Value of Intrarenal Artery Resistive Index for Detecting Diabetic Kidney Disease: A Cross-sectional Study

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Research Article

Keywords: diabetic kidney disease, estimated glomerular filtration rate, 24-hr urine protein, resistive index

Posted Date: April 22nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-440428/v1

Abstract

Background: The typical pattern of diabetic kidney disease (DKD) which follows glomerular hyperfiltration progressing to persistent albuminuria associated with hypertension and declining glomerular filtration rate (GFR) has changed over the years. The aim of the study is to examine the potential role of Doppler ultrasound in early identification of DKD.

Methods: A 137 patients with type 1 or type 2 diabetes mellitus (DM) patients in Ethiopia participated in the study. We analyzed the correlation between resistive index (RI) of intrarenal arteries and clinical characteristics, eGFR and 24-hr urine. We evaluated the linear relationship of RI with multiple variables using multiple regression analysis. Sensitivity, specificity and area under curve (AUC) of the receiver operating curve (ROC) were assessed.

Results: Among the 137 participants, 48.9% were patients with type 1 DM and 51.1% with type 2 DM. Mean age ± SD was 42±15 years. The median 24-hr urine protein was 156 (IQR=149.5) mg/24hr. Mean eGFR was 104.26±17.25 (mL/min/1.73 m^2). The mean RI was 0.7±0.06. The mean RI was significantly correlated with age and eGFR (r=0.64 & -0.56, P<0.001 respectively). Our multiple regression model relating mean RI to age, eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of diabetes and body mass index (BMI) was significant (overall F-test P-value<0.001). The AUC of the ROC curve of mean RI to identify a low eGFR was 0.82 (95% CI, 0.6 to 1). Sensitivity and specificity of 80% and 53% was calculated respectively.

Conclusion: A significant linear relationship has been observed between RI and eGFR. This indicates RI values can determine the level of renal function loss with high accuracy.

Background

The estimated prevalence of DKD is about 35.3% in Sub-Saharan Africa diabetic patients and it is higher in Type 2 DM (41.39%)(1). It is identified clinically by persistently high urinary albumin-to-creatinine ratio ≥ 30 mg/g and/or sustained reduction in eGFR below 60 mL/min/1.73 m^2(2). The classic pattern of DKD follows glomerular hyperfiltration progressing to persistent albuminuria associated with hypertension and declining GFR. This typical pattern has changed in recent years. A lower prevalence of albuminuria and higher prevalence of reduced GFR have been observed overtime(3). A decline in renal function was seen in about 24% of Type 1 and 9.3 to 61.6% of Type 2 diabetic patients before the occurrence of albuminuria(4, 5). This should prompt further investigation of other supplementary tools for early diagnosis of DKD.

Other biomarkers of glomerular and tubular injury, such as serum and urine markers are emerging in experimental nephrology in the early diagnosis of DKD. Additionally, metabolomics, metabonomics, genomics, proteomics and microRNAs analyses have shown a promising result in early detection of DKD (6). However, practice of these biomarkers in the clinical trial is still underway and proficiency of these biomarkers needs to be evaluated.

Doppler ultrasound has been extensively used in detecting reno-vascular diseases, it has shown to be noninvasive, safe, low cost and a repeatable tool. Mancini et al.(7) reported that diabetic patients with normal renal function and normo-albuminuria showed both a renal volume and RI values significantly higher compared to non-diabetic controls without kidney disease. This result suggests a potential role of Doppler ultrasound in the identification of morphologic and hemodynamic changes in the earlier stages of DKD (7).

The aim of this study was to evaluate the relationship of intrarenal RI with different levels of urine protein excretion and eGFR. We also wanted to investigate the role of doppler ultrasound in detecting DKD by measuring RI of intrarenal arteries.

Methods

Study design and setting

In this cross-sectional study, we recruited 142 adult (age ≥ 18 years) consecutive patients who visited the diabetic follow-up clinic at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The study was performed between August and November 2020.

Study Participants

Type 1 DM patients with diabetes duration of > 5 years or type 2 DM with any duration of diabetes were included in the study.

Because of the technical difficulty to do renal ultrasound examination, patients who are markedly obese (i.e., BMI > 40kg/m^2, according to WHO criteria) were excluded from the study.

Renal artery stenosis, hypertension, heart failure, pregnancy and hydronephrosis were other exclusion criteria. In addition, patients who have acute complications, such as diabetic ketoacidosis, hyperglycemic hyperosmolar state, lactic acidosis, and hypoglycemia were excluded.

