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Relationship between Intra-renal Resistive Index and Markers of Renal Function Status in Type 2 Diabetic Patients in Southern Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Diabetes mellitus (DM) is a chronic condition requiring global attention. Renal microangiopathy is a life-threatening microvascular complication often leading to derangements in renal function and progressive renal failure. Renal haemodynamic assessment by duplex Doppler ultrasound scan is a non-invasive method of assessing blood flow resistance within the renal vessels. The intra-renal resistive index (IRI) may be a useful tool in predicting pathological derangements of renal functions in diabetic patients.

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Materials and Methods: The study was a cross-sectional study involving 142 consecutive adults with type 2 DM enrolled from December 2017–December 2018. Study approval was obtained from the Ethical and Research Committee of the hospital. Urinalysis, spot urine albumin-to-creatinine ratio (UACR), serum creatinine levels were assessed and glomerular filtration rate estimated using Modification of Diet in Renal Disease equation. All participants had duplex Doppler ultrasound of both kidneys to obtain flow velocities from their interlobar arteries for IRI estimation. Results were analysed with Statistical package for social sciences (SPSS version 23) software.
Results: The study comprised of 87 (61.3%) females and 55 (38.7%) males with a mean age of 55.90±11.02 years. Mean duration of diabetes was 9.60±7.05 years. Mean estimated glomerular filtration rate (eGFR) was 79.18±27.69ml/min/1.73m^2, with 31 (21.8%) having their eGFR ≤60mls/min/1.73m^2. The mean UACR was 153.65±145.56mg/g with 123 (86.6%) participants having moderate to severe albuminuria The mean average IRI was 0.60±0.09. Participants with diabetic nephropathy (DN) had higher IRI than those without DN ($p<0.005$). Increased IRI was observed in 36(25.3%) of participants. IRI positively correlated with UACR ($p < 0.001$) and negatively correlated with eGFR ($p < 0.001$) and demonstrated a linear relationship with both UACR and eGFR. Increased IRI was associated with duration of diabetes and age.
Conclusion: IRI may be a useful non-invasive tool for early detection and risk prediction of DN.

Keywords: Diabetic nephropathy; intra-renal resistive index; urine albumin-creatinine ratio; renal function status.

1. INTRODUCTION

The World Health Organisation targets to reduce non-communicable diseases (NCDs) by a third by year 2030 [1]. Diabetes mellitus (DM) is a major NCD recognised as a "public health emergency in slow motion" [2] with reports of a rising prevalence [3,4]. Diabetic nephropathy (DN) is defined as a clinical syndrome characterised by persistent albuminuria (≥300mg/day or >200µg/min) that is confirmed on at least 2 occasions 3-6 months apart, a progressive decline in the glomerular filtration rate (GFR) and an elevated systemic arterial blood pressure [5]. DN can also be defined based on urine albumin–creatinine ratio ≥30mg/g of creatinine in the absence of other renal disease [6].

Diabetic Nephropathy is the single most common cause of end-stage renal disease (ESRD) [7] worldwide with a prevalence ranging between 15- 40% among patients with ESRD [8,9]. In Sub-Saharan Africa (SSA) including Nigeria it is the third most common cause of ESRD with chronic glomerulonephritis (CGN) and hypertension being more prevalent [10]. An estimated 9.2% of the overall adult diabetic population in Nigeria had DN as a complication [11]. Racial differences in prevalence have been reported [12-15] possibly due to socio-economic or environmental factors, barrier to care, adoption of western diet/lifestyle and some polygenetic predispositions [16,17].

The earliest clinical evidence of nephropathy is the development of micro-albuminuria [18] with a progressive GFR decline [19] with or without characteristic renal histopathology changes [20,21]. Renal histopathology is however indicated in suspected cases of non-diabetic renal disease in diabetic patients [22,23]. Biomarker identification with potential for early diagnosis and risk stratification of DN are ongoing, however none have out-performed micro-albumin in a larger scale [24].

