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## HIGH-SENSITIVITY C-REACTIVE PROTEIN IN TYPE 2 DIABETIC PATIENTS WITH AND WITHOUT THE METABOLIC SYNDROME

M.D. Joshi, MBChB, MMed, MPH, FACC, Senior Lecturer and Director, Clinical Epidemiology Unit, J. Wala, MBChB, Senior House Officer, K.S. Acharya, MBChB, MRCPire, Lecturer, Department of Medicine and A. Amayo, MBChB, MMed, Senior Lecturer, Department of Chemical Pathology, College of Health Sciences, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya

Request for reprints to: Dr. M.D. Joshi, Department of Medicine, College of Health Sciences, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya

## HIGH-SENSITIVITY C-REACTIVE PROTEIN IN TYPE 2 DIABETIC PATIENTS WITH AND WITHOUT THE METABOLIC SYNDROME

M.D. JOSHI, J. WALA, K.S. ACHARYA and A. AMAYO

### ABSTRACT

**Objective:** To describe the distribution of serum high-sensitivity C-reactive protein (hsCRP) in type 2 diabetes mellitus outpatients, and relate it to cardiovascular disease risk.

**Design:** Cross-sectional descriptive study.

**Setting:** Kenyatta National Hospital, a tertiary referral hospital.

**Subjects:** One hundred and ninety seven type 2 diabetic outpatients and fifty age- and sex-matched non-diabetic hypertensive outpatients.

**Results:** The distribution of hsCRP in the diabetic population was skewed, with a mean of 4.33 mg/L and a median of 2.53 mg/L. The majority (42%) of diabetics had hsCRP levels in the high-risk category (hsCRP > 3 mg/L). The median hsCRP was non-significantly higher in the diabetic patients with metabolic syndrome compared to those without (2.68 vs 2.30 mg/L,  $p=0.433$ ). The median hsCRP was non-significantly higher in the hypertensive group compared to that in matched diabetic non-metabolic syndrome group (2.30 vs 2.23 mg/L,  $p=0.297$ ). HsCRP increased with number of metabolic syndrome components, patients with four components having higher hsCRP levels than those with one, though the difference was not statistically significant (3.59 vs 1.57 mg/L,  $p=0.095$ ).

**Conclusion:** Our study, though cross-sectional in nature, supports the existence of a correlation between hsCRP levels and cardiovascular disease risk. The small difference in CRP levels between diabetic metabolic and non-metabolic groups underpowered the study. Cohort studies are needed to determine the predictive power of hsCRP for cardiovascular disease in our setup.

### INTRODUCTION

Cardiovascular diseases (CVD) are expected to be the main cause of death globally within the next 15 years. This is attributable to a rapidly increasing prevalence of CVD in developing countries and the rising incidence of obesity and diabetes (1).

Diabetes mellitus is often associated with other features of the metabolic syndrome, each of which is an independent risk factor for CVD (2-3). The risk of fatal coronary heart disease among subjects with diabetes is comparable to that observed in subjects

who have had a previous myocardial infarction (4). Although this increased risk previously was attributed mainly to hyperglycaemia, dyslipidaemia, and a prothrombotic state, recent observations in apparently healthy individuals have focused attention on inflammatory mechanisms that may be relevant in patients with diabetes as well (5).

A sensitive indicator of the body's response to inflammation is C-reactive protein (CRP), an acute-phase reactant, which has been demonstrated to act independently to further define the risk for an adverse cardiovascular event (6). To date, 22

prospective epidemiological studies in developed countries have demonstrated that hsCRP is a strong predictor of future CVD (7). Even in diabetes, subjects with high CRP levels had a seven-fold higher risk of cardiovascular events compared to subjects with neither diabetes nor the metabolic syndrome and low CRP levels (8). Whereas the role of hsCRP as a CVD risk factor has been demonstrated in the West, an increased infectious disease burden in less developed communities, which is presumably associated with higher serum CRP levels, might possibly confound this predictive value. There are no studies carried out in Africa to establish population levels for CRP. Neither do we have studies that assess hsCRP as a risk factor for cardiovascular disease. We set out to establish whether hsCRP, in patients at high risk for CVD and living in an environment with a high infectious disease burden, correlates with increased cardiovascular risk as estimated by the metabolic risk factor load.

