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AN ASSESSMENT OF FACTORS INFLUENCING RESISTIVITY AND PULSATILITY INDICES IN DIABETES MELLITUS

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Abstract

Background: Diabetic nephropathy (DN) is a common complication of diabetes mellitus, accounting for more than 25% of all end stage renal diseases and is the third most common cause of ESRD in sub-Saharan Africa. It has been shown that assessment of renal Doppler indices such as Resistivity Index (RI) and Pulsatility Index (PI) are effective methods of assessing renal functional status thus complementing use of laboratory values and other imaging modalities. In this study we assessed the effects of age, sex, hypertension and disease duration on renal Doppler indices in diabetic subjects.

Subjects and Methods: Eighty adult diabetic subjects were recruited consecutively along with 80 apparently healthy non diabetic controls matched for age, sex and body mass index (BMI).

They were taken through socio-demographic, clinical and laboratory evaluation to assess BMI, Blood Pressure, Glycated Haemoglobin, etc. Thereafter pulsed Doppler indices (RI and PI) of the right renal artery were obtained from the spectral waveform of the interlobar or arcuate arteries at 3 different regions (upper, middle and lower poles) and the mean values recorded during arrested respiration. Doppler evaluations were performed by one investigator who was blinded to the biochemical parameters obtained from all study subjects. Data was analysed using SPSS package version 17.

Results: The mean RI and PI values were significantly higher in diabetic patients than in controls (RI of 0.72 ± 0.06 Vs 0.63 ± 0.06, P < 0.0001) and (PI of 1.36 ± 0.24 Vs 1.08 ± 0.20, P< 0.0001). There was a graded increase in the mean values of the RI and PI with advancing age in diabetics as well as in controls. Significant positive correlation was also noted between the subjects ages and the renal Doppler values (p <0.05). Duration of diabetes as well as that of hypertension had a significant impact on the Doppler indices (RI and PI) which progressively increased with increasing duration. Gender did not have any influence on the renal Doppler indices.

Conclusion: Renal RI and PI were significantly higher in diabetics as compared to the control subjects. Age caused a significant increase in renal PI values in both the diabetic and control groups but only in the renal arterial RI values in the control group when the age grouping method was used. Hypertension and disease duration were also noted to significant increase in renal Doppler indices in the diabetic subjects.

Key words: Diabetes, Nephropathy, renal Doppler ultrasound, resistivity index, pulsatility index

INTRODUCTION

Diabetic nephropathy (DN) is a common complication of diabetes mellitus and is defined clinically by the presence of persistently positive urine dipstick test for albumin (2 or more positive tests obtained at least 3 months apart) in a person with diabetes mellitus (or a urinary albumin excretion rate of >0.3g per day

equivalent to >30mg/g of albumin-creatinine ratio) in the absence of other renal diseases. [1]

Diabetic nephropathy usually affects both kidneys simultaneously and accounts for more than 25% of all end stage renal diseases.[2] The prevalence of clinical DN is reported to be between 15 and 40% globally.[3,4] In fact, it is the third most common cause of ESRD in sub-Saharan Africa, with chronic glomerulonephritis and hypertension being more prevalent.[5]

Detection of the early changes of diabetic nephropathy has therefore been a subject of great interest, so that measures can be initiated to prevent progression of the disease. Recent studies have shown that Doppler ultrasound evaluation of the renal vessels using Resistive (RI) and Pulsatility indices (PI) are effective methods of assessing renal functional status as compared with use of laboratory values along with the use of other imaging modalities[6]. The indices can also be used to predict subjects at high risk of nephropathy and other possible disease outcomes .[6] A study by Ishimura et al[7] showed that intra renal RI values can be used as markers of systemic atherosclerosis which may be caused or modified by factors such as hypertension, dyslipidemias, diabetes, aging, and smoking. The Doppler parameters that are reliably used mostly in assessing the intra vascular resistance of vessels are resistivity and pulsatility indices. The arterial resistivity index (RI) developed by Pourcelot L [8] is a measure of pulsatile blood flow that reflects the resistance to blood flow caused by microvascular bed distal to the site of measurement while Pulsatility index (PI) is a measure of the variability of blood velocity in a vessel.[8] The RI can be calculated from spectral measurements by using the equation RI = (PSV − EDV)/PSV, where PSV is the peak systolic velocity and EDV is the end-diastolic velocity.[9] The PI is calculated from the equation PI = (PSV − EDV)/MV, where MV is the mean flow velocity during the cardiac cycle. . Sociodemographic variables variables like age and gender have been reported to influence these Doppler indices.[10, 11]