Diabetes mellitus alters vascular resistance in the kidneys [25,26]. The intra-renal resistive index (IRI) is commonly used as an index of intra-renal arterial resistance and may enhance the quality of diagnosis and measure of severity of DN and patient prognosis [27-29]. Intra-renal resistive index (IRI) may therefore serve as a useful non-invasive tool for early diagnosis, measure of progression as well as predict outcome in DN [25-28].

This study intends to assess the usefulness of intra-renal resistive index as a non-invasive tool for prediction and early diagnosis of DN compared to conventionally used serum creatinine levels and urine albumin-creatinine ratio.

2. MATERIALS AND METHODS

This study was conducted in the clinics and wards of the Department of Internal Medicine, University of Port Harcourt Teaching Hospital

(UPTH) Rivers State, Nigeria from December 2017 to December 2018.

The study was a cross-sectional study comprising 142 consecutive adults living with type 2 diabetes attending medical consultant clinics (Endocrine / Metabolic clinic and Renal clinic) and those admitted into the medical wards of the hospital who gave informed consent. The exclusion criteria included type 2 diabetic patients with (i) urinary evidence of other causes of chronic kidney disease e.g., haematuria, red cell casts, white cell casts, tubular casts etc. (ii) Patients with renal vascular pathologies (iii) Patients with intra-abdominal space occupying lesions compressing the kidneys or renal neoplasm. (iv) Patients with obstructive uropathy. (v) Patients who have undergone renal transplant. (vi) Patients with uraemia and CKD stage 5. (vii) Patients with HIV-associated nephropathy (HIVAN). (viii) Patients who are pregnant. (ix) Patients with previous history of ischaemic heart disease, stroke or peripheral vascular disease.

All 142 participants were subjected to detailed history, physical examination, relevant biochemical analysis, renal ultrasound scan and renal duplex Doppler scan. Clinical information retrieved from above exercise were entered into a proforma and data sheet. Anthropometric measurements such as weight, height was measured. Weight was measured in kilograms to the nearest 0.5kg using a balance weighing bathroom scale with subjects in minimal light clothing and their shoes removed. Height was measured in metres to the nearest 0.5metres using a stadiometer, with the patient standing upright, feet together, without shoes or head covers. The body mass index (BMI) was calculated using the formula BMI =Weight in Kilograms (Kg) / Height^2 in metre^2 (m^2).

Diabetes mellitus was diagnosed based on previous history and treatment of diabetes and/or using the WHO guideline [30] of a fasting plasma glucose of ≥7.0mmol/L (126mg/dl) or a 2 hours post prandial or oral glucose tolerance test (OGTT) of 11.1mmol/L (≥200mg/dl) or HbA1c of ≥6.5%.

Blood pressure was measured using Vintage Accoson® mercury sphygmomanometer with the patient in both supine and sitting positions after a 5-10minute rest and confirmation that the patient avoided exercise, caffeine and smoking 30 minutes before measurement. A cuff of appropriate size was wrapped around the proximal two-thirds of the upper arm (supported at heart level) and inflated 20mmHg above the level where the radial pulse could no longer be palpated. Systolic and diastolic blood pressure (BP) levels were taken at the first and fifth korotkoff sounds respectively. Hypertension was defined as BP ≥140/90mmHg using the JNC-7 guideline for diagnosis and classification of hypertension [31].

10 millilitres of random spot urine of each participant were collected into a sterile urine bottle. 5 millilitres of the urine sample analysed for urine specific gravity, pH and presence of protein, red or white cell casts. Participants' urine with presence of red cell casts were excluded from the study. The remaining 5 millilitres of the urine sample collected from each participant who meet the inclusion criteria had their urine albumin-creatinine ratio (UACR) determined using MICROALBUMIN (Immunoturbidimetric) test kit (Fortress diagnostics limited, Antrim, Northern Ireland, United Kingdom). UACR was calculated as albumin (mg) /creatinine (g). Normo-albuminuria, micro-albuminuria and macro-albuminuria was defined as UACR of <30 mg/g, 30 - 300 mg/g and >300 mg/g respectively. All urine samples were analysed in the Research laboratory of UPTH by the investigator and the laboratory scientist.

