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Diagnostic Value Of Renal Resistive Index In Predicting Histopathological Severity Of Diabetic Nephropathy In Type 2 Diabetes Mellitus

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Abstract

Background: Diabetic nephropathy is considered as one of the most severe complications of Type 2 Diabetes Mellitus, and is a major cause of chronic kidney disease and end-stage renal failure in the global context. The early signs of renal injury are a significant clinical problem because traditional biomarkers, including estimated glomerular filtration rate (eGFR) and albuminuria, mainly indicate functional deficiency at late stages of the disease, but not the early structural alterations.

Objective: This study was intended to determine the usefulness of the Renal Resistive Index (RI), which is a Doppler ultrasonography-derived index, in determining the severity of diabetic nephropathy.

Methodology: This cross-sectional study was analytical involving 40 patients with Type 2 Diabetes Mellitus. The department of Radiology and Nephrology at Mayo Hospital, Lahore was used as the source of data. The SPSS version 27 was used to examine demographic, clinical, biochemical and Doppler parameters. The descriptive statistics, correlation analysis, and linear regression were used to evaluate the correlation between RI and parameters of renal functions.

Results: The average age of the patients was 48.6 and the standard deviation was 7.9 with a male majority (67.5%). The average life span with diabetes was 7.6 years with a standard deviation of
2.2. High serum creatinine (2.05 ± 1.18 mg/dL) and low eGFR (67.2 ± 23.8 mL/min) revealed the presence of poor renal functioning. A majority of patients (62.5%) had high RI values (>0.80). The rise of RI was statistically significant as the severity of albuminuria rose ($p < 0.001$). Positive correlations were observed to be strong between RI and serum creatinine ($r = 0.87$) and microalbumin ($r =$

0.79), whereas a negative correlation was found to be strong between RI and eGFR (r = -0.91). RI was also confirmed as an important predictor of renal dysfunction by regression analysis.
Conclusion: To summarize, Renal Resistive Index is an effective non-invasive biomarker that is highly correlated with renal functioning and severity of the disease in diabetic nephropathy. Its adoption as a standard clinical procedure can improve the process of early disease identification, risk assessment, and disease progression tracking.

Chapter 1
INTRODUCTION

Type 2 diabetes Mellitus (T2DM) is a worldwide epidemic, and the complications of diabetes are a major issue threatening the health frameworks of people. Diabetic Kidney Disease (DKD) is one of these and one of the most serious ones since it eventually develops into end-stage renal disease (ESRD) in a significant percentage of patients and requires dialysis or transplantation [1]. The classical route to diagnosing and following DKD depends on the appearance of microalbuminuria in a sequential order, and the subsequent decrease in the eGFR [2]. Nevertheless, this paradigm has a major flaw. The first weakness is that there is a so-called non-albuminuric diabetic kidney disease, in which patients show a reduction of GFR without albuminuria development ever [3]. This phenotype can explain 1/3 of all the cases of DKD. Moreover, albuminuria may be fluctuating and affected by the presence of such factors as exercise, infection, and hypertension diminishing its specificity [4]. Most importantly, the fact that sustained deterioration in eGFR indicates the destruction of enormous amounts of nephrons is a situation of no-return in most instances. Such a diagnostic lag provides an important window of time during which early intervention may be the most effective intervention, but to which we do not have a sensitive and routine diagnostic tool.

Pathophysiologic processes in early DKD are hyperfiltration of glomeruli, endothelial dysfunction, and thickening of the capillary basement membrane, which gradually result in further intrarenal vascular resistance [5]. This vascular impedance and compliance is directly measured as the Renal Resistive Index (RRI) which is computed based on Doppler waveform analysis as (Peak Systolic Velocity - End-Diastolic Velocity)/Peak Systolic Velocity). High RRI (>0.70) is not unique to diabetes but rather a manifestation of underlying renal parenchymal injury such as tubulointerstitial fibrosis and arteriosclerosis the same phenomena of progressive DKD [7]. As shown by previous researchers, RRI is elevated in diabetic patients than in healthy controls and linked to the length of diabetes and the other vascular complications [8]. Thus, the present study will serve the purpose of the entire assessment of the use of RRI as an early, non-invasive biomarker to identify and stratify renal damage in a cohort of T2DM patients, which would play a crucial roThe Renal Resistive Index (RI) and Pulsatility Index (PI), traditionally used in Doppler ultrasonography to assess renal blood flow and vascular resistance, have significant clinical applicability that extends far beyond diagnostic purposes. A high RI, which reflects increased resistance to blood flow within the intrarenal arteries, is often a consequence of structural and functional changes in the renal vasculature, such as arteriosclerosis, interstitial fibrosis, and microvascular rarefaction. These changes impair renal perfusion and oxygenation, leading to progressive nephron loss and the accelerated decline of kidney function thereby contributing to faster progression of chronic kidney disease (CKD). Moreover, a high RI has been strongly correlated with increased cardiovascular morbidity and mortality, as it mirrors systemic vascular stiffness and endothelial dysfunction pathophysiological processes that are shared between renal and cardiovascular diseases [9].

Diabetes mellitus is now one of the fastest-growing metabolic syndrome in the world with Type 2 Diabetes Mellitus (T2DM) being the most prevalent clinical manifestation. The increased prevalence of diabetes in the world is closely associated with urbanization, aging, decreased physical activity, and changes in diets to high-calorie diets [16]. The chronic hyperglycemia causes alteration of carbohydrate and lipid metabolism, which causes chronic vascular impairment in various organs such as kidney and cardiovascular tissue [17]. Diabetic prevalence is projected to acquire an upward trend with no end in sight with epidemiology showing a major increase in epidemics especially where genetic predisposition and lifestyle behaviors exist in combination [18, 19].