Data Collection

Age, sex, type of diabetes, duration of diabetes, weight, height, and other comorbidities of all patients were documented in a questionnaire.

Patients were evaluated by doppler ultrasound first then sent for laboratory investigations.

Urine protein measurement was performed by collecting a 24hr urine to measure urine protein concentration. Patients were instructed to collect urine starting in the morning. The first (overnight) urine on day 1 was discarded. All urine passed during the day and night will be included in the collection bottle. The first (overnight) urine on day 2 was included.

Moderately increased proteinuria defined as 24-h urinary protein excretion rate between 150 and 500mg/day and severely increased proteinuria as protein excretion rate > 500mg/day.

Serum creatinine was determined. Creatinine was measured using the Jaffe method. Calibrators and reagents are from Abbott and IDMS traceable.

To estimate glomerular filtration rate from serum creatinine, we used the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Eq. (8), GFR (mL/min/1.73 m^2) = 141 * min (Scr/k, 1) $^{\alpha}$ *max (Scr/k, 1) $^{-1.209}$ *0.993^{Age}* 1.018(if female) * 1.159 (if black), where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is − 0.329 for females and − 0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.

Color Doppler ultrasound scan was performed by one radiology resident after he received training by the principal investigator. The first 10 examinations were performed under supervision. A 3-6MHz convex array transducer (Sonoscape ultrasound machine) was used for the examination. Patients were examined in supine position, the transducer placed in longitudinal axis, color doppler imaging was used to identify the segmental arteries and RI was collected in the segmental arteries two times in each the upper, middle and lower pole of both kidneys. The six values were averaged to obtain the mean RI for each side of the kidney. The average value between the right and left kidney was the RI used for analysis.

RI was calculated by the built-in software as follows: RI = (peak systolic velocity -end-diastolic velocity)/peak systolic velocity.

The threshold for an increased renal resistive index (RRI) is ≥ 0.70 for either right and or left RRI.

The research budget was limited to cover all the laboratory and other expenses; therefore, we applied a convenient sampling technique.

Ethical approval to conduct the study was obtained from Institutional Review Board of College of Health Sciences (058/19/Radio). Procedures were performed in accordance with the 1964 Helsinki declaration. All participants have provided informed consent.

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) program version 25.0 (Chicago, IL, USA). The data presented as mean ± standard deviation (SD), median with interquartile range (IQR) or frequencies and percentages. Chi-square was used to see the association between categorical variables. Bivariate correlation among continuous variables was evaluated by Pearson's correlation coefficient. Ordinal variables were evaluated by Spearman's rho correlation. A regression analysis was performed to determine more related variables for the dependent variable (RI). Area under the ROC curve (AUC) of the receiver operating characteristic (ROC), sensitivity, and specificity were calculated to assess the significance of diagnostic value for RI. P- value less than 0.05 was considered significant.

Results

Baseline characteristics

-Of the 142 patients, 137 completed the laboratory investigations and were analyzed (Fig. 1). Basic characteristics of 137 patients are summarized in Table 1. Eighty-eight (64.2%) were female and 49 (35.8%) were male. Mean age ± SD was 42 ± 15 years. The mean BMI was 24.9 ± 4.1 kg/m^2. Mean systolic and diastolic blood pressure (SBP and DBP) were 121.9 ± 17.1 and 70 ± 8.6 mmHg respectively. Patients with type 1 DM were 67 (48.9%) and with type 2 DM were 70 (51.1%). The median duration of diabetes was 11 (IQR = 9) years. Dyslipidemia and cardiovascular diseases were seen in 10 (7.3%) and 3 (2.2%) of the patients respectively. Forty-two (30.7%) had other comorbidities. Eighty-two (59.9%) had no comorbidities.

Table 1. Basic characteristics of study participants

Characteristics	Value
Age	42±15
Sex (F/M)	88/49
BMI (Kg/m^2)	24.9±4.1
SBP (mmHg)	121.9±17.1
DBP (mmHg)	70±8.6
Type of diabetes (type1/type 2)	67/70
Duration of diabetes	11 (IQR=9)
Other comorbidities (%)	
-Dyslipidemia	7.3
-Cardiovascular disease	2.2
-Other	30.7
-None	59.9
Current FBG (mg/dl)	144 (IQR=71)
HBA1c (%)	8.4±2
Serum creatinine(sCr.) (mg/dl)	0.77±0.13
24-hr urine protein (mg/24hr)	156 (IQR=149.5)
Mean RI	0.7±0.06
eGFR (mL/min/1.73 m2)	104.26±17.25
Total	N=137

Note: Values are given in number, percentage, mean±SD or median (IQR)

Abbreviations: BMI=body mass index, DBP=diastolic blood pressure, eGFR= estimated glomerular filtration rate, FBG= fasting blood glucose, HBA1c= glycated hemoglobin A1c, SBP=systolic blood pressure, RI=resistive index

Relationship Between Independent And Outcome Variables

The degree of urine protein excretion is associated with the value of RI (P = 0.04). However, further linear association test revealed a non-significant correlation (r_s = -0.1, P = 0.24) between the two variables.

