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Renal resistive index and its association with insulin resistance in patients with Type 2 Diabetes mellitus

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Abstract
Background: *Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) and a major cause of cardiovascular mortality.*
Aim: *The aim of this study is to assess the significance between renal resistive index with albumin creatinine ratio and to explore possible correlation with HbA1c, homeostasis model assessment-estimated insulin resistance (HOMA-IR) in type 2 diabetic patients.*
Materials and methods: *Sixty type 2 diabetic patients with more than 5 year diabetic duration in the age group of 35 to 60 years were selected for this study and 30 age matched healthy individuals were selected as control group. The renal Doppler studies were performed using a low-frequency ultrasound transducer and a standardized diagnostic scanning protocol for image acquisition. Glycated hemoglobin (HbA1C), Insulin, microalbumin were analyzed by conventional standardized methods.*
Results: *Interlobar and Arcuate artery Renal resistive index values were significantly increased in diabetic patients compared with controls and also significantly increased values were observed in microalbuminuric diabetics compared with normoalbuminuric diabetics. The Interlobar artery resistive index levels were positively correlated with the albumin creatinine ratio (ACR), glycated hemoglobin (HbA1C) and insulin resistance.*
Conclusion: *RRI might be a non invasive diagnostic marker of early renal vascular changes and is positively correlated with insulin resistance and HbA1c in type 2 diabetes mellitus.*
Keywords: *Diabetic nephropathy, Renal resistive index, Insulin resistance, Glycated hemoglobin (HbA1C)*

I. Introduction

Diabetes mellitus is associated with microvascular and macrovascular complications. Diabetic nephropathy (DN) is a primary cause of end-stage renal disease (ESRD) and cardiovascular mortality [1, 2]. Due to the global increase in prevalence of diabetes, there has been a concomitant rise in the number of patients with diabetic nephropathy indicating a prevalence of 30-40% of patients with type 1 (T1DM) and type 2 diabetes (T2DM) being affected [3,4]. Microalbuminuria is the gold standard for detection and prediction of diabetic nephropathy in clinical practice. At the same time, microalbuminuria represents a marker of the generalized endothelial dysfunction present in DM, linking renal involvement with cardiovascular and cerebral impairment [5, 6]. However, many patients, who were normoalbuminuric and just recently had positive test for microalbuminuria, have advanced renal histopathological changes, decreased glomerular filtration rate (GFR) and progressive loss of kidney function [7, 8].

Ultrasound and Doppler imaging has also traditionally been used in the assessment of chronic renal disease. Not only does Doppler ultrasonography detect renal macroscopic vascular abnormalities but it also identifies changes in blood flow at the microvascular level [9]. Renal resistive index (RI), as a promising marker for various types of vascular damage used in detecting reno-vascular diseases, showing to be a non-invasive, safe, low cost and repeatable tool [10,11]. Renal RI (RRI) is defined as a ratio of the difference between maximum and minimum (end-diastolic) flow velocity to maximum flow velocity derived from the Doppler spectrum of intrarenal (segmental/interlobar) arteries [12]. RRI provides prognostic information relating to systemic vasculature and an elevated RRI is associated with adverse outcomes in hypertensive, diabetic, and elderly patients [13-16]. So, in the present study we aimed to evaluate the relation between renal resistive index with albumin creatinine ratio and to find the possible correlation with HbA1c, homeostasis model assessment-estimated insulin resistance (HOMA-IR) in type 2 diabetic patients.

II. Materials and methods

The study groups comprised of 60 type 2 diabetic patients of both sexes, aged between 35-60 years on oral hypoglycemic drugs, attending diabetic out-patient department of Rajah Muthiah Medical College and

Hospital, Annamalai University, Annamalainagar, Tamil Nadu, India, were selected for our study. We excluded the patients based on the following criteria: patients on insulin, hypertension, smokers, alcoholics, tobacco chewers, abnormal urinary sediment, urinary tract infection, history of other renal disease and active or chronic persistent infection or inflammatory disorders, neoplastic disorders, uncontrolled thyroid disorders, severe liver dysfunction, history of acute myocardial infarction, stroke, and occlusive peripheral vascular disease. The included diabetic patients were categorized into two groups based on urinary albumin creatinine ratio (ACR) as patients (30 no) with normoalbuminuria (< 30 mg/g creatinine), patients (30 no) with microalbuminuria (30–299 mg/g creatinine). Thirty healthy age, sex matched subjects were selected as controls. The informed consent was obtained from all the study subjects and the study was approved by the Institutional Human Ethics Committee (IHEC). Experiments were done in accordance with Helsinki declaration of 1975.

