-6 has been related also to increased amount of oxidised-LDL in diabetic subjects.[26]

In the last couple of years, IL-6 has been noted to also have anti-inflammatory properties, aside the traditional description as a pro-inflammatory cytokine. This feature includes its ability to decrease secretion of TNF-alpha, IFN-gamma and increase levels of IL-1R-antagonists and TNF receptor, in the course of inflammation.[58] The particularly high levels of IL-6 warrants particular mention, even among the controls albeit hospital patients. However, reports already noted that blacks have higher IL-6 levels than whites,[59,60] and the level of this cytokine has been found to be higher in low socio-economic status individuals.[61,62] The impact of low socio-economic status might not be significant here as almost 70% of the diabetic population had a post-secondary certificate (result not shown). Furthermore, the G/G IL-6 genotype variation which is said to result in higher levels of IL-6 production has been mainly described in blacks.[63]

The high level of IL-6 found in diabetes mellitus patients in Nigeria appears to be more related to hepatic disorders than observed higher measures of central adiposity in them. While it advisable to have measures to address increased central adiposity in diabetic patients in the region, we here suggest further study of the state of the liver in the patients. Such further studies may reveal other issues that may be related to the high level of IL-6 in Nigerian DM2 patients.

Shortcoming: The short coming we notice in this work is the small number of subjects enrolled in it.

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