Ten millilitres (10mls) of venous blood were drawn from all patients using a suitable vein, with a loose-fitting tourniquet after an overnight fast of about 8-12 hours. 2.0ml into fluoride oxalate bottle for fasting glucose estimation, 3.0ml into ethylenediaminetetrachloroacetic acid bottle for glycosylated haemoglobin (HbA1c) level estimation while 5.0ml into lithium heparin bottle for serum electrolytes, bicarbonates, urea and creatinine as well as fasting lipid profile (which includes total cholesterol, triglycerides, low density lipoproteins and high-density lipoproteins) and uric acid estimation. All blood samples were analysed by the Research laboratory of UPTH.

Estimated GFR was calculated using the Modification of Diet in Renal Disease (MDRD) [32] equation. The severity of CKD was assessed in accordance with the National Kidney Foundation developed criteria as part of its Kidney Disease Outcome Quality Initiative (NKF-KDOQI) [33] grading classification for CKD. Participants with an eGFR <15mls/min/1.73m^2 were excluded from the study.

All 142 participants had renal ultrasound for kidney morphology assessment and renal duplex Doppler studies to measure the renal resistivity indices of both renal arteries. Real time grey scale ultrasonography using Mindray diagnostic ultrasound system, Model; DC-7 fitted with 3.5MHz curvilinear transducer was used to obtain images for RI measurement. The patient was placed prone on the ultrasound table/couch with the renal angle exposed. Generous amount of ultrasound gel was applied to the exposed area of interest. The transducer was positioned so as to visualize the lateral or postero-lateral aspect of the kidney to establish an appropriate approach toward vascular structures in the periphery of the hilum and permitting visualization of the kidney without obstruction by gases present in the segments of the intestine and causing artefact.

Doppler analysis was then performed using colour, power and flow patterns. The 7.5MHz transducer was used to give measurable waveforms for appropriate vessel localization. The renal artery was located and traced to the segmental arteries then unto the interlobar arteries which were then insonated with a 2-4 mm Doppler gate. The spectral waveforms from the arteries were obtained from three different sites (the cranial, middle and caudal poles). Three reproducible waveforms from each kidney were obtained. The IRI was automatically calculated by the machine and the values from these were averaged by the investigator to establish mean IRI values for each kidney. IRI values ≥0.7 was considered elevated.

The current treatment of the participants was neither stopped nor altered.

Data collected was analysed using IBM Statistical Package for the Social Sciences (SPSS) version 23 where it was checked for data entry errors, coded and analysed. Descriptive and analytical data analysis was conducted. Continuous variables were summarized using mean ± standard deviation while categorical variables were summarized as frequency and percentages. Inferential statistics was conducted with means (standard deviations) of continuous variables compared using the students t-test, while categorical variables were compared with the chi-square test or Fishers` exact test as appropriate. Associations between variables were determined using Pearson's correlation (r) and linear regression analysis (B) with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant. All results were presented in tables or graphs as appropriate.

3. RESULTS

Females had more representation in the study and the mean age of the participants was 55.90±11.01 years with majority in the middle age group of 46-65 years (53.6%). All participants had formal education with 58.7% attaining tertiary level of education. Table 1 shows the socio-demographic characteristics of participants.

