IS THERE AN ASSOCIATION BETWEEN OBESITY AND RENAL FUNCTION IN AN ADULT POULATION? - A DESCRIPTIVE STUDY

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ABSTRACT

Background: *Obesity has become a worldwide epidemic and its prevalence has been projected to grow by 40% in the next decade. This increasing prevalence has implications for the risk of diabetes, cardiovascular disease and also for chronic kidney disease (CKD). CKD can be classified into CKD 1, CKD 2, CKD 3A, and CKD 3B with progressing degrees of severity. Obesity is one of the strongest risk factors for new-onset CKD.*

Aim: *To determine whether there was any association between the markers of adiposity and renal function in a Nigerian Adult population in hypertensive patients attending the cardiology clinic of the University of Port Harcourt Teaching Hospital UPTH.*

Methods: *One hundred and forty-four Hypertensive subjects and 72 age- and sex-matched controls were recruited. Their waist circumference, body mass indices and fasting lipid profile were determined. Diabetics were excluded from the study. Multiple logistic models were constructed to elucidate the independent determinants of estimated glomerular filtration rate eGFR.*

Results: *The mean age of the age of the hypertensive participants was 51.4±12.9 years, while the control population had a mean age of 48.47±12.89 years. The mean waist circumference of the hypertensive patients was 97.51±11.9cm while that of the control group was 86.11±18.5cm (p<0.0001). Fifty percent of the entire study population were obese with males making up to 20.6% and the females 74.4% (p<0.001). Although obesity was found both in the hypertensive-obese and hypertensive non-obese populations, the hypertensive-obese subjects had more subjects in CKD 3A and CKD 3B, when compared with the hypertensive non-obese subjects (p=0.021).*

When binary logistic regression analysis of the whole population was performed waist circumference was predictive of renal function: waist circumference 1.10 (1.01-1.20), (p=0.029).

Conclusion: *There was a significantly positive association between central obesity and renal function decline. It can be used to predict the pathogenesis of CKD, which may be independent of blood pressure levels.*

Key words: *Obesity, chronic kidney disease, hypertensive, renal function, Nigerian.*

BACKGROUND

Obesity is a worldwide health problem. Socio-economic burden and the prevalence of obesity worldwide have increased substantially over the past decades[1]. Obesity is a well-established risk factor for cardiovascular diseases and hypertension, which predisposes to developing chronic kidney disease (CKD). Certain mechanisms have been postulated as the link between obesity and hypertension. These include, activation of the sympathetic nervous system (SNS), the amount of intra-abdominal and intra-vascular fat, sodium retention leading to increase in renal reabsorption, and the renin-angiotensin system, all of which are considered to have important functions in the pathogenesis of obesity-related hypertension.[2] Numerous population-based studies have established a significant association between obesity and the development and progression of CKD.[3-9] The prevalence of chronic kidney disease (CKD) is substantially increasing over the past decades in many developed and developing countries, representing a global challenge for public health.[4] Notably, the rise of CKD parallels a rise in the prevalence of obesity in the recent years.[10] Obesity is also reported as a direct contributor for CKD independent of traditional CVD risk factors in other studies.[11,12] Weight loss is benefit for obese adults with CKD 1 to 4 who are not being treated by dialysis.[13] The Framingham Heart Study investigated the association between BMI and onset of stage 3 CKD, reporting that obese people had a 68% increased odds of developing stage 3 CKD, although the relationship was mediated by other CVD risk factors.[4] Several prospective studies have suggested that high BMI is associated with the increased risk of end-stage renal disease(ESRD) in Japanese men and Americans.[14-16]

Central obesity defined by waist circumference (WC) is reported to increase CKD risk regardless of BMI in a cohort study.[17] Reports from the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS) demonstrated that waist-to-hip ratio (WHR), but not BMI, was positively correlated with a greater risk of incidence of CKD and mortality among individuals with stage 3 to 4 CKD.[18,19] The mechanism linking obesity and CKD incidence and progression may be related to hemodynamic distortions brought about by the activation of the renin-angiotensin-aldosterone pathway which culminates in salt-water retention and renal parenchymal fibrosis.

In the current study, we examined the association of obesity indices with the prevalence of non-diabetic kidney disease in a consecutive number of outpatient non-diabetic, hypertensive patients attending a tertiary healthcare facility. We hypothesized that CKD, would be more prevalent in the obese subjects irrespective of blood pressure levels.