Diabetic kidney disease (DKD) has been identified as one of the most severe long-term effects of T2DM and is the major cause of kidney chronic failure in the world. The kidney is involved in the disease process in about a third of diabetic patients [20]. Advanced renal failure is a high risk of hospitalization and mortality in diabetic patients [21, 22]. The related economic cost of dialysis and kidney transplantation further highlights the importance of detecting and preventative measures of monitoring at a young age [23]. Diabetic nephropathy pathophysiology is complex with metabolic and hemodynamic processes triggered by a long period of hyperglycemia. The enhancement of the production of advanced glycation end products and the activation of inflammatory mediators stimulate endothelial dysfunction and oxidative stress [24, 25]. This is the stimulation of mesangial expansion and glomerular sclerosis through these molecular changes, which ultimately leads to a decrease in renal capacities of filtration [26].

Renin-angiotensin-aldosterone system activation also promotes structural remodelling and intraglomerular hypertension [27].

Early diabetic kidney disease is marked by glomerular hyper-filtration and microvascular dysfunction which comes before the disease starts showing. Both the glomerular basement membrane thickening and podocyte injury are present well before the renal function deterioration could be detected [28]. Gradual deposition of extracellular matrix results in interstitial fibrosis and tubular atrophy that are the signs of permanent kidney damage[29]. These unspoken changes in the structure point to the significance of sensitive diagnostic signs that can help identify the initial stages of the disease [30,31].

Recent clinical assessment of DKD mainly relies on estimates of glomerular filtration rate (eGFR) and amounts of urinary albumin being excreted. Although there is a general acceptance of these biomarkers, they predominantly manifest a functional loss, as opposed to structural loss [32]. As various researchers have demonstrated, considerable nephron loss can be present even before the patient has some abnormal laboratory values [33]. As such, the use of biochemical markers alone can slow down therapeutic intervention and control of the disease [34, 35]. Recent studies have pointed to a non albuminuric phenotype of diabetic kidney disease where renal function progressive decays without much proteinuria. This observation is a challenge to the classical progression model which merely relies on albuminuria [36,37]. There are also chances of structural vascular damages without albumin leakage indicating other possible pathological mechanisms. Looking at this phenotype has raised the need to find out more imaging-based diagnosis methods that can be used to identify vascular abnormalities earlier [38].

Measurements of albuminuria can also be affected by short term physiological exertions like exercise, infection, state of hydration, and fluctuation in blood pressure. These differences lessen the diagnostic accuracy and can create discrepancies across the clinical interpretation [39]. Moreover, glycemic fluctuation and pharmacological intervention may change the urinary protein excretion without structural kidney damage [40]. Consequently, the biomarkers that are more stable and reproducible are needed to measure the disease accurately [41, 42].The intrarenal vascular resistance is

critical in the development of diabetic kidney injury. Prolonged metabolic stress leads to the thickening of arterial walls, endothelial dysfunction and decreased nitric oxide levels [43]. These changes in the vessels sacrilege renal perfusion and oxygen transport and encourage fibrosis and loss of nephrons through hypoxia. The changes in renal hemodynamics are a manifestation of the beginning of disease progression, and they are observed before the functional deterioration is observed [44, 45].

Doppler ultrasonography has turned out to be a useful non-invasive modality in assessing the renal blood flow dynamics. The method enables real-time evaluation of resistance in vessels without radiation or the use of contrast agents [46]. It is inexpensive, easily available and repeatable, and hence suitable to undertake regular clinical screening of diabetic patients [47]. The Doppler assessment offers functional data to that of biochemical studies [48,49]. Renal Resistive Index (RRI) is computed based on systolic and diastolic velocity of flow in intrarenal arteries. It is a parameter of downstream vascular impedance and compliance in the arteries in renal parenchyma [50]. High RRI values have been linked to aging, hypertension, and vascular systemic rigidity [51, 52]. Therefore, RRI is becoming more of a microvascular injury marker but not a hemodynamic measure [53].

Histological examination has shown that there are strong correlations between high RRI and structural abnormalities in the kidneys including interstitial fibrosis and arteriosclerosis. These pathological results are the focus of the development of diabetic nephropathy [54]. RRI thus offers some indirect information on the severity of histopathology without the need to perform invasive diagnostic practices [55,56]. These associations facilitate its possible as an imaging surrogate endpoint of renal damage [57]. The gold standard of assessing histopathological injury is the renal biopsy; a series of risks is associated with it such as bleeding complications and patient discomfort. There are a lot of diabetic patients who cannot be considered as appropriate to be subjected to biopsy because of comorbid conditions [58,59]. Its accessibility and cost of procedures also restrict its routine clinical application [60]. There is therefore an urgent need of reliable alternatives that could forecast histological severity which are non-invasive [61, 62].

RRI has also been associated with systemic abnormalities of the cardiovascular, which is a generalized endothelial dysfunction. Research also reveals correlations of high RRI levels with left ventricular hypertrophy and arterial stiffness [63]. These results show that the renal vascular resistance is a reflection of the health of the systemic vascular [64]. Therefore, RRI evaluation could give predictive data that is not limited to renal disease per se [65, 66]. There are positive signs of emerging evidence on the ability of RRI to detect early renal vascular impairment in diabetic patients with normal serum creatinine levels and preserved and normal eGFR. Early diagnosis is possible at this stage which enables prompt adoption of renoprotective measures [67]. Early treatment has been demonstrated to retard the progression of the disease and complications [68]. Hence, the inclusion of Doppler parameters into the everyday assessment can help make better clinical decisions earlier [69, 70]. Contemporary pharmacological treatments, recapitulated by reninangiotensin blockers and sodiumglucose cotransporter-2 blockers, have an effect on the renal hemodynamics. Follow-up of RRI could also be used to assess therapeutic response and stabilization of disease [71, 72]. Biomarkers that can be visualized are becoming highly appreciated in individual-based medicine practices [73]. This indicates the possibility of RRI in long-term monitoring of patients [74, 75].