## MATERIALS AND METHODS

A cross-sectional descriptive study was carried out at Kenyatta National Hospital medical outpatient clinics from which the study population of type 2 diabetics and an age- and sex-matched comparison group of non-diabetic hypertensives were randomly selected. The case definition for type 2 diabetic patients was based on clinical criteria (known diabetic patients who had developed diabetes after the age of 30 years and did not require insulin therapy initially (9). The case definition for the metabolic syndrome was based on the NCEP ATP III criteria, with the patient requiring at least three of the following five features: fasting triglyceride  $>1.69$  mmol/L; HDL cholesterol  $<1.04$  mmol/L if male or  $<1.29$  mmol/L if female; blood pressure (BP)  $\geq 130/85$  mmHg or on anti-hypertension medication; waist circumference  $>88$  cm for females and  $>102$  cm for males; or fasting glucose  $\geq 6.1$  mmol/L or on medication for diabetes mellitus (10). Hypertensive patients were defined as those diagnosed to be hypertensive (BP  $>140/90$  mmHg) or on anti-hypertensive medications.

Patients were excluded (on basis of history and medical records) if they were less than 18 years; were diagnosed with an acute infectious process; were known to have inflammatory processes like malignant diseases, connective tissue diseases, inflammatory bowel disease, or an

active diabetic foot; were known to have Human Immunodeficiency Virus (HIV) infection; or were known to be receiving immunosuppressive therapy, statins, or thiazolidinediones within preceding 30 days. Apart from the aforementioned exclusion criteria, hypertensive patients were also excluded if they were known to be diabetic or were found to have impaired fasting blood glucose ( $>6.1$  mmol/L). Diabetic patients were stratified into two groups: those with the metabolic syndrome and those without. To detect (with a likelihood of 90%) a significant difference between the means of hsCRP in these two groups, a sample size of 98 in each group was required (22). An arbitrary sample of 50 age- and sex-matched hypertensive patients was recruited as a comparison group. Permission to carry out the study was obtained from the KNH Scientific and Ethical Research Committee and informed written consent was obtained from each participant.

*Data collection:* A standardised interview was conducted that involved taking a thorough targeted medical history including socio-demographic parameters and lifestyle characteristics. A focused medical examination was carried out to assess waist circumference, weight, and blood pressure using standard clinical methods.

Five milliliters (ml) of fasting venous blood was collected aseptically from the antecubital fossa. The specimens were centrifuged within four hours and the serum kept frozen at  $-20^{\circ}$  Celsius until further analysis. Determination of serum lipids (including direct LDL cholesterol measurement) and serum hsCRP was done using an automated clinical chemistry analyzer (Abbott AEROSSETM). A latex particle-enhanced immunoturbidimetric assay was used for the determination of CRP in serum (CRP Turbidimetric Latex — High Sensitivity, Quimica Clinica Aplicada S.A., Spain). The US Food and Drug Administration (FDA) approved the use of this latex-enhanced method in risk assessment of cardiovascular disease. We utilised the recommended hsCRP risk categories of low risk ( $<1$  mg/L), medium risk ( $1-3$  mg/L), and high risk ( $>3$  mg/L) (11).

The recommended procedures for specimen collection, preparation, and storage were followed strictly to minimise pre-analytical sources of errors. Before analysis, all the assays were calibrated according to the manufacturers' specifications. Three levels of commercial controls (high, medium,

and low) were used to validate the calibration. The controls were included in all batches of analysis. Results were only accepted if the controls were within the accepted limits.

*Statistical analysis:* Data were entered into a computer database and described in terms of frequency distribution, means, and figures (percentages, proportions, and ratios). A significant difference between means was determined using the student t-test (for numerical variables) and chi-square test (for categorical variables). Correlation of hsCRP with components of the metabolic syndrome was carried out using Spearman rank correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

Between November 2005 and April 2006, a total of 215 type 2 diabetic outpatients were randomly selected and screened. Eighteen patients were excluded for the following reasons: chronic kidney disease (four patients), use of a statin (three patients) or a thiazolidinedione (one patient), infected diabetic ulcer (two patients), cancer of the breast (one patient), and inflammatory bowel disease (one patient). The mean age of the excluded patients was 48.56 years, and 50% were male.

Consequently, 197 type 2 diabetic patients were recruited and stratified as having (n=98) or not having

(n=99) the metabolic syndrome according to NCEP ATP III criteria. The characteristics of the recruited diabetic population are shown in Table 1. Age ranged from 30 to 80 years, with a median age of 56 years and a mean of 56.07 years (SD 9.81 years). The majority (64.5%) were in the 50-69 years age group. The duration of diabetes ranged between 1 and 30 years, with a median duration of four years and a mean duration of 6.32 years (SD 6.37). Sixty five percent of diabetics were on oral hypoglycaemic agents, 29% were on insulin monotherapy, and 6% were on diet alone. Forty two patients (21.3% of diabetics; all males) gave a history of cigarette smoking. Almost half the patients (49.2%) were hypertensive. Only 29 (14.7%) patients were on aspirin therapy.