METHODS

Study population

Study subjects were randomly recruited from hospital staff, patients attending the general out-patients, and medical out-patients clinics of the University of Port-Harcourt Teaching Hospital from January 2016 to August 2016. Individuals who were diabetics, those who had hematologic and hepatic pathologies, determined clinically and by laboratory

evidence were excluded from the study. Women who were on oral contraceptive pills and on hormone-replacement therapy were equally excluded from the study. One hundred and forty four hypertensive subjects were recruited as cases, while 72 normotensives were recruited as controls. All participants underwent a routine clinical and blood biochemical examination. Written informed consent was obtained from participants, and the ethical committee of the hospital granted approval for the study.

Demographic and clinical characteristics

Demographic and clinical characteristics such as age, gender, duration of hypertension and current anti-hypertension therapy were obtained by a structured questionnaire. Blood pressure was measured with a standard mercury sphygmomanometer using standard protocols.[20] Height, weight, waist circumference, hip circumference were measured manually. Height and body weight were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. WC was measured midway between the inferior border of the last rib and the crest of the ilium in a horizontal plane. Hip circumference was measured around the pelvis at the point of the maximal protrusion of the buttocks.

Laboratory examination

Fasting venous blood were collected and analyzed in the chemical pathology laboratory of the University of Port Harcourt Teaching Hospital for serum electrolytes, urea, creatinine, blood glucose, and lipid profile. Glomerular filtration rate [GFR] for all patients were calculated using the Cockcroft – Gault Equation[21] having been validated in Nigerians. All the patients who were previously diabetic or who had glucose abnormalities or glycosuria in their urinalysis results were excluded from the analysis.

Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) less than 60mls/min/1.73m^2, and based on the estimated GFR all patients were staged for chronic kidney disease. The Kidney Disease Improving Global Outcomes (KDIGO) guideline was used to stage participants for GFR categories of CKD[22]

Statistical analysis

Data was expressed as mean± standard deviations and frequencies as a percentage. Continuous variables were compared with the Students t-test or one-way analysis of variance as considered appropriate. Proportions or categorical variables were compared with the Chi-square test. Relations among continuous variables were assessed using Pearson correlation coefficient and linear regression analysis. Multiple logistic models were constructed to elucidate the independent determinants of eGFR. The odds ratio and 95% confidence intervals were calculated. All analyses were performed by SPSS statistical software (version 19.0, SPSS Inc). *P* values of <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

The baseline clinical characteristics and biochemical parameters of total subjects are as shown in Table 1.

The age of the study participants with hypertension ranged between 20 and 86

years with a mean age of 51.40±12.9 years. Over fifty-nine percent of the participants were in the 40-59 years' age-group. The mean age of the control population was 48.47±12.89 years with a range of 24 – 82 years. The case and controls were matched for age (p=0.118).

The age difference across the CKD groups was significant (p<0.00010, with the CKD 3B group having a mean age of 73.33±2.89 years (Table 2).

There were more females than males among the cases in a ratio of 1.32:1 as 56.9% of them were females and 43.1% were males. Among the controls also females accounted for 50.0% giving a female to male ratio of 1:1.

The mean waist circumference of the hypertensive patients was 97.51±11.9cm while that of the control group was 86.11±18.5cm (p<0.0001). Fifty percent of the entire study population was obese with males making up to 20.6% and the females 74.4% (X^2=61.264, p<0.001).

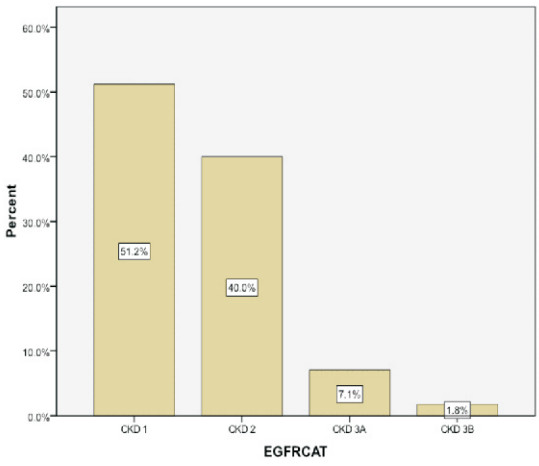

Fig. 1: Prevalence of CKD stages in the study population

The mean eGFR of the hypertensive subjects was significantly lower than that of the control cohorts (91.22±30.54 vs. 102.94±21.72, p=0.010). When the eGFR was used to stage the renal function of the entire study population, it was found that 51.2% were in CKD 1, 40.0% in CKD 2, 7.1% in CKD 3A, and 1.8% in CKD 3B. None of the subjects were in CKD 4 or CKD 5 (Fig. 1).