Diabetic Kidney Disease (DKD) is a common complication of Type 2 Diabetes that can lead to kidney failure. Current tests like eGFR and UACR detect kidney damage only in later stages. The Renal Resistive Index (RRI), measured by a simple Doppler ultrasound, may help spot early kidney changes. Proving its usefulness could make early detection and treatment of DKD easier and more affordable.

Aims and Objective

To determine the diagnostic usefulness of Renal Resistive Index (RRI) in determining the histopathological severity of diabetic nephropathy in patients with Type 2 Diabetes Mellitus.

Chapter 2
LITERATURE REVIEW

Geraci et al. (2025) evaluated the diagnostic and prognostic value of the Renal Resistive Index (RI) on patients with chronic kidney disease (CKD), even with Type 2 Diabetes Mellitus (T2DM). The patients enrolled in the study were 120 adults with 65 patients having diabetes and RI was measured through Doppler ultrasonography in the interlobar arteries. Besides RI, the cardiovascular variables, including the left ventricular mass index, renal functions variables including estimated glomerular filtration rate (eGFR) and albuminuria, were measured. The findings showed that diabetic patients recorded much higher RI values (mean RI = 0.78) than non-diabetic CKD patients (mean RI = 0.70). High RI was closely associated with lower eGFR, higher albuminuria, and risk of cardiovascular. The authors came to the conclusion that RI is a valid predictor of intrarenal resistance to vascularity and can be used as a two-fold predictor of both renal and cardiovascular risks in patients with diabetes. Nevertheless, the cross-sectional design of the study did not allow it to be causal or determine how RI changed with time. Moreover, due to non-standardized RI measurement protocols in different operators, reproducibility could be influenced. Although these are the limitations, the study offers strong arguments in support of the incorporation of RI to normal nephrology of diabetic patients to detect early risk stratification and cardiovascular surveillance [10].

Kharsa et al. (2023) used retrospective cohort study to investigate the relationship between the values of Renal Resistive Index (RI) and the development and mortality of kidney diseases in patients with Type 2 Diabetes Mellitus (T2DM). The paper has examined the clinical data of 200 patients including 90 diabetics and assessed RI through Doppler ultrasonography. Three-year follow-up was done on patients and the results were the development of end-stage renal disease (ESRD) and all-cause mortality. The results showed that patients whose RI surpassed the value of
0.80 had considerably higher percentages of renal loss and mortality especially in the diabetic group. The RI was also a predictive factor of adverse outcome despite the correction of age, baseline eGFR, and comorbid conditions. The authors concluded that RI is a strong prognostic factor in diabetic kidney disease and it could be used to determine high-risk patients that need further monitoring and aggressive treatment. Nevertheless, the study is retrospective, which predisposes the risks of bias and the absence of standardized protocols of RI measurement in various operators can influence the reproducibility of the outcomes. In addition, the research did not investigate how therapeutic interventions would influence the values of RI which would have given information on whether it can respond to treatment. Irrespective of these restrictions, the study highlights the significance of RI in risk stratification at long-term of diabetic patients with renal impairment [11].

Kuttancheri et al. (2023) investigated how Renal Resistive Index (RI) correlates with histopathological damage in patients with chronic kidney disease (CKD) regardless of the etiologies, diabetic or non-diabetic. This was a prospective study that included 60 patients with renal biopsy where RI was measured using Doppler ultrasound before the procedure. The glomerulosclerosis, interstitial fibrosis, and vascular alterations were studied, using histological examination. The authors concluded that moderate to severe levels of glomerulosclerosis and interstitial fibrosis were significantly correlated with RI values of more than 0.75 and especially in diabetic nephropathy. The patients with diabetes had increased RI values and a greater number of vascular lesions than did their Non-Diabetic counterparts. These authors concluded that RI is a good predictor of histopathological severity and can be used as a non-invasive

surrogate to the results of the biopsy in diabetic kidney disease. It is especially useful in a clinical environment where a biopsy is not only contraindicated but also impractical. Nevertheless, the small size of the sample and the use of one center design make it difficult to generalize the results of this study. Moreover, the research failed to provide longitudinal follow-up in order to determine changes of RI over time or in reaction to treatment. The variability among the operators in measuring RI was not also considered and this may affect the accuracy of the results. However, the research is valuable in its evidence of the usage of RI as a structural predictor of renal injury of diabetic patients [12].

Eleki et al. (2023) is a prospective study that was carried out in order to assess the predictive value of the Renal Resistive Index (RI) in the early detection of renal dysfunction in patients with Type 2 Diabetes Mellitus (T2DM). The participants that were enrolled in the study were diabetic patients with normal serum creatinine and normoalbuminuria at baseline. Doppler ultrasonography of the interlobar arteries was used to measure RI and patients were monitored over 12 months where estimated glomerular filtration rate (eGFR) and urinary albumin levels were measured periodically. The researchers discovered that patients with RI values of more than 0.72 were much more prone to develop microalbuminuria and suffer a decrease in eGFR over the follow-up period.

These results indicate that RI may identify subclinical vascular alterations of the kidney before biochemical markers get distorted. The authors inferred that RI is a non-invasive and sensitive instrument to early-stage diagnosis of diabetic kidney disease (DKD) which can help in early-stage intervention and possible postponement of the disease. The study however, remained confined to the single center study and could not be compared with other emerging biomarkers like cystatin C or even the NGAL. Also, the therapeutic interventions on RI values were not investigated in the study which would have shed light on how responsive it is to treatment. In spite of these shortcomings, the study contributes to the need to include RI in the standard screening regimen of diabetic patients who are at risk of developing renal impairment [13].