This study was embarked upon to assess the impact of sociodemographic and some clinical factors on renal Doppler indices in Nigerian subjects with diabetes.

Subjects and Methods

This case-controlled prospective study was carried out between June 2012 and May 2013 at the Department of Radiology. The study was carried out on 80 adult subjects, aged 30 years and above diagnosed as having type 2 Diabetes mellitus, who were recruited consecutively from the Endocrinology Medical Out-Patient Unit of the Department of Medicine. Eighty apparently healthy non diabetic subjects matched by age, sex and body mass index (BMI) were used as controls. Subjects with heart disease, renal disease, congenital anomalies, urinary tract infection, renal replacement therapy, sickle cell disease, hypertension, dyslipidaemia and renal artery stenosis were excluded. Subjects on insulin therapy as well as those with history of smoking, were also excluded from the study.

Ethical approval was obtained from Ethical and Research committee of the hospital and each subject gave a written informed consent to participate in the study. The socio-demographic data was obtained from all subjects and controls, these included age and sex, height, weight and body mass index (BMI). The respective BMI was then calculated using the formula: BMI= Weight in kilograms (Kg)/ Height x Height (m^2). The duration of diagnosis and presence of superimposed hypertension in the study subjects were also documented. Based on the duration of the diagnosis of the disease, study subjects were subdivided into four groups, which were those with duration less than 5 years, 5 to 10 years, 10-15 years and greater than 15 years duration.

Relevant history and examination of subjects to identify exclusion criteria were performed as well as well as review of patient's records where available.

Diabetes mellitus was diagnosed based on a previous history of diabetes and/or using the the WHO guideline.[12] Blood samples were

collected after an overnight fast for at least 8 hours, before Doppler study of the renal artery was done, to assess fasting blood sugar (FBS), lipid profile and glycated haemoglobin levels. The subjects' blood pressures were taken with a mercury sphygmanometer after 5 minutes of rest just before the Doppler study began and then 5 minutes after completion of the Doppler study.

A B-mode renal ultrasonography was first done to assess for the presence of congenital anomalies, infection, hydronephrosis and space occupying lesions. This was followed by a colour coded duplex ultrasound interrogation to localize the two renal arteries which were screened for features of renal artery stenosis following which pulsed Doppler indices (RI and PI) of the right renal artery were obtained, as studies have shown there is no significant difference between the RI and PI values of the right and left kidneys.[7] The Doppler indices were obtained from the spectral waveform of the interlobar or arcuate arteries in the right kidney at 3 different regions (upper, middle and lower poles) and the mean values recorded during arrested respiration. The Doppler sample volume was set at 2-4mm gate just appropriate to be placed in the mid portion of the diameter of the vessel to be insonated and the waveforms were optimized for measurement. Because of the variability of renal Doppler indices with cardiac cycle, a minimum of four identical consecutive spectral waveforms were obtained for analysis of the RI and the PI values. Manual tracing of the identical waveforms was done to obtain the Doppler indices.

Resistivity index values higher than 0.70 were considered abnormal.[10] A PI range of 0.96-1.18 was considered normal while values more than 1.2 were considered abnormal.[7] The ultrasound examination was carried out by one investigator who was blinded to the clinical and biochemical parameters of subjects. The use of antihypertensive and/or oral hypoglycaemic medications was not suspended before the Doppler indices were measured.