*Anthropometric measures of obesity:* Body mass index (BMI) values ranged from 17.9 kg/m<sup>2</sup> to 43 kg/m<sup>2</sup>, with a median of 28.3 kg/m<sup>2</sup>, and a mean of 28.8 kg/m<sup>2</sup> (SD 4.98 kg/m<sup>2</sup>). The distribution of BMI in the diabetic population is depicted in Figure 1. Forty percent of the patients were obese (as defined by BMI  $\geq 30$  kg/m<sup>2</sup>), while 65.5% of the patients had central obesity (as defined by a waist circumference  $>102$  cm in males or  $>88$  cm in females). Female patients were significantly more obese (mean BMI in females  $29.9 \pm 10.4$  kg/m<sup>2</sup>; mean BMI in males  $26.5 \pm 7.1$  kg/m<sup>2</sup>;  $p < 0.0005$ ) and had a significantly wider waist circumference than males (females,  $98.63 \pm 24.4$  cm; males,  $94.39 \pm 18.8$  cm;  $p = 0.016$ ). The majority (90.7%) of diabetics with central obesity were females.

Table 1

*Summary of characteristics of the study population*

Characteristic	Value
Age, x $\pm$ SD	56.07 $\pm$ 19.62 years
BMI, x $\pm$ SD	28.8 $\pm$ 9.96 kg/m <sup>2</sup>
Duration of diabetes, x (SD)	6.32 (6.37) years
Females, n (%)	134 (68)
Former smokers, n (%)	40 (20.3)
Aspirin use, n (%)	29 (14.7)
Hypertension, n (%)	97 (49.2)

X = Mean; BMI = Body Mass Index; SD = Standard Deviation

Table 2

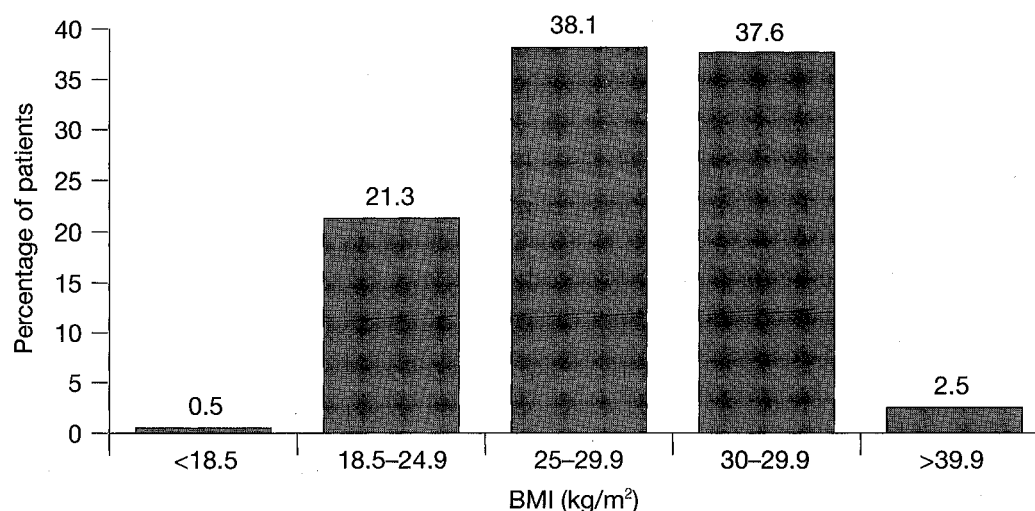
Clinical components of diabetic patients with and without the metabolic syndrome

Characteristic	All diabetic patients (x [sd]) (n = 497)		MS (x [sd]) (n = 98)		No MS (x [sd]) (n = 99)		P-value (for MS vs No MS (x))
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	56.07	8.81	55.98	8.80	56.16	10.77	0.897
Female, n (%)	134	68	85	86.7	49	49.5	
BMI (kg/m <sup>2</sup> )	28.8	4.98	30.43	4.63	27.20	4.82	<0.0005
Waist circumference (cm)	97.27	11.55	101.17	10.99	93.41	10.82	<0.0005
Systolic BP	136.6	21.7	139.03	22.26	134.14	21.01	0.114
Diastolic BP	85.2	11.9	86.89	12.02	83.43	11.62	0.042
Total cholesterol	5.12	1.26	5.13	1.37	5.10	1.15	0.886
LDL cholesterol	3.26	1.00	3.30	1.08	3.23	0.91	0.617
HDL cholesterol	1.30	0.31	1.22	0.28	1.38	0.32	<0.0005
Triglycerides	1.74	0.80	2.14	0.86	1.33	0.46	<0.0005

MS = Metabolic Syndrome; X = Mean; SD = Standard Deviation.