Table 1. Socio-demographic characteristics of participants

Variable	Frequency (n)	Per cent (%)
Sex		
Female	87	61.3
Male	55	38.7
Age Group (in years)		
≤45	28	19.7
46 – 55	37	26.1
56 – 65	39	27.5
>65	38	26.8
Marital Status		
Single	2	1.4
Married	128	90.1
Divorced	3	2.1
Widowed	9	6.3
Education Level		
Primary	19	13.4
Secondary	39	27.5
Tertiary	84	59.2

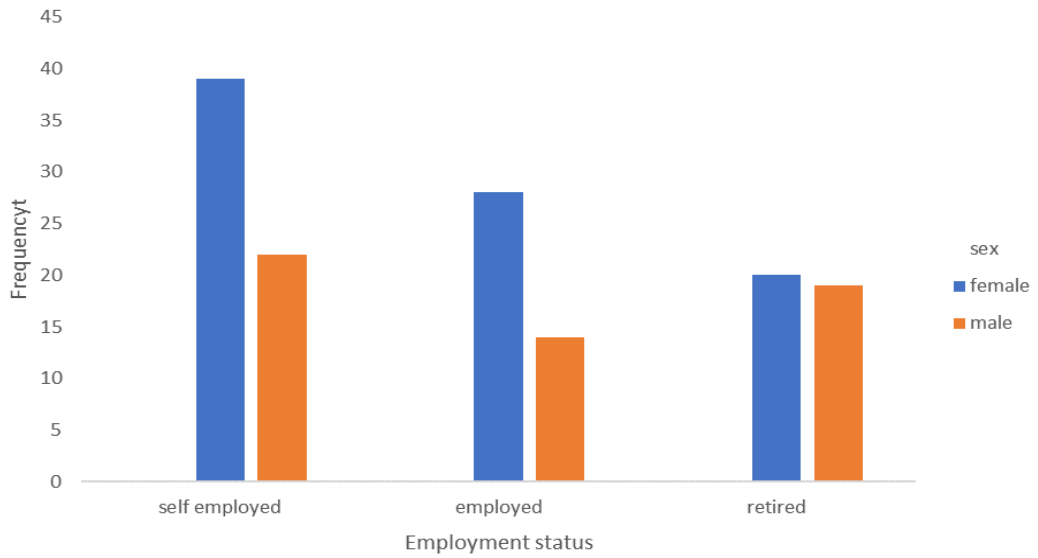

Fig. 1. Bar chart illustrating employment status of participants

Amongst the recruited participants, 61(43.0%) were self-employed, 42(29.6%) were gainfully employed while 39(27.5%) were retired. (Fig. 1) illustrating gender differences in employment status of participants.

The mean duration of diabetic disease among participants was 9.60 ±7.05 years. Participants with co-existing hypertension were 99 (69.7%) with a mean duration of 5.58± 5.55 years, while those without hypertension were 43 (30.3%).

Among participants, 97.2% used oral hypoglycaemic agents (OHA) and 28.9% used Insulin concurrently with OHA. All participants with co-existing hypertension used either Angiotensin converting enzyme inhibitors (ACE) or Angiotensin receptor blockers (ARB) in addition to concomitant use of Diuretics in 80.0% (85) and use of Calcium channel blockers in 86.6% (92). Other medications occasionally used by participants included multivitamin supplements 88.0% (132), non-steroidal anti-inflammatory drugs 25.3% (38) and herbal concoctions 10.0% (16). None of the participants used steroids.

There was a significant family history of diabetes mellitus and hypertension among participants. 94.4% had a family history of diabetes, 83.8% had family history of hypertension while only 6.3% had a family history of chronic kidney disease.

Participants recruited for this study had a mean body mass index (BMI) was 28.03 ±5.46Kg/m^2 with 93 (65.5%) of the participants being above recommended range for normal weight category and 2 (1.3%) of participants being underweight. The mean systolic blood pressure of participants was 136.23 ±19.06mmHg and a mean diastolic blood pressure of 81.43 ±10.88mmHg. Overall, 73(51.4%) of study participants were observed to have blood pressure levels ≤ 130/80mmHg.

None of the participants had presence of active urine sediments such as red cell casts, however 20 (13.3%) had some degree of proteinuria. About 80.0% of the participants had suboptimal glycaemic control with their glycated haemoglobin (HbA1c) levels greater than 6.5%. Other biochemical profile of the participants is highlighted in Table 2.