Statistical Package for Social Science (SPSS) for windows (SPSS Inc, USA Version 17.0) was used to analyze the data using appropriate descriptive and inferential statistics. Data were reported as mean and standard deviation (mean ± SD) for continuous variables. Independent Student *t* test was used to compare parametric values, whereas one way analysis of variance (ANOVA) was used to compare means of variables where there were three or more groups. Pearson's correlation coefficient was used to assess relationships between independent continuous variables. Statistical significance was set at $p < 0.05$.

Results

A total of 160 subjects were studied, which included 80 diabetic subjects and 80 age and sex matched healthy controls. The mean age, as shown in Table 1, for the diabetic subjects was 59.1 ± 9.9 years while that of the control group was 57.4 ± 10.1 years (p = 0.281). The total number of males was 34 (42.5%) as study subjects and 36 (45.0%) as controls while the female population comprises of 46 (57.5%) number of study subjects and 44 (55.0%) as controls. There was no significant difference (p=0.873) in proportion of the male and female population recruited for the study (Table 1). There was a significant difference in the mean fasting blood sugar level between the diabetics and controls with mean values of 7.83 ± 2.33mmol/l and 5.47 ±0.58 mmol/l respectively (p < 0.0001). The diabetic group had a mean HbA1c value of 7.2 ±1.7%.

Table 1: Table Showing Characteristics of Subjects

Characteristic	Diabetics (n = 80)	Controls (n = 80)	P value
Age (yrs) (mean SD)[†]	59.06 ± 9.88	57.35 ± 10.13	0.281
Male	59.29 ± 9.41	59.03 ± 11.54	0.916
Female	58.90 ± 10.31	55.98 ± 8.72	0.152
Age group (yrs) *n (%)*[‡]			
30 -39	1 (1.3)	2 (2.5)	
40 – 49	13 (16.3)	16 (20.0)	0.828
50 – 59	27 (33.8)	30 (37.5)	
60 – 69	27 (33.8)	22 (27.5)	
≥ 70	12 (15.0)	10 (12.5)	
Gender *n (%)*			
Male	34 (42.5)	36 (45.0)	0.873
Female	46 (57.5)	44 (55.0)	
BMI (Kg/m^2) **(mean ± SD)**	**27.66 ±** 5.42	26.57 ± 5.03	**0.11**
Systolic BP(mmHg)	127.89 ± 13.15	123.89 ± 13.15	**0.019**
Diastolic BP(mmHg)	76.58 ± 8.41	80.56 ± 5.60	**0.001**

The mean RI value of the diabetic patients was 0.72 ± 0.06 while that of the control group was 0.63 ± 0.06 ($p < 0.0001$). The mean value of PI was 1.36 ± 0.24 among the diabetic patients and 1.08 ± 0.20 in the control group ($p< 0.0001$).

Table 2: A table of ANOVA showing the relationship between several means of RI and PI by age of the studied population

	Mean RI ± SD	P value	Mean PI ± SD	P value
Diabetics				
30-39	0.67 ± 0.00		1.24 ± 0.00	
40-49	0.70 ± 0.04		1.31 ± 0.16	
50-59	0.71 ± 0.05	0.068	1.26 ± 0.16	0.015
60-69	0.75 ± 0.08		1.42 ± 0.33	
≥ 70	0.75 ± 0.03		1.51 ± 0.15	
Controls				
30-39	0.56 ± 0.01		0.94 ± 0.18	
40-49	0.58 ± 0.04		0.94 ± 0.22	
50-59	0.62 ± 0.05	<0.0001	1.04 ± 0.14	<0.0001
60-69	0.66 ± 0.05		1.13 ± 0.16	
≥ 70	0.69 ± 0.06		1.32 ± 0.18	