Further analysis revealed that among the hypertensive cases, 43.2% were in CKD 1 and CKD 2, while 10.2% and 2.7% were in CKD 3A and CKD 3B respectively. However, among the control cohort, 66.1% were in CKD 1, and 33.9% were in CKD 2 (Fischer value=13.165, p=0.002) (Fig. 2).

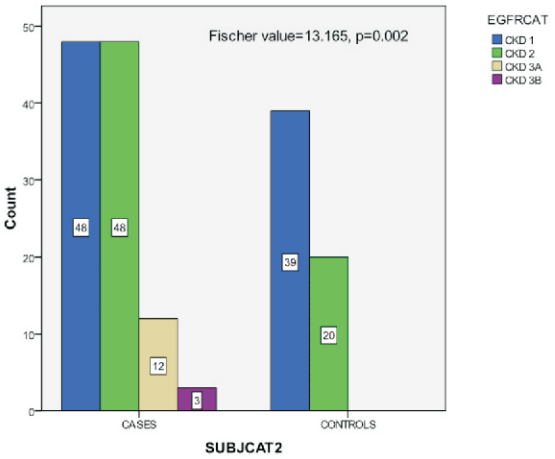

Fig. 2: Prevalence of CKD stages in both study cohorts

We found that within the entire study population, more of the obese subjects were in CKD 3A and 3B when compared with those who were non-obese, and this was statistically significant (Fischer exact value=7.423, p=0.043) (Table 3). Also, on further analysis, we found that among the hypertensive subjects, the hypertensive-

obese subjects had more cohorts in CKD 3A and CKD 3B, when compared with the hypertensive non-obese subjects (X^2=9.751, p=0.021). Among the control cohorts however, there was no statistical difference between the normal weight phenotypes and the obese subjects (X^2=0.288, p=0.592).

Relationship between markers of adiposity, age, SBP, DBP and eGFR

In bivariate correlation analysis, eGFR was significantly correlated with age, waist circumference, and BMI (p<0.0001, p=0.002, and p<0.0001). However, there was no significant correlation between eGFR and systolic blood pressure (SBP), and diastolic blood pressure (DBP) (p=0.073, p=0.694). Subsequent correlation analysis, with age been controlled as a possible confounder showed a positive correlation between BMI, WC and, eGFR (p<0.0001 and p<0.0001). Also when blood pressure was controlled, there was also a statistically significant correlation between WC, BMI, and eGFR (p<0.0001, p<0.0001).

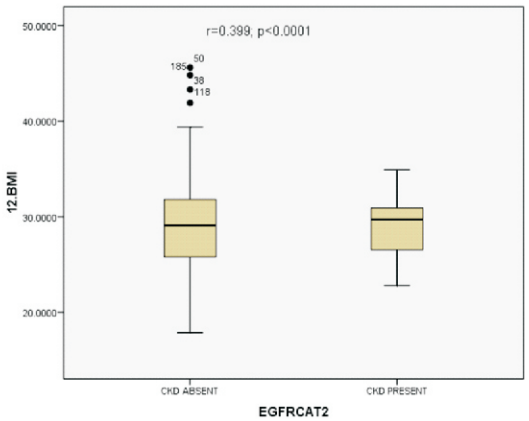

Fig 3: Relationship between CKD and BMI

Subsequently, stepwise multiple regression analysis was performed using age, BMI, SBP, and WC. As a result age, systolic blood pressure, WC, and BMI were included in the model as independent variables that interacted on eGFR. The variables combined explained 38.9% of the variance observed (F=26.049, p<0.001). Among the indices of adiposity, BMI was more strongly predictive of eGFR than WC (β= 0.468, p<0.0001 vs. β=-0.031, p=0.761).

When binary logistic regression analysis of the whole population was performed after adjusting age, BMI, waist circumference, DBP, the association between waist circumference and renal function was significant. In this model, the odds ratio (95% CI) of the covariates was as follows: age 1.17 (1.09-1.25), p<0.001; waist circumference 1.10 (1.01-1.20), p=0.029; DBP 1.00 (0.96-1.05), p=0.775; BMI 0.79 (0.62-1.00), p=0.054. (Table 5)