It was observed that 31 (21.8%) of the participants had eGFR values ≤60mls/min/1.73m^2 while 111 (78.2%) had their eGFR values above 60mls/min/1.73m^2 when categorized with the KDIGO classification of chronic kidney disease. See Table 3.

KDIGO staging criteria for CKD using UACR values showed that 66.2% of the participants had UACR values corresponding to stage 2 DN (incipient nephropathy) while 20.4% had stage 3 DN (Overt Nephropathy). The calculated Mean UACR was 153.65 ± 145.56mg/g (Table 4).

Table 2. Summary of biochemical profile of participants

Variable	Minimum value	Maximum value	Mean± Standard Deviation
Creatinine (µmol/L)	60.0	268.0	100.44±40.00
eGFR (ml/min/1.73m^2)	24.0	129.8	77.23±24.82
FBG (mmol/L)	3.7	23.0	8.36±3.69
HbA1c	5.0	15.9	8.32±2.31
Total serum protein (g/dL)	58.0	90.0	69.78±4.87
Serum albumin (g/dL)	24.0	54.0	36.58±4.29
TC (mmol/L)	2.5	7.8	4.41±1.08
Triglyceride (mmol/L)	0.5	3.2	1.38±0.60
HDL (mmol/L)	0.6	1.9	1.10±0.31
LDL (mmol/L)	0.8	6.0	3.00±1.07

TC- total cholesterol, HDL-high density lipoprotein, LDL- low density lipoprotein, eGFR- estimated glomerular filtration rate, FBG- fasting blood glucose

Table 3. Renal function status of participants using eGFR categories

Variable	Stage	Frequency (n)	Per cent (%)
eGFR categories			
Normal (≥ 90 ml/min/1.73m^2)	1	45	31.7
Mild reduction (60-89 ml/min/1.73m^2)	2	66	46.5
Mild to Moderate (45-59 ml/min/1.73m^2)	3a	13	9.2
Moderate to severe (30-44 ml/min/1.73m^2)	3b	8	5.6
Severe reduction (15-29 ml/min/1.73m^2)	4	10	7.0
Kidney failure (< 15 ml/min/1.73m^2)	5	0	0

eGFR- estimated glomerular filtration rate

Table 4. Renal function status of participants using UACR categories

Variable	Frequency (n)	Percent (%)
Urine Albumin to Creatinine ratio categories		
Normal (< 30 mg/g)	19	13.4
Mild to Moderately increased (30 - 299 mg/g)	94	66.2
Severely increased (≥300 mg/g)	29	20.4

Table 5. Hemodynamic parameters (Intra-renal Resistivity Index) of participants

Variable (n=142)	Frequency (n)	Per cent (%)
IRI (right)		
Normal (<0.70)	115	76.7
Increased resistivity (≥0.70)	27	18.0
IRI (left)		
Normal (<0.70)	113	79.6
Increased resistivity (≥0.70)	29	20.4
Average IRI		
Normal (<0.70)	105	73.9
Increased resistivity (≥0.70)	37	23.1

IRI- Intra-renal resistivity index

The ultrasonography scan findings revealed a mean bi-polar kidney length 10.34±0.93cm and a mean antero-posterior diameter of 4.57±0.55cm with a mean kidney volume was 147.51 ± 14.64cm^3. Whereas 112 (78.9%) participants had normal echogenicity with good cortico-medullary differentiation, 30 (21.1%) had increased echogenicity with poor cortico-medullary differentiation.

The duplex doppler hemodynamic parameters of participants using intra-renal resistivity index (IRI) showed that 37 (23.0%) of the participants had their mean average IRI increased (Table 5).