A one way analysis of variance (ANOVA) among study subjects is shown in Table 2 and it shows a graded increase in the mean values of the RI and PI with advancing age for diabetics as well as controls. The group differences in RI values among diabetic subjects were not statistically significant (p=0.068) but PI values were significantly higher with advancing age (p = 0.015) whereas for the control group both RI and PI significantly increased with ageing (p <0.0001).The Scheffe post hoc analysis for the control group shows the difference lies in comparing age groups 40 - 49 and 60 - 69 years (p <0.05), 40 - 49 and 70 - 79 years (p =0.0001) and age groups 50 - 59 and 70 – 79 years (p <0.05). The Scheffe post hoc analysis shows significant difference among age groups for the diabetic subjects as follows; 40s and 70s (p =0.004), 50s and 60s (p =0.028) as well as 50s and 70s (p<0.0001). The levels of significant differences among control groups were between 40s and 60s (p =0.025), 40s and 70s (p<0.0001) and group of 50s and 70s (p =0.001). The correlation 'r' values were noted to be 0.316 (p = 0.04) between the age and mean RI in the diabetics (Fig. 1); 0.339 (p = 0.03) between the age and mean PI in the diabetics (Fig. 2); 0.588 (p = 0.000) between the age and mean RI in the controls; and 0.508 (p = 0.000) between the age and the mean RI in the controls.

. The RI values were 0.72 ± 0.06 for the males and 0.73 ± 0.07 for the females (p=0.656) while the mean PI values were 1.35 ± 0.20 for the male population and 1.37 ± 0.27 for the females (p=0.692).

The controls had RI as 0.63 ± 0.06 for males and 0.62 ± 0.06 for the females (p=0.359) while the PI was 1.10 ± 0.19 for the males and 1.06 ± 0.21 for the females (p=0.316). There was however no significant difference in the Doppler indices between males and females in the diabetic and control groups.

Mean value of RI in this group was 0.75 ± 0.06. The diabetic subjects that had normal blood pressure since diagnosis of the disease were 42 (52.5%) in number and had a mean RI value of 0.71 ± 0.06. The mean value of PI for the diabetics was 1.44 ± 0.26 and for the control group was 1.29 ± 0.21. Comparisons of the RI and PI between the 2 groups of subjects showed statistically significant differences (p<0.05).

Table 3: A table of showing differences in Mean RI and PI by duration of DM and HTN in diabetics

Scheffe *post hoc* analysis for inter-group differences of RI in controls

30s vs. 40s; p = 0.987

30s vs. 50s; p = 0.634

30s vs. 60s; p = 0.165

30s vs. 70s+; p = 0.021

40s vs. 50s; p = 0.237

40s vs. 60s; p = 0.001

40s vs. 70s+; p = 0.000

50s vs. 60s; p = 0.150

50s vs. 70s+; p = 0.003

60s vs. 70s+; p = 0.362

Duration of diabetes had a significant impact on the Doppler indices with a significant difference among the different duration groups for RI (p = 0.009) and for PI (p = 0.020). The RI increases in a nonlinear fashion with increasing duration of DM and hypertension as follows: 0.70 ± 0.05 for < 5 years duration, 0.75 ± 0.07 for those between 5-10 years and 0.76 ± 0.05 for those who had the disease for more than 15 years. The post-hoc statistical analysis only showed significant difference between those with diabetes duration of less than 5 years and those between 5-10 years (p<0.05). The hypertensive group had RI of 0.74 ± 0.07 for those with less than 5 years duration, 0.75 ± 0.05 for those between 5- 10 years and 0.76 ± 0.06 for more than 10 years (Tab. 3). A significant positive correlation was noted between duration of diabetes and renal RI with an r value of 0.29 (p = 0.009); the correlation between duration of diabetes and renal PI with r value of 0.19 was however not significant (p = 0.09). These are illustrated as scatterplots on Fig. 3 and 4 respectively.