The randomized controlled trial by Pradhan et al. (2022) aimed at examining glucagon-like peptide-1 receptor agonists (GLP-1 RAs) versus sodium–glucose cotransporter2 inhibitors (SGLT2i) in patients with Type 2 Diabetes Mellitus (T2DM) on the changes in Renal Resistive Index (RI) and renal outcomes. In the study, 180 diabetic patients were randomly allocated to three groups of GLP-1 RA therapy, SGLT2i therapy and placebo. Doppler ultrasound was used to measure RI at 18 months and baseline and at 6 months intervals. The renal functioning was followed with the help of eGFR and the volume of urinary albumin. The findings indicated that the mean decrease in the RI values was significant (0.05) in both groups of the treatment which was associated with the increase in eGFR and the decrease in albuminuria. There were no significant changes in the placebo group. These results indicate that RI is sensitive to renoprotective interventions and can be used as a dynamic indicator of the treatment response in diabetic kidney disease (DKD). The authors have worked out that RI may be applied in order to track therapeutic reaction and inform clinical decision-making in patients with T2DM and early renal involvement. Yet, a number of limitations were faced by the study because it had a rather small follow-up period, as well as it was not ethnically diverse, which can impact the generalization of the findings. Also, the research failed to assess long-term cardiovascular outcomes that are closely correlated with renal health in diabetic populations. However, the trial is a good indication of the usefulness of RI in assessing the measures of success in pharmacological interventions in DKD [14].

The study by Afasr et al. (2017) is a cross-sectional study aimed at assessing the correlation between Renal Resistive Index (RI) and biochemical indicators of renal functioning in patients with Type 2 Diabetes Mellitus (T2DM). In the study, 100

diabetic patients who were seen in a tertiary care facility were used, and all of them received Doppler ultrasonography of the interlobararteries to determine RI. At the same time, a laboratory work was conducted to determine serum creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin excretion. The researchers discovered high values of RI of above 0.72 to be significantly linked with microalbuminuria and high levels of serum creatinine. It is noteworthy that RI showed a greater correlation with renal impairment compared to serum creatinine and albuminuria separately, which implies that it may be a more sensitive marker of initial renal vascular alterations. The authors concluded that RI has the potential to be used as a useful complement to conventional biochemical markers in early diagnosis of diabetic kidney disease (DKD). Nonetheless, this research was cross-sectional, which did not contribute to determining the time relationship or causality. The research also lacked a control of non-diabetic persons who would have given comparative information. The variability of the operator in Doppler measurements had been also not discussed which may have an impact on the consistency of RI values. Irrespective of these shortcomings, the study supports the clinical significance of RI as a non-invasive and convenient method of detecting early renal malfunction in patients with diabetes especially in the environment where lab resources are constrained [15].

In their study, Parolini et al. (2009) carried out a comprehensive longitudinal study to determine the prognostic value of the Renal Resistive Index (RRI) in patients with a variety of chronic nephropathies of different etiologies, such as diabetic kidney disease. Long term renal outcomes were followed with the help of Doppler ultrasonography in the measurement of intrarenal arterial RI. They indicated that patients who had high values of RRI recorded a much slower rate of renal deterioration regardless of the level of serum creatinine and proteinuria at the onset. Notably, they have noted that increased RRI indicates permanent structural changes, i.e., interstitial fibrosis, arteriosclerosis, and decreased vascular compliance, not temporary alterations in the hemodynamics. The results confirm the idea that RRI may be used as a surrogate of chronic histopathological damage. Nonetheless, the presence of mixed renal pathologies reduced the specificit y of the conclusions made in the case of diabetic nephropathy, and the necessity of the disease-specific examination emerged [73]

Radermacher et al. (2002) examined the predictive power of renal resistance index on the development of renal disease by use of a prospective cohort study. Intrarenal RI was measured by Doppler ultrasound and the patients were monitored in terms of worsening of the renal functions. The researchers found that values of RI above 0.80 were well correlated with rapid development ofrenal failure and unfavorable renal survival. It is worth noting that RI was an independent predictor in the second setting after the conventional predictors which include blood pressure, proteinuria, and initial glomerular filtration rate were considered. They suggested that RI is an indication of structural vascular injury and parenchymal stiffness and does not indicate independent changes in blood flow. The limitation was identified as the lack of histological correlation, but the prognostic significance is very strong to support the role of RI in the assessment of chronic kidney disease [74].

By comparing the results of Doppler ultrasound to the renal biopsy, Bigé et al. (2012) investigated the relationship between renal arterial resistive index and the histological severity of chronic kidney disease in a patient population. Their analysis has shown that there is a close correlation between high RRI values and significant histopathological abnormalities with progressive interstitial fibrosis, tubular atrophy, and glomerulosclerosis. They drew attention to the fact that patients with high RRI had poorer renal outcomes, which confirms the idea that RRI is a non-invasive manifestation of structural damage. Such results are especially important to diabetic nephropathy, in which the vascular and interstitial lesions take up the leading role in the disease evolution. Despite the small sample size, the research gives important

evidence in favor of the use of RRI as a surrogate endpoint, regarding the level of histopathological severity [75].

Sugiura and Wada (2009) assessed the prognostic value of renal resistive index in chronic kidney disease and they showed that high RI values were positively related to poor renal survival on their own. Their results indicated that RI indicates intrarenal vascular constriction and decreased compliance of the arteries, which are the typical features of chronic structural injuries. They also stressed that RI is not just a marker of the renal blood flow, but it is a composite measure of vascular remodeling and interstitial fibrosis. This strengthens the clinical usefulness of RI as an indicator of a permanent kidney damage especially in disorders with micro vascular damage like diabetic nephropathy [76].