- A chi-square test showed that there was no association between RI and other comorbidities (P = 0.16). Urine protein excretion level and eGFR were not associated as well, (P = 0.18).
- The correlation between mean RI and 24-hr urine protein and HBA1c were not significant (r = 0.06, P = 0.23) and (r = -0.099, P = 0.25) respectively. A weak but statistically significant correlation has been observed between RI and BMI, systolic and diastolic blood pressure (r = 0.17, P = 0.03, r = 0.25, P = 0.004 and r = -0.23, P = 0.008 respectively). Table 2 summarizes the correlation coefficients and P-values.

The mean RI was significantly correlated with age, duration of diabetes and eGFR (r = 0.64, 0.38 & -0.56, P < 0.001 respectively). Our multiple regression model relating mean RI to age, duration of diabetes, BMI, SBP, DBP and eGFR was significant (overall F-test P-value < 0.001). A low (variance inflation factor, VIF ≤ 2.5) multicollinearity was detected between the independent variables (eGFR, SBP, duration of diabetes and age). The model had a good fit (R^2 = 0.57). Controlling for all the other related variables, for both a 1-year increase in age and duration of diabetes, the average mean RI increases by 0.002 (std. error 0.000). For a 1 mL/min/1.73 m^2 decrease in eGFR, RI increases by 0.001 (std. error 0.000). For 1mmHg and 1kg/m^2 increase in SBP and BMI respectively RI increase by 0.001 (std. error 0.000 and 0.001). For 1mmHg decrease of DBP RI increases by 0.002 (std. error 0.001).

Table 2. Pearson's correlation coefficients between mean RI and various variables

Variables	r	P-value
Age	0.64	<0.001
eGFR	-0.56	<0.001
Duration of diabetes	0.38	<0.001
24-hr urine protein	0.06	0.23
BMI	0.17	0.03
SBP	0.25	0.004
DBP	-0.23	0.008
HBA1c	-0.099	0.25

Abbreviations: BMI=body mass index, DBP=diastolic blood pressure, HBA1c= glycated hemoglobin A1c, SBP=systolic blood pressure

Performance Status Of RI Compared To EGFR

The area under curve of the ROC curve of mean RI to identify a low eGFR (< 60 mL/min/1.73 m^2) was 0.82 (95% CI, 0.6 to 1) (Fig. 4). Sensitivity and specificity of 80% and 53% was calculated respectively.

Discussion

In this study, comparable number of type 1 and type 2 DM (67/70) patients participated. Most patients have long duration of diabetes and their glycemic control was poor. The overall magnitude of DKD in the study group was 12.4% which was confirmed by either eGFR or 24-hr urine protein level.

This study has some limitations such as, the lack of other optional laboratory tests, which led us to determine urine albumin excretion by measuring 24-hr urine total protein. This is subject to error due to the variation in concentration and inaccurate urine collection method. Other limitations are, potential confounding in the interpretation of findings and small sample size of the study.

The majority of patients with severely increased proteinuria had normal eGFR. A comparable proportion of patients had normal and severely increased proteinuria but low eGFR.

Likewise, the degree of proteinuria and RI values are not correlated. This contradicts with previous studies (9–11), where they showed a significant correlation of RI with level of urine albumin excretion in both type 1 and type 2 DM.

In this study, a significant linear relationship between RI and age, duration of diabetes and eGFR, has been observed. Multiple studies have demonstrated similar findings (10–12) and these parameters independently predict the value of RI in DM patients.

The performance of RI values in identifying patients with low eGFR and others was excellent. Additionally, the sensitivity and specificity of RI in these groups is satisfactory.

Conclusion

the present study suggests that RI values predict the degree of renal function loss with high accuracy. This warrants that doppler ultrasound can be used as a supplementary test for detection of DKD in both type 1 and type 2 diabetes. However, additional studies are required to further investigate clinical application of this tool.

Abbreviations

AUC: area under curve; BMI: body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; DBP: diastolic blood pressure; DKD: diabetic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; HBA1c: glycated hemoglobin A1c; SBP: systolic blood pressure; sCr.: serum creatinine; RI: resistive index; ROC: receiver operating curve.