Figure 1

Distribution of BMI in the diabetic patients

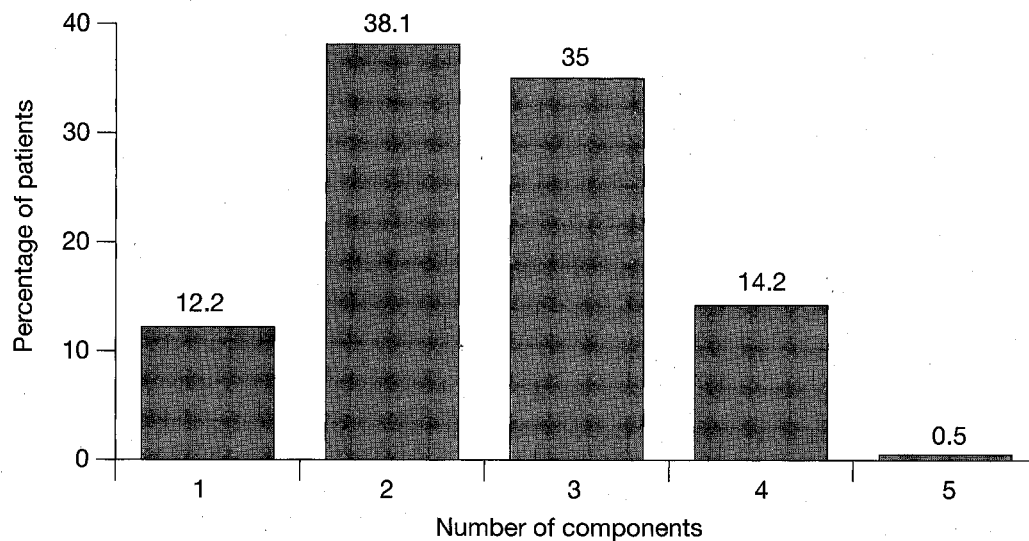


**Lipid profile:** Total cholesterol levels ranged from 2.24 to 8.88 mmol/L, with a median of 4.93 mmol/L and a mean of 5.12±2.5 mmol/L. LDL cholesterol levels ranged from 0.91 to 5.91 mmol/L, with a median 3.17 mmol/L and a mean of 3.26±2.0 mmol/L. HDL cholesterol levels ranged from 0.68 to 2.16 mmol/L, with a median of 1.29 mmol/L, and a mean of 1.30±0.6 mmol/L. Triglyceride levels ranged from 0.53 to 5.03 mmol/L, with a median of 1.56 mmol/L and a mean of 1.74±1.6 mmol/L. Only a meager 6.6% of the patients achieved the current target LDL cholesterol level of 1.8 mmol/L. Females had

a significantly higher LDL (3.36±2.1 vs 3.05±1.7 mmol/L; p=0.041) and HDL (1.35±0.6 vs 1.21±0.6 mmol/L; p=0.004) cholesterol levels. However, the two genders were not significantly different in terms of their mean total cholesterol and mean triglyceride levels.

**Metabolic syndrome components:** We recruited 98 patients with the metabolic syndrome (MS) and 99 patients without the metabolic syndrome. The distribution of the number of MS components in the entire diabetic study sample is depicted in Figure 2.

**Figure 2**  
Distribution of MS components in the entire diabetic population



A minority (12%) were solely diabetic, while the rest (88%) had more than two MS components and 76.2% of the non-MS diabetic patients demonstrated one other MS component.

The characteristics of patients classified as either having or not having MS are shown in Table 2. The majority of MS patients were females (86.7%). Sixty three point four percent of all female patients, but only 20.6% of all male patients had MS.

There was no significant difference in terms of mean ages, total cholesterol and LDL cholesterol levels between the MS and the non-MS groups. As expected, the components used to classify MS (waist circumference, blood pressure, HDL cholesterol, and triglycerides) differed significantly between the two groups. MS patients were sub-classified according to whether or not they had dyslipidaemia, defined as having the combination of elevated triglycerides ( $\geq 1.69$  mmol/L) and low HDL cholesterol ( $< 1.03$  mmol/L in males,  $< 1.26$  mmol/L in females). Thirty four patients had dyslipidaemia (representing 34.7% of patients with metabolic syndrome).