Conti et al. (2014) performed ultrasonographic and histopathological correlation analysis in order to identify the usefulness of intrarenal resistive index in patients with lupus nephritis. The renal resistive index measured by doppler ultrasound was compared with the results of renal biopsy, that is, vascular lesions, interstitial fibrosis, and glomerular damage. The researchers found that patients that had a greater RI values had much more serious vascular and interstitial lesions (especially arteriosclerosis and interstitial fibrosis) that are considered to be predictors of irreversible damage to the kidneys. Even though the study population comprised of non-diabetic patients, the pathophysiology processes that were observed, endothelial dysfunction, vascular stiffness and diminished renal compliance are similar to those in diabetic nephropathy. The data are highly consistent with the hypothesis that RI indicates chronic presence of histopathological severity, but not temporary changes in hemodynamics, which supports the hypothesis that it is a non-invasive surrogate endpoint of renal structural injury [77].

Tervaert et al. (2010) suggested an extensive pathological classification system of diabetic nephropathy, which includes the histological severity of diabetic nephropathy, including glomerular, interstitial, and vascular lesions. This study highlighted the fact that the occurrence of disease is not only based on the damage of the glomeruli but also is heavily dependent on the vascular remodeling process and interstitial fibrosis. These pathological alterations cause augmented intrarenal vascular opposition and slower arterial compliance which are straightforwardly quantified through Doppler-based measures like the Renal Resistive Index. They also emphasized the fact that vascular lesion may be premonitored by overt functional deterioration and therefore considered imaging biomarkers of vascular resistance may indicate the presence of disease earlier in the progression of the disease than biochemical biomarkers. This categorization gives a good histopathological basis to the fact that RRI can be used as an indirect, non-invasive disease severity measure in diabetic nephropathy [78].

The review of the histopathological evolution of diabetic nephropathy by Fioretto and Mauer (2007) is comprehensive, as it describes the sequential structural alterations, which take place during the disease progression. Early changes as outlined by the authors comprised thickening of the glomerular basement membrane, mesangial matrix enlargement and podocyte injury, which was then succeeded by gradual interstitial fibrosis and vascular sclerosis. Notably, they highlighted the fact that such structural defects are also likely to occur long before the albuminuria or estimated glomerular filtration rate starts to change. The review pointed at the importance of microvascular damage and impaired capillary perfusion in the pathogenesis of the disease, which directly affect the rise of intrarenal vascular resistance. These results are a strong indication of the applicability of Doppler ultrasound-derived RRI as a sensitive measure that has the capacity to identify the initial renal vascular alterations prior to the onset of irreversible functional damage [79].

Persson and Rossing (2018) provided a critical review of existing diagnostic methods of diabetic kidney disease and revealed the shortcomings of traditional biomarkers

like albuminuria and eGFR. The authors emphasized the current recognition of non-albuminuric diabetic kidney disease where their structural and vascular damage are extensive without high levels of excretion of urinary proteins. They highlighted that there is a necessity of complementary diagnostic instruments that can detect early intrarenal vascular dysfunction. It was suggested that imaging modalities especially Doppler ultrasonography that measures Renal Resistive Index are useful non-invasive techniques to identify early hemodynamic and structural changes. They made a conclusion that the incorporation of RRI into the regular clinical evaluation may enhance the early diagnosis and risk stratification of diabetic patients [80].

Heerspink et al. (2019) have developed a meta-analysis comprising of large meta-analysis designs to assess the validity of surrogate markers to predict the progression of kidney disease in randomized clinical trials. They found out that variations in albuminuria are not always an indication of structural damage and long-term renal outcomes. They underlined the importance of the fact that vascular and interstitial damage could be silent with the stable biochemical parameters. These results justify the increased desire of alternative markers of structural and hemodynamic changes, e.g. Renal Resistive Index. RRI provides an optional solution to conventional biochemical markers and can be used to complement other relevant tools because it can detect and monitor the progression of diabetic kidney disease in its early stages [81].

Pavkov et al. (2024) have undertaken a review of the world burden of kidney disease among patients with diabetes and have stressed the role of timely detection of individuals at the high-risk stage to avoid end-stage renal disease. They emphasized the fact that diabetic kidney disease is often underdiagnosed at its early stages because of the use of biochemical markers manifested in the late stages. They talked about the new role of non-invasive imaging methods especially Doppler ultrasound that measures intrarenal blood flow as a viable and cost effective screening test. Renal Resistive Index was found as a promising parameter that can be effectively used in the detection of early vascular dysfunction and administration of timely therapeutic intervention [82]. Umanath and Lewis (2018) have surveyed the most current developments in the knowledge and management of diabetic nephropathy with special attention to the early identification of the disease. They emphasized that microvascular damage and endothelial dysfunction are key in disease-initiation and disease-progression. The parameters of Doppler ultrasound such as Renal Resistive Index were mentioned as significant markers of intrarenal vascular injury. They highlighted that RRI is associated with the severity and progression of the disease, and it potentially can be applied to track the therapeutic response in any patient who has undergone renoprotective therapies [83].

Deferrari and Vettoretti (2015) studied the correlation between subclinical renal damage, pulse pressure and vascular stiffness in chronic kidney disease patients. Their experiment has revealed that the augmented stiffness of the arteries is connected to the hampering of renal microcirculation, perfusion, and the continuous loss of nephrons. The authors highlighted that vascular stiffening leads to augmented conveying of pulsatile pressure to intrarenal blood vessels, which favors endothelial dysfunction and interstitial fibrosis. Because Renal Resistive Index is dependent on the compliance of the arteries and downstream resistance, the research is good indirect evidence that a high RRI is an indicator of both systemic and renal vascular pathology. These processes are especially applicable to diabetic nephropathy, wherein chronic hyperglycemia increases the rate of arterial hardening and microvascular damage, so RRI is an excellent measure of the severity of the disease [84].