Declarations

Ethics, approval and consent to participate

All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval to conduct the study was obtained from Institutional Review Board of College of Health Sciences (058/19/Radio). All participants have provided informed consent.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, FBG, upon reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This project was supported by MEPI-JF (Medical Education Partnership Initiative-Junior Faculty) research carrier development grant. The funders played no role in study design; data collection, analysis, or reporting; or the decision to submit for publication.

Authors' contributions

FG, YM and DK designed the study. FG acquired the data. FG, YM and DK analyzed and interpreted the data. FG, YM and DK contributed important intellectual content during manuscript drafting. All authors read and approved the final version.

Acknowledgment: We thank Carolyn Maloney (Sunnybrook Hospital) for giving a short, hands-on training on doppler examination. We also thank Dr. Fikadu H/Mariam and study site diabetic and GI clinic nurses for their countless contribution during the data collection.

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Figures

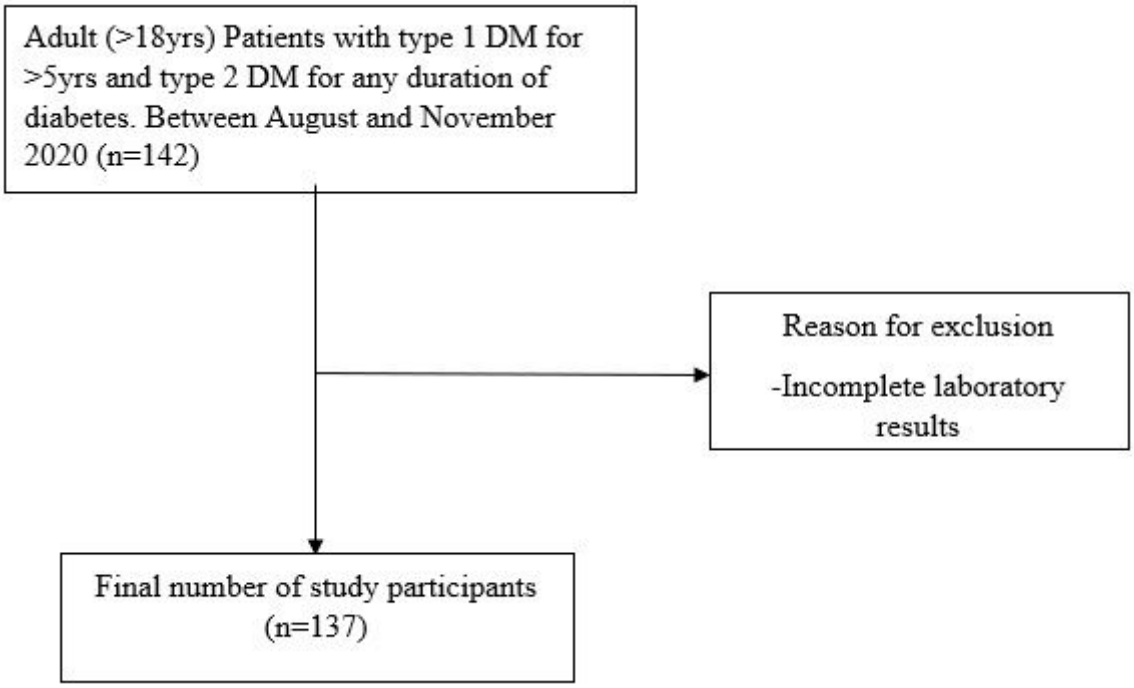

Figure 1

Flowchart of study participants selection.

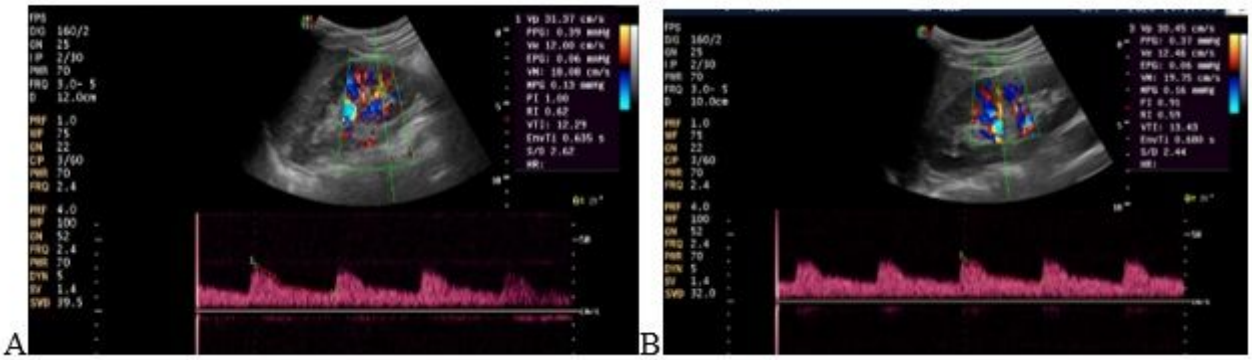

Figure 2

A 20-year-old male, type 1 diabetes for 9 years, with intrarenal artery RI value of 0.62 in the lower pole (A) and 0.59 in the mid pole (B).