There was a significant difference between average IRI across age groups (p=0.003) however, no association was observed between UACR categories across the various age groups of participants(p=0.484). Our study did not find any significant difference in the average IRI values of participants with DM alone or those with co-existing hypertension (p = 0.06); nevertheless, duration of diabetes mellitus was observed to be associated with increased average IRI (p = 0.004). No significant difference was observed between duration of diabetes and eGFR categories (p = 0.087) or UACR categories (p=0.509) respectively.

Participants with DN were more likely to have higher IRI values compared to those without DN (p<0.005). The odds of having a high IRI was 10 times greater among persons with DN than those without DN (O.R = 10.67 95% C.I =1.39 to 81.91) as highlighted in Table 6.

Intra-renal resistivity index (IRI) showed a positive correlation with UACR and a negative correlation with eGFR. The strength of association as shown by the correlation coefficients appears stronger between IRI and UACR than IRI and eGFR (Table 7). The association between IRI and indices of renal dysfunction were statistically significant.

Linear regression analysis of the association between IRI and UACR showed that there was a predictive increase in IRI values as the UACR value increases. Conversely, there was a predictive increase in the IRI values as the eGFR decreases and this association were all statistically significant, p < 0.001 (Table 8).

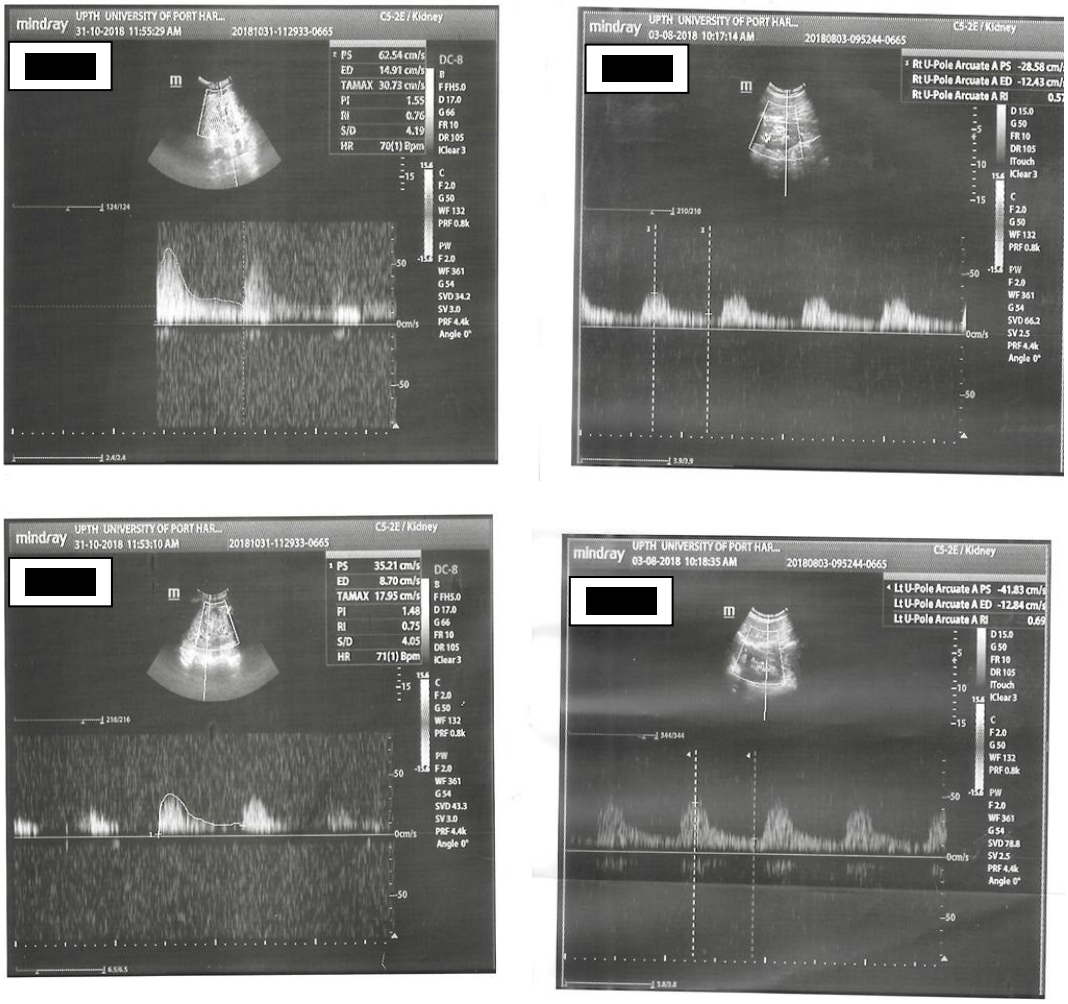

Fig. 2. Renal duplex Doppler images of the inter-lobar arteries showing hemodynamic waveform measurements of the Peak systolic velocity, End diastolic velocity and the calculated IRI values

Table 6. Association between diabetic nephropathy and Intrarenal Resistive Index (IRI)

Diabetic nephropathy	IRI Mean category		Fisher's exact	Odds ratio
	Normal	High		
No	24 (22.9)	1 (2.7)	0.005*	10.67 (1.39 to 81.91)
Yes	81 (77.1)	36 (97.3)		

**Significant association at p <0.05*

Table 7. Association between IRI and indices of renal dysfunction (UACR and eGFR)

Variable	Correlation coefficient (r)	p-value
IRI (Right)* UACR	0.614	<0.001
IRI (Right)* eGFR	-0.371	<0.001
IRI (Left)* UACR	0.640	<0.001