Biochemical analysis:

A random spot urine and fasting blood samples were obtained from the subjects immediately after enrolment. Blood samples were centrifuged at 2000×g for 10 min. Samples were analyzed for fasting blood glucose, lipid Profile(Total Cholesterol, HDL, Triglycerides), by using Auto analyzer. HbA1C estimated by Ion exchange resin method and Insulin assessed by ELISA and the 2 hour post prandial venous blood sample collected for plasma glucose (PPG) analysis. Homeostasis model assessment for insulin resistance evaluation (HOMA-IR) was calculated using the equation: fasting plasma insulin × glucose/22.5 [17]. Urine samples were analyzed for microalbumin, creatinine by using auto analyzer.

Measurement of ultrasound Doppler Renal resistive index (RRI):

Ultra sound Doppler renal examination was performed with a 3.5 MHz convex transducer (Toshiba Medical Systems, Tochigi, Japan). Initially routine renal B-mode US examinations were performed for each patient. Ultrasound testing was performed on the same day and measurements was preferentially be repeated in different parts of both kidneys (superior, median, and lower) out of which at least three reproducible waveforms have been obtained. RRI is calculated with the following formula: (peak systolic velocity – end diastolic velocity)/ peak systolic velocity, and the mean value of three measurements at each kidney. In each subject, RI at the interlobular and arcuate artery near the border of the central echo complex was measured [18].

Statistical analysis

Statistical analyses were carried out with SPSS 20.0. Values were expressed as mean ± standard deviation, p value < 0.05 was considered statistically significant. Normally distributed data were analyzed by using one-way ANOVA. The Pearson correlation test was used for correlation analysis.

III. Results

Table 1: Baseline data of controls, normoalbuminuric and microalbuminuric type 2 diabetic patients

Parameters	Controls (n=30)	Normoalbuminuric T2DM (n=30)	Microalbuminuric T2DM (n=30)
Age	47.7±3.9	48.1±6.7	49.1±4.4
Body mass index (BMI)	24.3±1.3	26.9±3.6 [a*]	26.5±3.5 [a#]
Waist/Hip ratio	0.91±0.03	0.92±0.06	0.92±0.04
Systolic BP(mmHg)	113.9±7.1	123.5±15.5 [a#]	126.6±12.5 [a*]
Diastolic BP (mm Hg)	74.1±3.4	78.7±7.5 [a#]	78.5±6.6 [a#]

a - Controls vs Normoalbuminuria T 2DM, Microalbuminuria T2DM
b -Normoalbuminuria T 2DM vs Microalbuminuria T 2 DM
* p value <0.001, # p value <0.05
Data are expressed as mean ±SD, p<0.05 was considered statistically significant.

Table 2: Clinical data of controls, normoalbuminuric and microalbuminuric type 2 diabetic patients

Parameters	Controls (n=30)	Normoalbuminuric T2DM (n=30)	Microalbuminuric T2DM (n=30)
Urine albumin Creatinine ratio (mg/gm. of creatinine)	18.6±2.7	22.8±3.2 [a*]	127.3±40.9 [a*,b*]
FPG(mg/dl)	82.2±5.7	123.0±22.6 [a*]	135.3±33.4 [a*]
PPG(mg/dl)	107.8±9.2	170±20.7 [a*]	203.4±42.4 [a*,b*]
HbA1C	5.5±0.4	7.1±0.8 [a*]	8.2±0.9 [a*,b*]
Serum urea(mg/dl)	24.5±4.3	27.8±4.2 [a#]	31.4±5.0 [a*,b#]
Serum creatinine(mg/dl)	0.6 ±0.1	0.7±0.2	0.9±0.3 [a*,b#]

Serum cholesterol (mg/dl)	168.9±8.8	185.3±19.4 [a*]	194.9±22.7 [a*]
Serum Triglycerides (mg/dl)	95.9±7.1	130.1±35.9 [a*]	140.2±35.0 [a*]
HDL cholesterol (mg/dl)	44.0±2.4	39.2±2.9 [a*]	38.5±2.4 [a*]
LDL cholesterol (mg/dl)	105.7±8.8	120.0±16.0 [a*]	128.3±22.2 [a*]
Insulin (µIU/mL)	6.4±0.7	10.3±2.7 [a*]	14.2±3.4 [a*,b*]
HOMA-IR	1.3±0.18	3.1±0.9 [a*]	4.7±1.6 [a*,b*]

a - Controls vs Normoalbuminuria T 2DM, Microalbuminuria T2DM
b -Normoalbuminuria T 2DM vs Microalbuminuria T 2 DM
* p value <0.001, # p value <0.05
Data are expressed as mean ±SD, p<0.05 was considered statistically significant