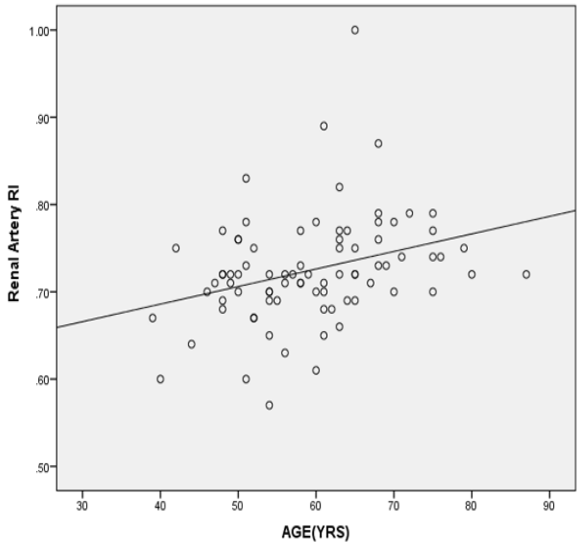

Fig. 1: A scatterplot illustrating the relationshi between diabetic subjects' age and renal artery RI (r = 0.316, *p* = 0.04)

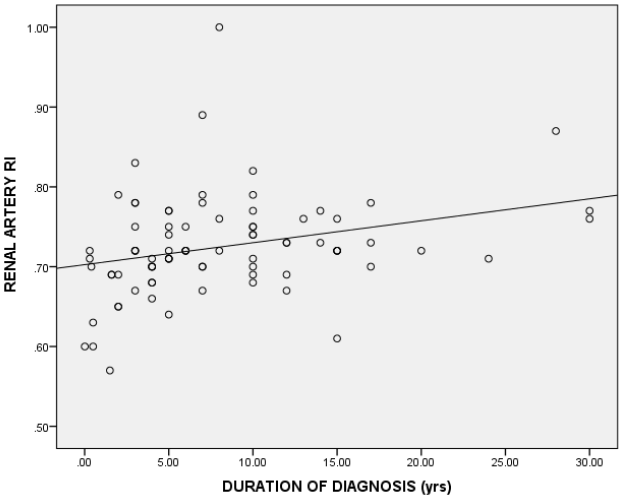

Fig. 3: A scatterplot illustrating the correlation between duration of diagnosis in years and renal artery RI (r = 0.29, *p* = 0.009)

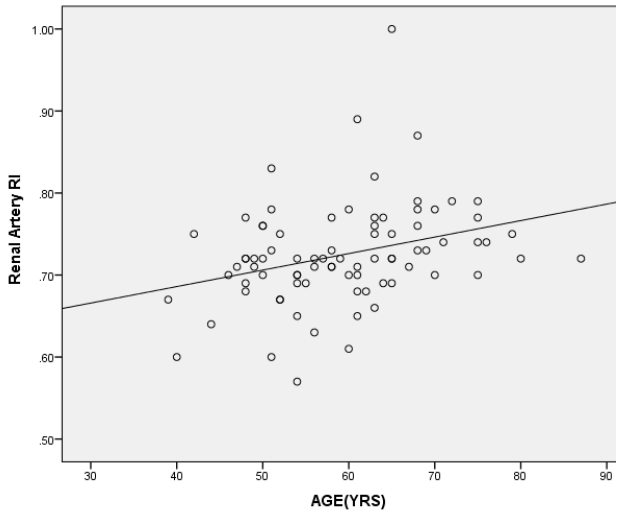

Fig. 2: A scatterplot illustrating the relationship between diabetic subjects' age and renal artery PI (r = 0.339, *p* =0.03)

The mean PI values are as follows : 1.29 ± 0.21 for < 5 years duration of DM, 1.47 ± 0.28 for those between 5-10 years, 1.30 ± 0.17 for 10-15 years of diabetes and 1.42 ± 0.26 for greater than 15 years duration. The post-hoc analysis showed statistical difference between those with diabetes duration of less than 5 years and those between 5-10 years ($p<0.05$). The hypertensive group has 1.42 ± 0.31 for < 5years duration, 1.41 ± 0.24 for 5-10 years duration and 1.51 ± 0.17 for more than 10 years.

There were no significant differences in group mean values of doppler indices with varying durations of hypertension (p = 0.745 for RI, p = 0.660 for PI).