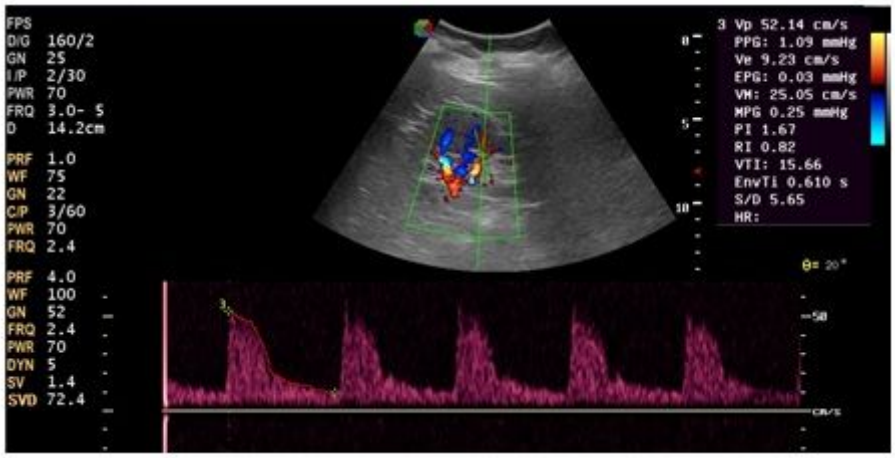

Figure 3

A 73-year-old male, type 2 diabetic for 30 years, with RI value of 0.82

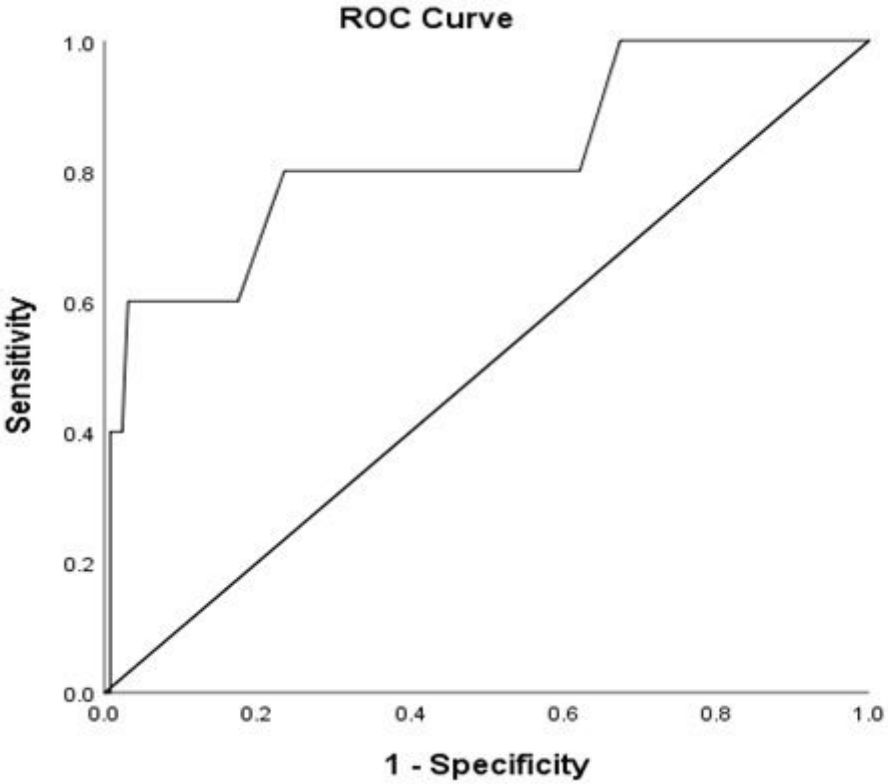

Figure 4

ROC curve analysis of mean RI in identifying a low (<60 eGFR mL/min/1.73 m2). Area under curve the ROC curve, 0.82 (95% CI, 0.6 to 1).