Table 3: Interlobar (IL), arcuate artery (ARC) resistive index in controls, normoalbuminuric and microalbuminuric type 2 diabetic patients

Parameters	Controls (n=30)	Normoalbuminuria T2DM (n=30)	Microalbuminuria T2DM (n=30)
Right Kidney IL RI	0.54±0.02	0.66±0.05 [a*]	0.83±0.1 [a*,b*]
Left Kidney IL RI	0.53±0.05	0.68±0.06 [a*]	0.79±0.1 [a*,b*]
Right Kidney ARC RI	0.51±0.06	0.72±0.07 [a*]	0.83±0.1 [a*,b*]
Left Kidney ARC RI	0.55±0.03	0.64±0.04 [a*]	0.82±0.1 [a*,b*]

a - Controls vs Normoalbuminuria T 2DM, Microalbuminuria T2DM
b -Normoalbuminuria T 2DM vs Microalbuminuria T 2 DM
* p value <0.001, # p value <0.05
Data are expressed as mean ±SD, p<0.05 was considered statistically significant

Table 4: Correlation between ACR& measured parameters in type 2 diabetic patients

Parameters	**Correlation Coefficient(r)**
Right Kidney IL RI	0.658**
Left Kidney IL RI	0.763**
Right Kidney ARC RI	0.282*
Left Kidney ARC RI	0.367**

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Table 5: Correlation between HOMA IR &measured parameters in type 2 diabetic patients

Parameters	**Correlation Coefficient(r)**
Right Kidney IL RI	0.569**
Left Kidney IL RI	0.442**
Right Kidney ARC RI	0.295**
Left Kidney ARC RI	0.232

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Table 6: Correlation between HbA1c&measured parameters in type 2 diabetic patients

Parameters	**Correlation Coefficient(r)**
Right Kidney IL RI	0.485**
Left Kidney IL RI	0.383**
Right Kidney ARC RI	0.213
Left Kidney ARC RI	0.312*

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Figure 1: Interlobar artery resistive index in control subject