**High-sensitivity c-reactive protein:** HsCRP levels ranged from 0.15 to 17.94 mg/L, with a median of 2.53 mg/L and a mean of 4.33 mg/L (SD 4.84 mg/L). The 25th, 50th, and 75th percentiles were 1.01, 2.53, and 5.44 mg/L, respectively. Twenty six (13.2%) patients had an hsCRP level of  $> 10$  mg/L. The distribution of hsCRP across the diabetic population, as illustrated in Figure 3, was skewed,

and thus the median value was used as the measure of central tendency. When categorised according to pre-defined hsCRP risk prediction categories of low-risk ( $< 1$  mg/L), intermediate risk (1-3 mg/L), and high-risk ( $> 3$  mg/L), the majority of patients (41.6%) had hsCRP levels in the high-risk category (Figure 4). Median hsCRP values did not differ significantly across gender (men 2.34 mg/L, women 2.55 mg/L ( $p=0.917$ )).

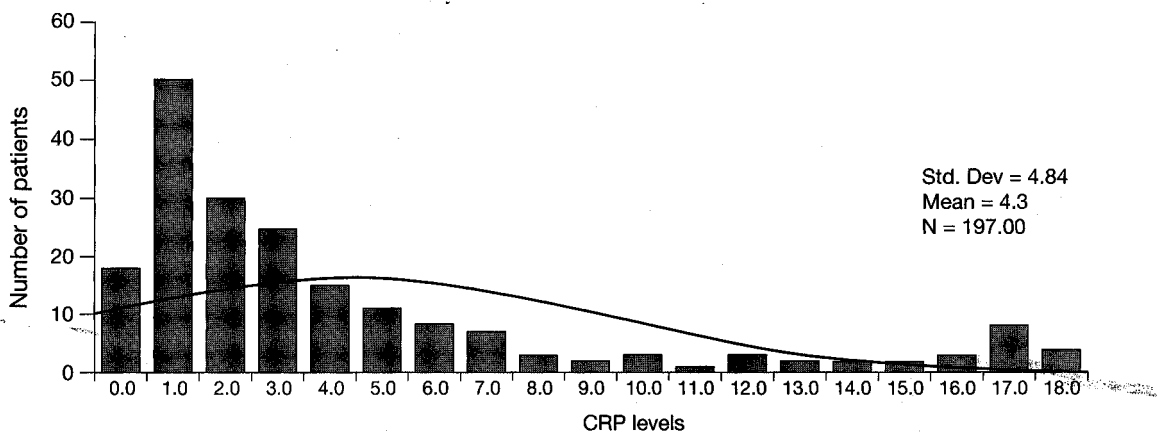
HsCRP did not differ significantly across BMI categories, (Figure 5) ( $p=0.529$ ). The median hsCRP was non-significantly higher in patients with central obesity than in those without (3.12 vs 2.16;  $p=0.179$ ). The median hsCRP in the MS group (2.68 mg/L) was higher than that in the non-MS group (2.30 mg/L), although this difference was not statistically significant ( $p=0.433$ ). There was also no statistically significant difference between the median hsCRP levels of the MS patients with dyslipidaemia and those without (2.71 mg/L vs 2.46 mg/L, respectively;  $P=0.907$ ). The percentage distribution of patients with a high-risk hsCRP ( $> 3$  mg/L) when the diabetic patients were grouped according to the number of metabolic syndrome components they possess is shown in Figure 6. In each grouping, the proportion of patients with hsCRP in the high-risk category increased as the number of components increased; thus, 25%, 42.5%, 43.3%, and 50% of the patients with 1, 2, 3, or  $\geq 4$  components, respectively, had hsCRP levels in the high-risk category. The median hsCRP of patients with four components was higher than

that in patients with only one component (3.59 vs 1.57 mg/L), though this difference did not achieve statistical significance ( $p=0.095$ ).

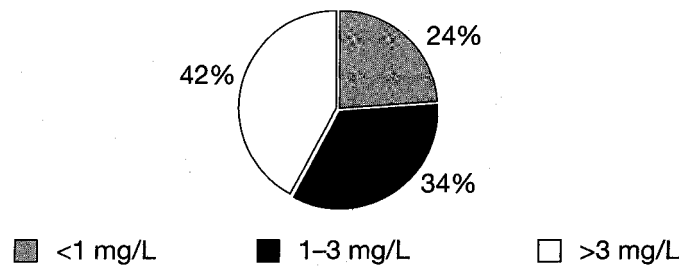
**Hypertensive patients:** Fifty age and sex-matched non-diabetic hypertensive patients were recruited as a comparative group. The ages of these hypertensive patients ranged from 30 to 79 years, with a mean age of  $53.68 \pm 22.0$  years, and a median of 54.50 years. The BMI ranged from 30 to 79 kg/m<sup>2</sup>, with a

mean of 27.21 kg/m<sup>2</sup>, and a median of 27.04 kg/m<sup>2</sup>. Forty six (92%) of the hypertensive patients were females. The median hsCRP of this hypertensive group was not significantly different from that of their matched diabetic non-MS group (2.30 mg/L vs 2.23 mg/L,  $p=0.297$ ). The majority (42%) of the hypertensive group had hsCRP in the high-risk category, whereas 24% and 34% were in the low (<1 mg/L) and intermediate (1-3 mg/L) risk categories, respectively.