IRI (Left)* eGFRr	-0.399	<0.001
IRI (Mean)* UACR	0.612	<0.001
IRI (Mean)* eGFR	-0.451	<0.001

**Significant, IRI- intrarenal resistive index, UACR- urine albumin-creatinine ratio, eGFR- estimated glomerular filtration rate*

Table 8. Relationship between UACR, eGFR and IRI

Variable	Linear Regression (t)	p-value
IRI (Right)*UACR	8.370	<0.001
IRI (Right)*eGFR	-5.457	<0.001
IRI (Left)*UACR	9.370	<0.001
IRI (Left)*eGFR	-6.146	<0.001

** Statistically significant, UACR- urine albumin to creatinine ratio, eGFR- estimated glomerular filtration rate*

4. DISCUSSION AND CONCLUSION

Type 2 diabetes mellitus patients often develop impairment in their renal function and the prevalence of CKD in these patients have been reported by several authors [34] to be in the range of 20-30%' however, these studies were based mostly on eGFR values ≤60ml/min/1.73m^2. This study identified 31 (21.8%) of the participants with eGFR values ≤60mls/min/1.73m^2, which is similar to that reported by Kumiko et al. [35] as well as other authors in Southern Nigeria [36,37].

In type 2 DM, micro-albuminuria is the earliest clinical manifestation of DN [18-19] and many studies have suggested its use as a diagnostic tool for DN [38]. In our study, a total of 123 (86.6%) of the participants had albuminuria of ≥30mg/g (Table 4) which is similar to the findings of Janmohamed et al. [39] but slightly higher prevalence of albuminuria as reported by some authors in southern Nigeria [37,38,40].' This further highlights that in early diabetic nephropathy eGFR estimates only, may not be truly representative of the renal status of diabetic patients or predict the renal prognosis.

The intra-renal resistivity index is determined from the intra-renal arterial waveforms using duplex Doppler ultrasound with a reference value in adults to be 0.60±0.1 [41]. DM has been reported to alter vascular resistance in the kidneys. This study observed that 37(23.1%) of the participants had their average IRI values ≥ 0.7, suggestive of severity of DN from altered vascular resistance within the renal vessels. This observed estimate of increased IRI value in the sample population does not however differ widely from the estimate of participants with renal dysfunction observed using eGFR criteria.