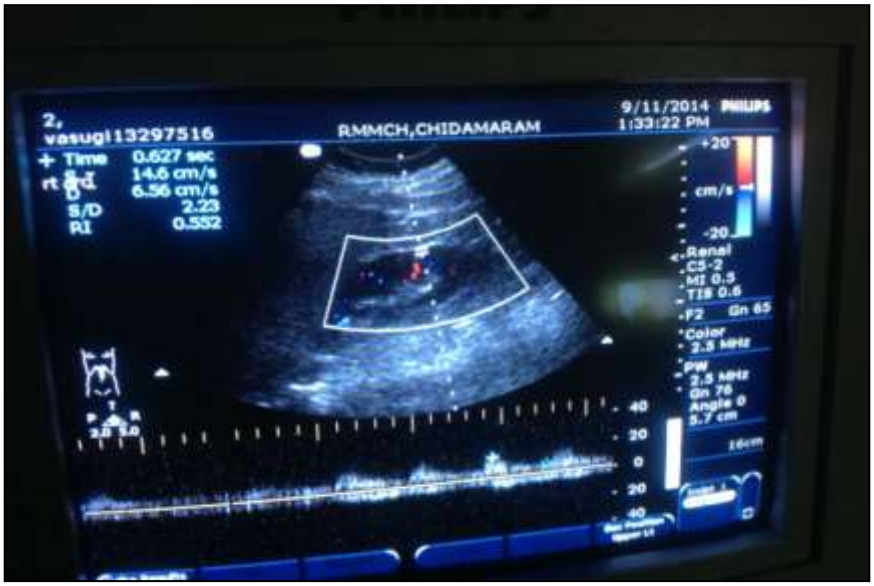

Figure 2: Arcuate artery resistive index in control subject

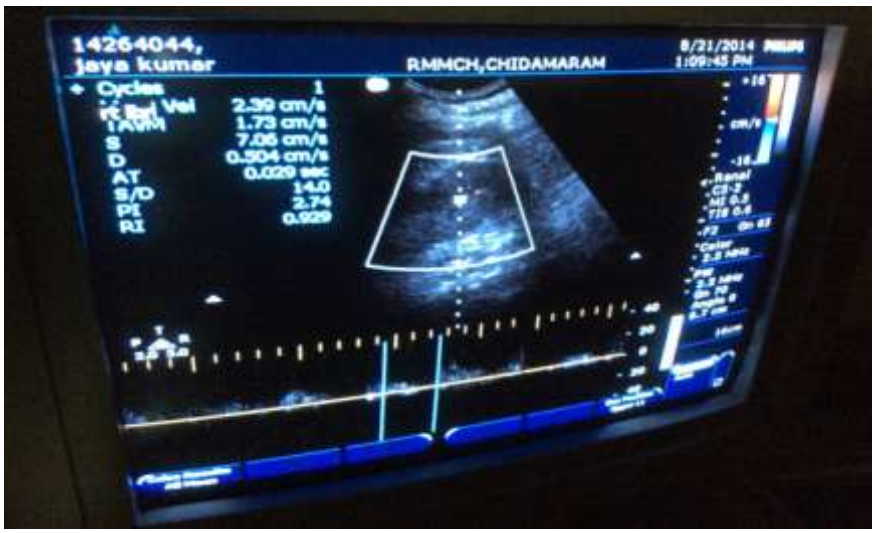

Figure 3: Interlobar artery resistive index in diabetic subject

Figure 4: Arcuate artery resistive index in diabetic subject

IV. Discussion

Diabetic nephropathy is the most common cause of end-stage renal disease in the world, and could account for high mortality rate in patients with diabetes [18]. Chronic hyperglycemia induces dysfunction in various cell types of the kidney, ultimately leading to progressive renal failure [19-25]. The annual incidence of this disease has more than doubled in the past decade, and at present it accounts for almost 50% of all end-stage renal diseases [26]. In the present study, we observed that interlobar and arcuate artery resistive index values were significantly increased in type 2 diabetic patients compared with controls and also significantly increased values were observed in microalbuminuric diabetics compared with normoalbuminuric diabetics. A high renal RI may reflect increased stiffness of preglomerular arteries and increased intrarenal vascular resistance, including postglomerular circulation [27].

Hashimoto J and Ito S [28] reported that microalbuminuria is associated with increased RRIs and that in turn, depend on increased central pulse pressure and aortic stiffness as well as abnormal renal hemodynamics – namely increased peripheral resistance and/or increased flow pulsation. Histological studies demonstrated that RRI not only reflects changes in intrarenal perfusion and renovascular resistance but was increased in several pathological conditions, such as renal atherosclerosis and tubulointerstitial damage [29-31]. RI is a noninvasive diagnostic procedure, which strongly predicts the outcome of renal function in type 2 diabetic patients, even when GFR patterns are still normal [32].

The present study showed that interlobar and arcuate artery resistive index has strong positive correlation with ACR. Previous studies reported an association between RI and other markers of arterial stiffness as pulse wave velocity and ankle-brachial blood pressure index [33-35] and some studies reported the association between RI value and the extension of interstitial fibrosis [36] and the severity of renal impairment [37-42].

In addition present study shows that strong positive correlation of interlobar artery resistive index with HOMA-IR & HbA1c. Chronic hyperglycemia, insulin resistance, and low-grade systemic inflammation leading to endothelial damage in diabetes [43]. Insulin resistance is characterized by pathway-selective impairment in PI3K-dependent signaling in both metabolic and vascular insulin target tissues, whereas other insulin-signaling branches, including Ras/mitogen-activated protein kinase-dependent insulin signaling typically regulates mitogenesis, growth, and differentiation [44]. In the endothelium, decreased PI3K signaling and increased mitogen-activated protein kinase signaling in response to insulin may lead to decreased production of nitric oxide (NO)and increased secretion of endothelin-1, a characteristic of endothelial dysfunction[45]. Moreover, the small and medium size vessels respond inappropriately to vasodilatory stimuli such as acetylcholine, the production of which is mediated by nitric oxide (NO) [46]. NO plays numerous physiological roles in the kidney, including control of renal and glomerular hemodynamics, by interfering at multiple and physiologically critical steps of nephron function [47]. NO is also responsible for mediation of pressure natriuresis, maintenance of medullary perfusion, blunting of tubuloglomerular reabsorption, and modulation of renal sympathetic nerve activity [48]. Youssef DM and Fawzy FM had reported a positive correlation between HbA1c and mean RI and concluded that RI is increased early in TI-DM, and it can be a predictor of DN [49]. Therefore, increased

renal resistive index in the kidney has been regarded as an index of progressive renal damage in diabetic patients.

In conclusion, RRI might be a non invasive diagnostic marker of early renal vascular changes and is positively correlated with insulin resistance and HbA1c in type 2 diabetes mellitus. Further more studies on a larger sample size is needed to confirm our findings.

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