Mendonca and Gupta (2010) tested the prognostic value of Renal Resistive Index in chronologically followed patients with chronic kidney disease. Their results revealed that, higher RRI patients had a much quicker deterioration of renal functioning as well as worse renal survival, regardless of their initial glomerular filtration rate, and

proteinuria. Theyemphasised that RRI is not a mere indicator of renal blood flow only but shows long-term structural changes such as interstitial fibrosis, tubular atrophy, and vascular remodelling. They also supported the fact that RRI combines both intrarenal and systemic vascular alterations and is a strong predictor of irversible renal damage. The findings favour clinical use of RRI in risk stratification and predicting the clinical progression of diabetic nephropathy[85].

Iwashima et al. (2018) examined the predictive worth of Renal Resistive Index on renal results in patients who underwent an interventional procedure relating to renal vascular disease. The researchers have found that high baseline RRI was a definite indicator of low renal recovery and adverse outcomes, independent of the success of renal blood flow restoration. The conclusion of the authors was high RRI indicates developed parenchymal and vascular damage restricting renal reversibility. The findings highlight the idea that RRI is chronic histopathological severity and not temporary hemodynamic changes. As a chronic and prognosis predictor of disease, RRI is useful

in the context of diabetic nephropathy in which interstitial and vascular damage is commonly developed by the time the disease is diagnosed [86].

As explained by Milovanceva-Popovska and Dzikova (2008), Doppler ultrasonography has been used in nephrology with its role in determining renal hemodynamics and vascular resistance. The authors placed emphasis on the renal Resistive Index as is a reproducible parameter that is operator independent when standard protocols are adhered to. They talked about the fact that increased RRI is an indicator of impaired vascular compliance, elevated interstitial pressure, and microvascular rarefaction. They highlighted the fact that Doppler-derived parameters offer useful data which supplements biochemical measurements and structural imaging. These benefits render RRI especially appropriate in tracking chronic illnesses like diabetic nephropathy where abusive testing is inconvenient [87].

Cooper (1998) has presented an overall summary of the pathways of pathogenesis of diabetic nephropathy with chronic hyperglycemia being the central cause of oxidative stress, endothelial dysfunction, and inflammatory stimulation. These mechanisms culminate in a progressive thickening of the glomerular basement membrane, mesangial enlargement and subsequent interstitial fibrosis and vascular sclerosis. They also highlighted the fact that vascular damage is a significant predictor of disease progression and adverse renal outcomes. These pathological alterations cause intrarenal vascular resistance and hence, they provide a good mechanistic explanation of high Renal Resistive Index values in diabetic patients. This initial study is a basis of investigating the feasibility of the biological plausibility of RRI to serve as a surrogate of histopathologic severity [88].

Tuttle et al. (2014) have provided a common opinion on diabetic kidney disease and that early detection of kidney damage is essential to avert the development of end-stage renal disease. They referred to the shortcomings of standard diagnostic measures, stating that albuminuria and eGFR tend to represent a late functional injury and not an early structural one. The use of imaging strategies (such as Doppler ultrasonography) was suggested to complement the use of early vascular changes. Renal Resistive Index was noted as a promising non-invasive test that can be able to tell high-risk patients earlier and provide them with a unique therapeutic approach [89].

An et al. (2015) looked at the association between clinical outcomes and renal histological changes on diabetic nephropathy patients. Their analysis showed that vascular and interstitial lesions especially arteriolar hyalinosis and interstitial fibrosis were more predictors of renal outcomes

than those of glomerular changes. They noted that these structural anomalies have a strong linkage with the inadequacy of intrarenal blood circulation and a rise in the vascular resistance. These data are a good evidence that the high level of Renal

Resistance Index is associated with the severity of the histopathologic changes and can be used as the non-invasive predictor of the disease progression in diabetic nephropathy [90].
Additional discussion by Parolini et al. (2009) underlined the fact that Renal Resistive Index combines various pathological causes such as vascular stiffness, interstitial fibrosis and decreased renal compliance. They pointed out that RRI is a strong prognostic predictor of renal outcomes in diverse etiologies and it is a powerful predictor of renal outcomes even after the control of traditional risk factors. They supported the idea that RRI indicates the cumulative damage of the structural burden in the kidney. The results can be especially applied to diabetic nephropathy where multi-core injury plays a role in disease progression [91].
Guo et al. (2025) presented a state-of-the-art Doppler-based research, which optimized the non-invasive methods of diagnostics of diabetic nephropathy. They have shown that there is a strong and consistent relationship between renal artery resistive index and histopathological severity, that is, the glomerulosclerosis, interstitial fibrosis and vascular lesions. Theyalso highlighted that RRI was very diagnostic in distinguishing mild and advanced stages of the disease. They found that RRI could play a major role in decreasing the usage of invasive renal biopsy, especially in patients who have contraindications to biopsy, and complement its usage as a consistent surrogate endpoint of histopathological analysis [92].

Chapter 3
MATERIAL AND METHODS

Design of Study: Analytical Cross-Sectional Study.
Setting of the Study: Department of Nephrology/Radiology and Medicine of Mayo Hospital, Lahore, Punjab, Pakistan.
Period of the study: 4 months to complete the data collection.
Sample Size: **40**
This means 40 or more measurements/surverys are needed to have a confidence level of 95% that the real value is within 5% of the measured/surveyed value.
Sampling Technique: Conveniant Sampling Technique.

Inclusion Criteria:
Adults aged 30-70 years.
Has had a diagnosis of T2DM of at least Ten years.
Informed consent = willing and able.

Exclusion Criteria:
Known renal disease (non-diabetic other) (e.g., GN, PCKD).
Renal transplant history, renal artery stenosis, solitary kidney.
Conditions that are independent of diabetes and occur in RRI: e.g., congestive heart failure (NYHA Class III/IV), atrial fibrillation, severe hydronephrosis.
The presence of acute kidney trauma or urinary tract infection by the time of enrollment.
Pregnancy.
Ethical Considerations
Written informed consent (attached) will be taken from all the participants.
All information and data collection will be kept confidential.
Participants will remain anonymous throughout the study.
The subjects will be informed that there are no disadvantages or risks on the procedure of the study.
They will also be informed that they will be free to withdraw at any time during the process of the study.