Several risk factors have been identified for development and progression of DN such as age, hypertension, duration of diabetes, poor glycaemic control etc. [42] some of which have been noted to affect the IRI values as seen in our study. We observed a statistically significant association between IRI and aging (p=0.003), as well as duration of diabetes (p =0.004). This observed association between aging and increased IRI may be due to increased arteriosclerosis associated with aging resulting in essential hypertension and thus renal hemodynamic and vascular changes.

Hypertension increases the risk of progression of DN and is an established complication of DN however, hypertension did not seem to influence increased IRI among participants of this study as no statistical difference was observed between IRI of participants with DM alone and those with co-existing hypertension (p=0.06). The concomitant use of anti-hypertensive medications may be responsible for this finding. RAS inhibitors like Valsartan and Lisinopril are able to improve renal function by reducing renal vascular resistance and thus preventing future renal failure [43].

In our study, IRI had a strong positive correlation with UACR (r =0.612, p = <0.001, Table 7) this is similar to reports from Marcini et al. [44] who compared IRI values and UACR categories in diabetic patients with their age and sex matched controls. He observed a significant difference in IRI between diabetic patients and their controls, with increasing IRI values as albuminuria increases. Other related studies [45] have reported similar observations and have concluded that IRI was significantly affected by worsening proteinuria. Conversely, IRI has been shown to correlate negatively with eGFR [35] as was also observed in our study (r = 0.451, p = <0.001. Table 7). IRI is thought to increase significantly from extensive glomerulosclerosis, microangiopathy [28, 35] interstitial fibrosis and tubular atrophy as chronic kidney disease progresses to end stage renal disease.

Linear regression analysis of the association between IRI and UACR as well as IRI and eGFR (Table 8) showed a linear relationship between IRI with UACR and eGFR (p < 0.001) respectively, one can therefore infer that IRI may be predictive of DN in T2DM patients and may serve as a useful non-invasive tool for diagnosis of DN especially in the early clinical stages of DN where hyper filtration is predominant resulting in low serum creatinine levels and high estimated glomerular filtration rate [46].

Although eGFR is a convenient and useful tool to evaluate renal function, it may not accurately predict early pathologic derangements in DN. Similarly, UACR though a useful diagnostic tool in the diagnosis and staging of DN, recent studies concerning the pathophysiology of DN have challenged the concept that declining renal functions in DN is always accompanied by albuminuria [47]. IRI correlates strongly with both UACR and eGFR and recent comparative studies with novel biomarkers of its predictive value for kidney injury has shown very high sensitivity [48]. It may therefore be a very useful tool for early diagnosis of DN and evaluating pathogenesis of renal damage in T2DM.

Duplex Doppler ultrasound of the kidneys provides a non-invasive and rapid evaluation of intra-renal hemodynamic parameters and IRI may be a useful non-invasive tool for early diagnosis as well as predicting risk for DN in T2DM patients.

5. STUDY LIMITATIONS

The study was a cross-sectional study and so conclusion of the diagnosis of DN could not be made based on a single point sampling of participants. Secondly, the study was hospital-based and all recruited participants were receiving medications for elevated plasma glucose levels, and other co-morbid conditions such as hypertension, and dyslipidaemia which may have influenced study outcome. Lastly, this work was a single center study; therefore, findings cannot be generalized to the entire Nigerian patients living with type 2 diabetes mellitus.

6. RECOMMENDATIONS

Based on the findings of this study, type 2 diabetic patients should be routinely screened for micro/macro-albuminuria for the estimation of UACR and categorization of diabetic nephropathy. Secondly, duplex Doppler ultrasound of the kidneys for estimation of IRI should be included in the yearly investigations of T2DM patients presenting to our clinics. Lastly, longitudinal prospective studies may be necessary to evaluate the usefulness of IRI in prediction, evaluation and prognosis of DN.

CONSENT AND ETHICAL APPROVAL

Ethical approval was sought and obtained from Ethics and Research Committee of the hospital. Written informed consent was obtained from the participants and data collected from participants were kept confidential.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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