TABLE 1: BASELINE CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Variables	Hypertensives (n=144) Mean±SD	Controls (n=72) Mean±SD	t-test p-value
AGE (Years)	51.40±12.90	48.47±12.89	0.0118*
BMI (Kg/m²)	29.47±4.87	27.17±4.98	0.001*
WC (cm)	97.51±11.92	86.11±18.69	<0.0001*
SBP (mmHg)	149.00±22.50	115.00±11.26	<0.0001*
DBP (mmHg)	92.95±13.62	70.61±9.12	<0.0001*
Cr (µmol/l)	92.90±20.40	87.28±13.90	0.035*
eGFR (ml/min/1.73m²)	91.23±30.54	102.94±21.72	0.010*

BMI=Body mass index; WC=waist circumference; SBP=systolic blood pressure; DBP=diastolic blood pressure; Cr=creatinine; eGFR=estimated glomerular filtration rate. *=Significant p value

TABLE 2: BASELINE CLINICAL CHARACTERISTICS OF STUDY POPULATION ACCORDING TO CKD STAGES

Variables	(n=87) CKD 1 Mean±SD	(n=68) CKD 2 Mean±SD	(n=12) CKD3A Mean±SD	(n=3) CKD3B Mean±SD	ANOVA P value
AGE (Years)	47.18±9.15	52.09±11.85	66.25±12.69	73.33±2.89	<0.0001*
WC (cm)	98.16±13.87	91.84±11.54	102.83±11.46	87.67±5.77	0.003*
BMI (Kg/m²)	30.88±4.98	27.28±4.66	29.60±3.34	27.40±3.98	<0.0001*
SBP (mmHg)	131.11±23.05	139.21±24.20	145.0±25.76	148.33±20.21	0.062
DBP (mmHg)	83.28±17.05	84.56±16.41	85.00±11.68	90.00±17.32	0.876
Cr(µmol/L)	82.75±14.19	101.34±18.82	109.33±11.94	108.00±10.39	<0.001*
eGFR (ml/min/1.73m²)	117.87±18.56	76.21±9.57	53.75±4.40	39.37±6.64	<0.001*

BMI=Body mass index; WC=waist circumference; SBP=systolic blood pressure; DBP=diastolic blood pressure; Cr=creatinine; eGFR=estimated glomerular filtration rate. *=Significant p value

TABLE 3: PREVALENCE OF ABDOMINAL OBESITY ACCORDING TO CKD STAGES

VARIABLE	Overall Prevalence of obesity	CKD 1	CKD 2	CKD 3A	CKD 3B	Fischer value	Fischer test p value
Abdominal obesity	50.9%	59.3%	30.2%	8.1%	2.3%	7.423	0.043*
Non-obese		42.2%	50.6%	6.0%	1.2%		

TABLE 4: BASELINE CLINICAL CHARACTERISTICS OF THE SUBJECTS WITH RESPECT TO OBESITY

Variables	Obesity Present	Obesity Absent	t-test p-value
Age (Years)	51.72±11.19	49.16±14.56	0.150
BMI (kg/m²)	31.86±4.45	25.44±3.20	<0.0001*
WC (cm)	103.70±9.48	83.49±13.33	<0.0001*
SBP (mmHg)	140.34±23.93	135.15±26.54	0.134
DBP (mmHg)	89.40±16.62	81.56±14.94	<0.0001*
eGFR (ml/min/1.73m²)	100.52±29.81	89.55±25.63	0.011*

BMI=Body mass index; WC=waist circumference; SBP=systolic blood pressure; DBP=diastolic blood pressure; Cr=creatinine; eGFR=estimated glomerular filtration rate. *=Significant p value

Table 5: LOGISTIC REGRESSION ANALYSIS OF THE STUDY POPULATION ADJUSTING FOR CONFOUNDERS

VARIABLES	OR	P-VALUE	95% CI
BMI	0.79	0.054	0.626-1.004
DBP	1.00	0.775	0.964-1.050
WC	1.10	0.029*	1.010-1.201
AGE	1.17	<0.0001*	1.091-1.252

BMI=Body mass index; WC=waist circumference; SBP=systolic blood pressure; DBP=diastolic blood pressure. *=Significant p value

DISCUSSION

We investigated the relationship between the markers of adiposity and renal function in hypertensive, and apparently healthy individuals. Our results indicate that there was an association between obesity and CKD. We found that more of the obese subjects were in advanced CKD than the non-obese subjects. This finding was in concert with those reported by Oh *et al*, and Stefansson *et al*[23,24] Several mechanisms have been advanced to explain this association. Obesity is widely known to increase nephron loss by renal hyperfiltration, which leads to increase in intraglomeular pressure, glomerulosclerosis, and loss of GFR over time. The mechanism of hyperfiltration is highlighted in this study by the significantly higher eGFR levels recorded in the obese subjects (See Table 4). Obesity is also strongly associated with the secretion of diverse pro-atherogenic and inflammatory cytokines such as leptin, adiponectin, interlukin-6, tumor necrotic factor-α, aldosterone, which are known to cause renal fibrosis, contributing to the development of CKD.[25-27]