**Figure 3**  
Distribution of hsCRP in the diabetic population



**Figure 4**  
Percentage of patients in different hsCRP categories



**Figure 5**  
Median hsCRP levels at different BMI categories

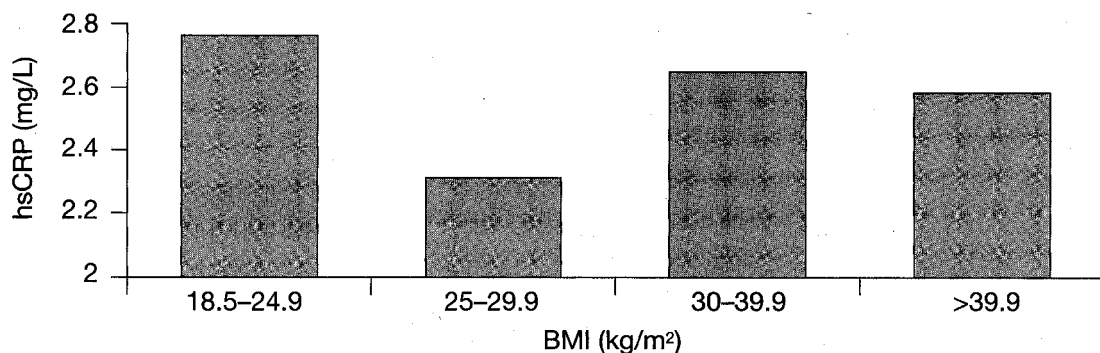
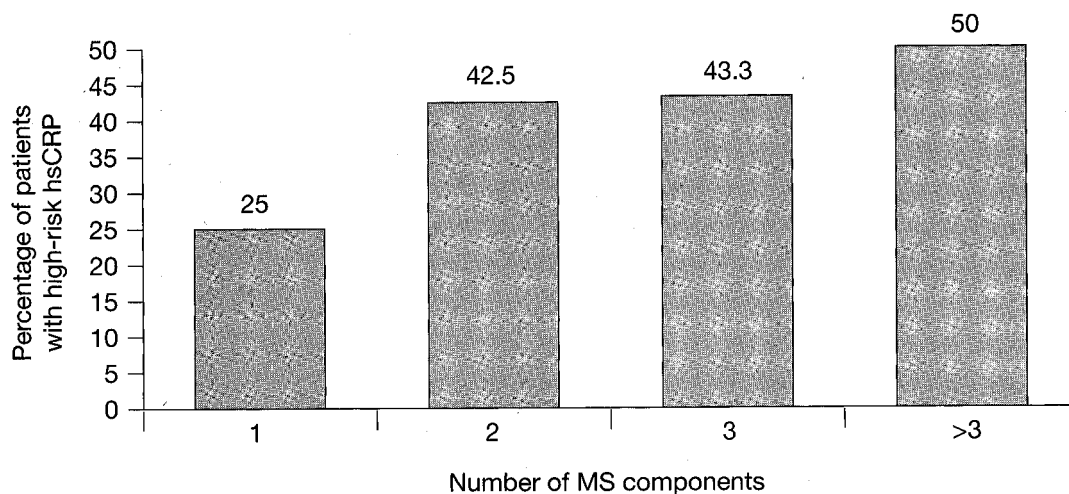


Figure 6

Percentage distribution of patients with hsCRP in high-risk category (>3 mg/L) according to number of components



## DISCUSSION

Our study is the first we are aware of from Africa that attempts to establish if there is a correlation between hsCRP and established cardiovascular risk factors. We recruited type 2 diabetic patients, a high-risk patient population that is considered as a coronary artery disease risk equivalent.

The sample of type 2 diabetic patients recruited in this study was similar in demographics to those in two prior studies undertaken at this tertiary care facility (12,13). They were under-treated with low-dose aspirin (only 14.7%), and only three were excluded for being on statin therapy.

As expected, several cardiovascular risk factors existed in our study population. Forty percent were obese as defined by BMI (and only a fifth had normal BMI), and 66% had central obesity as defined by waist circumference above NCEP ATP III cut offs. Only 6.6% were at target LDL cholesterol level of 1.8 mmol/L. Eighty eight percent had at least one other component of the metabolic syndrome. These factors, along with the patients' diabetes status and age strata, placed this population at high CVD risk.