Mention if there will be any known risks associated with this research.
Mention if there will be benefits to the participant that would result from their participation in this research.
We will do everything we can to protect your privacy. Your identity will not be revealed in any publication resulting from this study.
Your participation in this research study is voluntary. You may choose not to participate and you may withdraw your consent to participate any time. You will not be penalized in any way should you decide not you participate or to withdraw from this study.

Data Collection Procedure

The structured proforma was used to collect data upon informed consent of every participant. Demographic, clinical, biochemical, and imaging information was documented in an orderly manner. Doppler ultrasonography was done on all patients to measure Renal Resistive Index. Enough care was observed to ensure accuracy and consistency in data collection. Simple demographic data such as age, gender, and diabetes time of onset were taken. The average age of the adults was 48.6/7.9 years, most of them male (67.5%). The mean time of diabetes was 7.6 ± 2.2 years. This information assisted in learning the background of the study population. Blood samples were taken to determine parameters of renal functioning. The median serum creatinine was 2.05 +
1.18 mg/dL, which showed that there was impaired renal functioning. The average eGFR level was
67.2 and 23.8mL/min, which demonstrated poor kidney functioning. The level of albuminuria was also taken to assess the severity of the disease. Renal Doppler ultrasonography was done under the normal protocols and by an experienced radiologist. Interlobar arteries were used to calculate the Renal Resistive Index (RRI). About 62.5 percent of the patients were found to have high RRI values (>0.80). This showed a rise in intrarenal vascular resistance and potential structural injury. Renal Resistive Index (RRI) was the independent variable in this study. Dependent variables were serum creatinine, eGFR and albuminuria. The variables were chosen to measure the severity of the disease and renal performance. Their association was useful in determining the predictive value of RRI.Data Analysis Procedure
The SPSS version 27 was used to analyze the data. Descriptive statistics (mean ± SD, frequencies, percentages) were calculated for all variables. One-way ANOVA was used to compare the mean RI of the albuminuria severity groups. The correlation examined by Pearson was used to evaluate associations between RI and parameters of renal functioning (creatinine, eGFR, microalbumin). Simple linear regression was used to test the predictive value of RI on each of the dependent variables. A p-value <0.05 was considered statistically significant.

Chapter 4
RESULTS

There were 40 patients analyzed. The mean age was 48.6 ± 7.9 years, with a male predominance (67.5%). The average age of diabetes was 7.6 years plus or minus 2.2 years.The examination of renal functions showed high serum creatinine (2.05 ± 1.18 mg/dL) and low eGFR (67.2 ± 23.8 mL/min).Most patients had albuminuria, with 47.5% having severe (3+) albuminuria.The average renal resistive index was 0.79 + 0.11 and 62.5 percent of patients were found to have big RI.There was also a statistically significant effect of RI on the severity of albuminuria ($p < 0.001$).Correlation analysis showed that there was a strong positive relation of RI and serum creatinine and microalbumin and a strong negative relation between eGFR and RI.The regression analysis also established RI to be a major predictor of renal dysfunction thus its diagnostic importance in the severity of diabetic nephropathy.

Table 4.1 showsdemographic characteristics

Variable	Frequency	Percentage (%)
Male	27	67.5
Female	13	32.5
Total	40	100

The gender distribution of the study population is given in table 4.1. Out of a total of 40 patients, 27 (67.5%) were male and 13 (32.5%) were female. This implies that the number of male respondents was higher than the number of female participants.The increased male proportion could be attributed to either the increased prevalence of diabetic nephropathy in males or may be through increased access and reporting of this disease in men.Nevertheless, the underrepresentation of both genders is balanced enough to enable the meaningful comparative analysis.

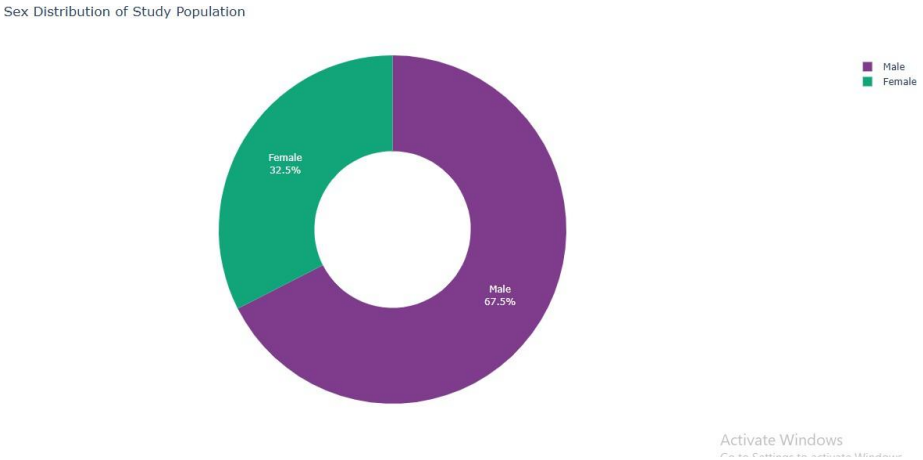

Figure 4.1: indicates the percentage of men and women who were included in the study.The study population was predominantly composed of male patients which implies that the reported diabetic nephropathy cases were dominated by males.

Table 4.2: shows age and duration of diabetes

Variable	Mean ± SD	Min	Max
Age (years)	48.6 ± 7.9	30	58
Duration of diabetes (years)	7.6 ± 2.2	4	12

Table 4.2 presents the descriptive statistics of age and duration of diabetes.The average age of the patients was 48.6 ± 7.9 years with the range of 30-58 years.It means that the study population mostly represented middle-aged people, which is compliant with the epidemiology of Type 2 Diabetes Mellitus.The average years of diabetes was 7.6 + 2.2 years with a range of 4-12 years.This indicates that a majority of the patients have had chronic diabetes and this is a critical area that leads to the occurrence and development of diabetic nephropathy.After a long period of exposure to hyperglycemia, microvascular damage occurs that is manifested in structural changes in the kidneys.