The higher risk of CKD could also be due other specific pathologic changes seen in obese individuals such as ectopic lipid accumulation,[28] the development of glomerulomegaly[29] and focal or segmental glomerulosclerosis.[30]

In addition to increased renal hyperfiltration consequent on obesity, increased adiposity also increases the risk of the development of hypertension. The factors generally considered responsible for obesity-related alterations in the pressure-natriuresis curve include enhanced sympathetic tone, activation of the renin-angiotensin system (RAS), hyperinsulinemia, structural changes in the kidney, and elaboration of adipokines such as leptin. 6 Similarly, leptin, a hormone produced in fat activates the sympathetic nervous system to cause hypertension. To buttress this hypothesis, leptin-induced hypertension has been experimentally prevented in animal models by combined α- and β-sympathetic blockade. This and other findings strongly suggest that leptin contributes to obesity hypertension primarily through sympathetic activation. The effects of sympathetic activation in obesity hypertension seem to be related to activation of renal nerve traffic and to subsequent alteration of the pressure-natriuresis relationship.[31,32]

There is also elevation of renin activity observed in obesity due to the increased of sympathetic activity. This translates to elevations in angiotensin II which directly increase renal tubular reabsorption of sodium and stimulate synthesis of the sodium-retaining hormone aldosterone. Aldosterone is known to act on angiotensin II type 1 (AT 1) receptors which induces a state of oxidative stress, inflammation, and fibrosis in the renal parenchyma leading to renal impairment.[33]

We also found in this study that the hypertensive-obese subjects were more likely to be in more advanced CKD stages than the normotensive-obese cohorts. This is to be expected, because obesity is often known to co-exist with other cardiovascular disease risk factors, such as hypertension, diabetes and dyslipidemias. The multiplier effect of the interplay of these risk factors invariably drives the progression of CKD. Obesity raises blood pressure by increasing renal tubular sodium reabsorption, impairing pressure natriuresis, and causing volume expansion via activation of the sympathetic nervous system and renin–angiotensin–aldosterone system and by physical compression of the kidneys, especially when there is increased visceral adiposity[34,35]

On further analysis, we found that there were significant associations between declining GFR and BMI, WC, and age. These markers of adiposity were consistently related to GFR even after they were controlled for age and blood pressure. These findings are in agreement with that reported by Oh *et al*[23] This goes to further highlight the independent deleterious consequences of obesity.

Comparisons of BMI with outcomes such as CKD have produced conflicting results and can be confounded by differences in regional or ectopic fat deposition or differences in muscle mass, which can be affected by aging. As, BMI does not discriminate between fat mass and muscle mass, or does not reflect fat distribution; individuals who are

exceptionally muscular could be classified as obese on the basis of BMI alone. The effect of BMI on CKD could therefore be attenuated when the confounding effect of age was controlled, since it is recognized that in general, muscle mass and muscle strength decrease with age. A study reported that the muscle mass of an elderly man aged 70 years is approximately 15% less than that of an adult aged 20 years.[36]

When the variables were however included in a binary logistic regression model, we found that only waist circumference [OR 1.10] and age [OR 1.17] retained their statistical significance. This result was similar to the result published by Gomez et al in Madrid, where they found that abdominal obesity was associated with a higher risk of renal insufficiency (OR 1.40), even after adjustment for other components of the metabolic syndrome, such as dyslipidemia, hyperglycemia, hypertension, and BMI in patients with essential hypertension.[37] Likewise, the ARIC study and Cardiovascular Health Study demonstrated that waist-to-hip ratio (WHR) – a marker of central obesity, but not BMI positively correlated with a greater risk of CKD.[18,19]

CONCLUSION

In conclusion, our data supports the evidence that obesity may be a risk factor for impaired renal function. We also found that central obesity may be a better predictor of renal function decline than BMI. Further studies in a larger population are warranted to confirm our finding.

Limitations

1. This was a cross-sectional study and thus could not prove causation, only correlation.
2. Obesity was measured indirectly with anthropometric data, and not directly with gold standard dual energy X-ray absorptiometry, computed tomography or magnetic resonance imaging methods.

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