The levels of hsCRP in our diabetic population ranged from 0.15 mg/L to 17.94 mg/L, with a median of 2.53 mg/L. However, we have no local or regional population-based hsCRP levels to place our reported values in perspective. A recent population-based study of adults in the United States reported values ranging from 0.1 to 29% mg/L, with a median of 2.1 mg/L, and a distribution that was highly

skewed to the left (14). Our values were also skewed to the left, yet a postulated high infectious disease burden would be expected to shift the distribution to the right. By the recommended USA cut offs for hsCRP, 42% of our diabetic patients had hsCRP in the high-risk category. Whether these cut-offs are applicable in our setup can only be determined by local population-based studies.

To date, several prospective epidemiological as well as cohort studies have demonstrated that hsCRP is a strong predictor of future cardiovascular events, adding prognostic value even beyond that available from the Framingham risk score (7), with its strongest predictive value in the range of 1-5 mg/L (15). HsCRP retains its predictive value even in diabetics; a prospective study by Schuize *et al* that involved 746 men with type 2 diabetes demonstrated that patients with hsCRP in the top quartile were three times more likely to develop cardiovascular events (16).

Our study demonstrates a higher hsCRP in increasing CVD risk groups (diabetics with MS [2.68 mg/L], diabetics without MS [2.23 mg/L], and non-diabetic hypertensives [2.30 mg/L]). However, the differences did not attain statistical significance. We interpret our results as suggesting a trend of hsCRP tracking increasing cardiovascular risk, from non-metabolic diabetic patients to hypertensive non-diabetic patients and onto metabolic diabetic patients in the highest risk. We attribute our inability to show a statistically significant difference to the homogeneously high cardiovascular risk in these three groups, which limited our study power. At design stage, we anticipated a hsCRP difference

between diabetic MS and the diabetic non-MS groups of 0.69 mg/L (22), but we only found a 0.38 mg/L difference. To detect this difference, we would require a sample size of 131 in each group to minimise the chances of a type 2 error.

In addition, it should be noted that the presence of the metabolic syndrome was not ruled out in the hypertensive non-diabetic group, a group with a mean BMI of 27.2 kg/m<sup>2</sup>, 92% of whom were females, and almost two thirds had central obesity. Therefore, it is highly likely that the majority of these patients had the metabolic syndrome. This might explain why their median hsCRP was comparable to that for diabetic non-metabolic patients, three quarters of whom had two components of the metabolic syndrome.

This data implies that the metabolic risk factor load, rather than diabetic status per se, was the force driving increasing hsCRP across the three groups. Evidence in support of this postulate also arises from the comparison of hsCRP between diabetic patients with no other component of the metabolic syndrome (median hsCRP 1.57 mg/L) and diabetic patients with three other metabolic components (median hsCRP 3.59 mg/L). However, this difference was not statistically significant ( $p=0.095$ ) due to the small numbers in each group. The proportion of patients with hsCRP in the high-risk category rises as the number of metabolic components increased, from 25% of patients with one component to 50% of patients with four or more components. Furthermore, hsCRP in patients with central obesity was higher than that in those without central obesity. As well as being a key component of the metabolic syndrome, central obesity is postulated to be the source of pro-inflammatory cytokines, including CRP, that are central to the inflammatory theory of atherosclerosis. In all, our data suggests that hsCRP levels in our study sample increase with increasing metabolic risk factor loading.

Nevertheless, it should be recognised that the cut-off used for the individual components of the metabolic syndrome are derived from Western guidelines (17). The metabolic syndrome concept was designed to identify persons (often obese) who are at greatest risk of atherosclerotic cardiovascular disease, and hence, in greatest need of clinical intervention (18). However, there is no definite

rationale for choosing the five criterias, and their cut-off points are arbitrary (19). In addition, there are ethnic specific differences encountered in the assessment of central obesity, a key feature of the metabolic syndrome. Although emphasis is laid on ethnic-specific cut points for waist circumference, none is available for sub-Saharan Africans; instead, it is advised that we use European cut points until more data is available (20). Evidently, it is not known to what extent this definition, or even the one used in this study, misclassifies individuals in our setup.

We had hypothesised that the presumably increased background inflammation that exists in our population as a result of the higher infectious disease burden, may obscure or confound the correlation of hsCRP with CVD risk. This, however, is not supported by our data. Our hsCRP distribution was skewed towards lower values (as it was in the US population-based study), and only 13.2% of the diabetic patients had hsCRP values >10 mg/L, a cut-of above which inflammation will be suspected and so warrant a repeat of the hsCRP (21).