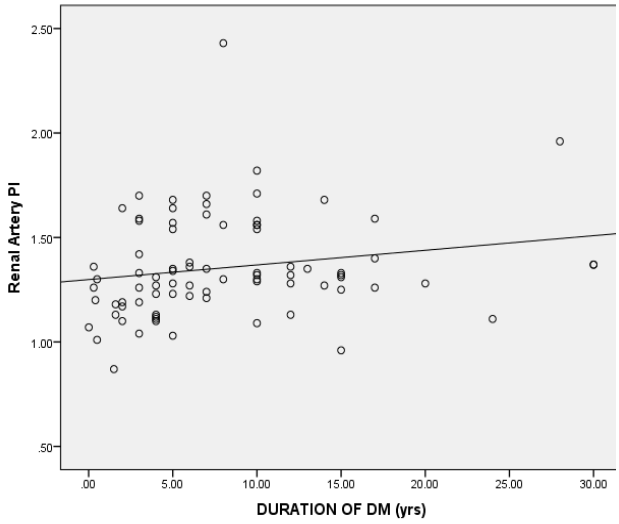

Fig. 4: A scatterplot illustrating the correlation between duration of diagnosis in years and renal artery PI (r = 0.19, *p* = 0.09)

DISCUSSION

Duplex ultrasound scan of the kidneys has become an integral part of the management of diabetes related renal complications and is used in the diagnosis, staging, and prognostication of diabetic nephropathy. The use of Doppler ultrasound scan also makes it possible to evaluate and monitor the renal vascular system adequately for early changes in the physiologic haemodynamics of DN defined by the presence of increase in urinary albumin excretion and renal insufficiency.[7,13] Some factors are known to influence renal Doppler indices and thus could significantly impart on the interpretation of the values. Some socio-demographic parameters have been found to directly or indirectly transform renal arterial Doppler values and as such caution has to be exercised in the interpretation of some values obtained.[7,10]

The Doppler RI and PI values were noted to increase steadily with advancing age in both the diabetic and control populations. Analysis of variance (Tab. 2) however showed no statistically significant difference in the mean RI between the diabetic age group (p >0.05), but differences in Doppler indices were found to be significant among the controls (p <0.05). Similar findings were noted in the PI values of the diabetic and control populations. The increases in Doppler indices values with increasing age agrees with previous studies.[7,10] There is an age dependent increase in RI and PI values in normal subjects. The diabetic population also showed a similar pattern of results with reference to the PI values. Age was also noted to be an important variable affecting the RI in other studies done by Thukral et al[15] and Ishimura et al.[7] The marked effect of age on Doppler indices values seen in other studies and in the control group of index study may be explained by the increasing occurrence of atherosclerosis with age thus increasing the renal vascular resistance.[16] Diabetes is a well-recognized risk factor for atherosclerosis hence the similar pattern observed.

The diabetic subjects with concomitant hypertension had significantly higher RI and PI values compared to the those without hypertension. (p < 0.05). This would likely be due to the confounding effect of the hypertension in causing atherosclerosis and vessel wall stiffening which ultimately increases the vascular resistance.[14]

The duration of the disease diagnosis in study subjects ranged from 1day to 30 years. The lower limit of this range can be explained by the fact that some study subjects were incidentally discovered at screening for control subject recruitment. Other factors such as drug type and compliance and associated co-morbidities may play significant roles but were not assessed in this study. Thukral et al[15] however did not find any correlation between the duration of diabetes and the Doppler indices.

Conclusion

Renal Doppler indices (RI and PI) were significantly higher in diabetics than in control subjects. There is graded age dependent increase in RI and PI in diabetics and in control

subjects. This study also found that with increase in disease duration, the renal Doppler indices tend to increase in diabetics and the development of hypertension in diabetics further worsens renal Doppler indices. The clinical implication of this is that older patients with diabetes are at a higher risk of developing nephropathy along with subjects with long standing disease.

As a small sample population was recruited in this study, a community based study of a larger population may be essential to further assess the impact of socio-demographic factors and disease duration on renal Doppler indices.

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