Our study is limited firstly by the absence of African population normal reference values for hsCRP, and secondly by the inability to actively exclude pathological conditions that are associated with elevated hsCRP levels. In this respect we relied solely on clinical criteria. However, all three groups suffered this limitation non-differentially, thus nullifying this effect on our results.

In conclusion, our study, though cross sectional in nature, supports the existence of a correlation between hsCRP levels and CVD risk in our population. Our results need to be confirmed by a larger, adequately powered study. In addition, population-based studies are necessary to establish the local distribution of hsCRP and to develop cut-off values that will be used for cardiovascular risk prediction in our population. Finally, cohort studies are needed in our local population to determine the power of hsCRP in predicting absolute cardiovascular disease risk.

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## REFERENCES

1. Howard, B.V., Rodriguez, B.L., Bennett, P.H., *et al.* Prevention Conference VI: Diabetes and cardiovascular disease. Writing Group I: epidemiology. *Circulation.* 2002; **105**: e137.
2. Zimmet, P. Alberti, K.G. and Shaw, J. Global and societal implications of the diabetes epidemic. *Nature.* 2001; **414**: 782-787.
3. The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *J. Amer. Med. Ass.* 2001; **285**: 2486-2497.
4. Echel, R.H., Wassef, M., Chait, A., *et al.* Prevention Conference VI: Diabetes and cardiovascular. Writing Group II: pathogenesis of atherosclerosis in diabetes. *Circulation.* 2002; **105**: e138-e143.
5. Hanson, G.K. Inflammation, atherosclerosis, and coronary artery disease. *N. Eng. J. Med.* 2005; **352**: 1685-1695.
6. Haverkate, F., Thompson, S.G., Pyke, S.D.M., *et al.* Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet.* 1997; **349**: 462-466.
7. Ridker, P.M., Wilson, P.W. and Grundy, S.M. Should C-reactive protein be added to the metabolic syndrome and to assessment of global cardiovascular risk? *Circulation.* 2004; **109**: 2818-2825.
8. Malik, S., Wong, N.D., Stanley, F., *et al.* Cardiovascular disease in US patients with metabolic syndrome, diabetes, and elevated C-reactive protein. *Diabetes Care.* 2005; **28**: 690-693.
9. Powers, A.C. Diabetes mellitus. In: Harrison's Principles of Internal Medicine, 16th ed, D. Kasper *et al* (eds). New York, McGraw-Hill, 2005.
10. Echel, R.H., Grundy, S.M., and Zimmet, P.Z. The metabolic syndrome. *Lancet.* 2005; **365**: 1415-1428.
11. Yu, H. and Rifai, N. High-sensitivity C-reactive protein and atherosclerosis: From theory to therapy. *Clin. Biochem.* 2000; **33**: 601-610.
12. Mwendwa, F.M., Otieno, C.F., Vaghela, V., *et al.* Risk factor profile and the occurrence of microvascular complications in short term type 2 diabetes mellitus at Kenyatta National Hospital, Nairobi. *East Afr. Med. J.* **82**: s163-s172.
13. Otieno, C.F., Vaghela V., Mwendwa F.M., *et al.* Cardiovascular risk Factors in patients with type 2 diabetes mellitus in Kenya: Level of control attained at the outpatient diabetic clinic of Kenyatta National Hospital. *East Afr. Med. J.* **82**: s184-s190.
14. Woloshin, S. and Schwartz, L.M. Distribution of CRP values in the United States. *N. Eng. J. Med.* 2005; **352**: 1611-1612.
15. Yeh, E.T. and Willerson, J.J. Coming of age of CRP. *Circulation.* 2003; **107**: 370-372.
16. Schulze, M.B., Rimm, E.B., Li, T., *et al.* C-reactive protein and incident cardiovascular events among men with diabetes. *Diabetes Care.* 2004; **27**: 889-894.
17. Isomaa, B., Alingren, P., Tuomi, T., *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001; **24**: 603-609.
18. Grundy, S.M. The metabolic syndrome still lives. *Clin. Chem.* 2005; **51**: 1352-1357.
19. Reaven, G.M. The metabolic syndrome: Requiescat in pace. *Clin. Chem.* 2005; **51**: 931-938.
20. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Brussels: IDF, 2005. Available at: [http://www.idf.org/webdata/docs/IDF\\_Metasyndrome\\_definition.pdf](http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf) (accessed May 2006).
21. Wilson, P.W., D'Agostino, R.B., Levy, D., *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998; **97**: 1837-1847.
22. Frohlich, M., Imhof, A., Berg, G., *et al.* Association between C-reactive protein and features of the metabolic syndrome: A population-based study. *Diabetes Care.* 2000; **23**: 1835-1839.