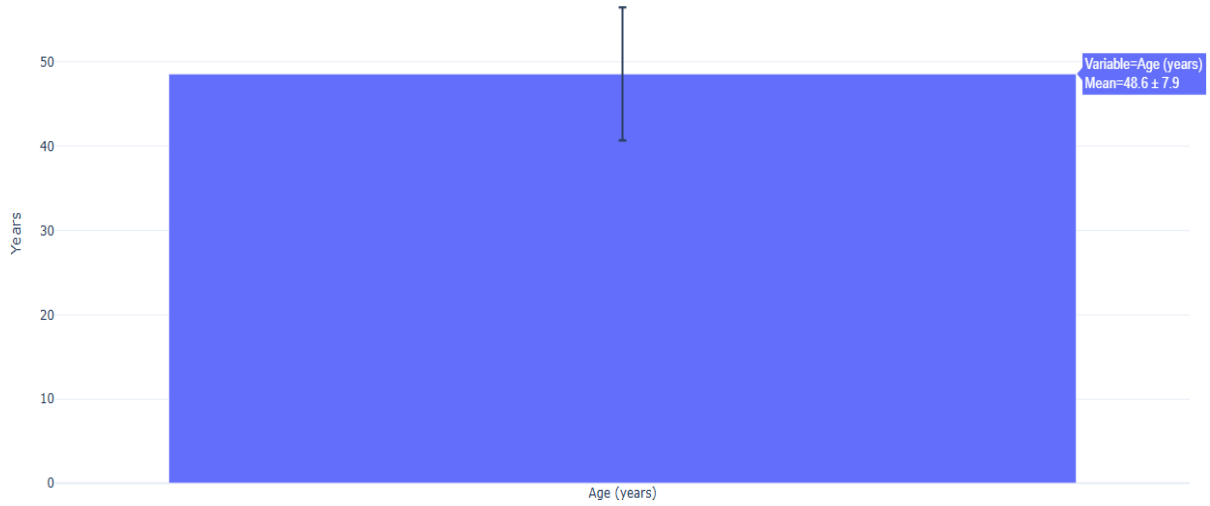

Figure 4.2 shows the average age of the registered patients with standard deviation.The sample size was predominantly of middle age, as is typical of Type 2 Diabetes Mellitus and its kidneycomplications.

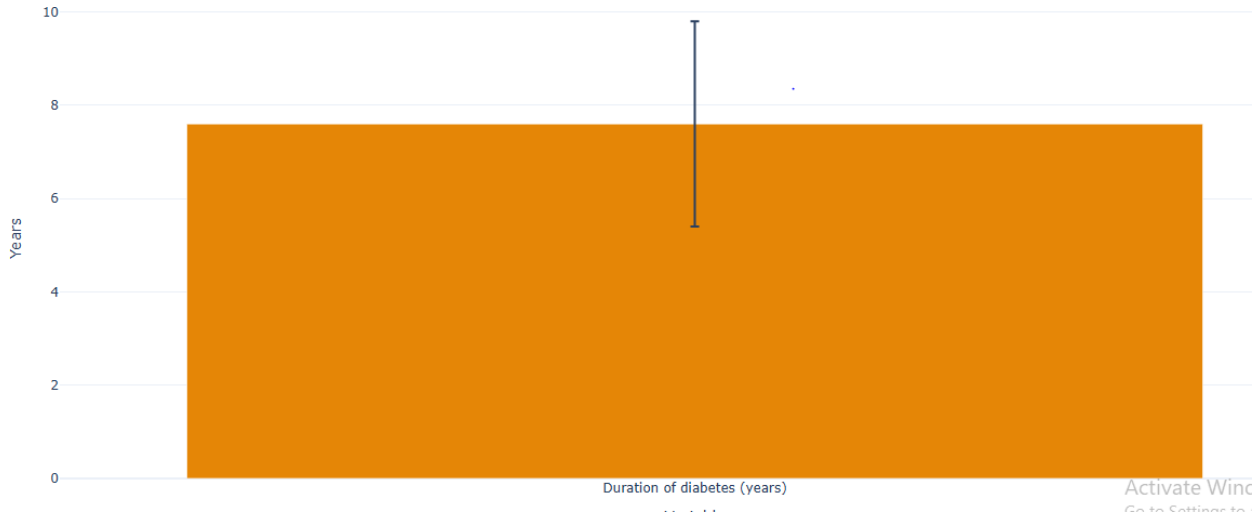

Figure 4.3 This is a graph that demonstrates the mean years of diabetes with variation among the study population.The majority of the patients were already diabetic and this fact proves that chronic diabetic exposure is a contributing factor to the development of renal vascular and parenchymal damage.

Table 4.3 shows kidney function parameters

Variable	**Mean ± SD**	**Min**	**Max**
Serum Creatinine (mg/dL)	2.05 ± 1.18	0.8	4.5
eGFR (mL/min)	67.2 ± 23.8	19	99

Table 4.3 is a summary of the biochemical parameters of renal functioning. The average serum creatinine was 2.05 +/- 1.18 mg/dL, which showed that a high number of patients had high levels of creatinine, which is an indicator of poor kidney functions. The average eGFR was estimated to be 67.2 ± 23.8 mL/min, and this is lower than the average eGFR in most instances. A large standard deviation indicates

that there was a variation in the state of renal functioning, which implies that patients were not at the same stages of kidney disease, but at the stage of mild impairment, as well as severe dysfunction.

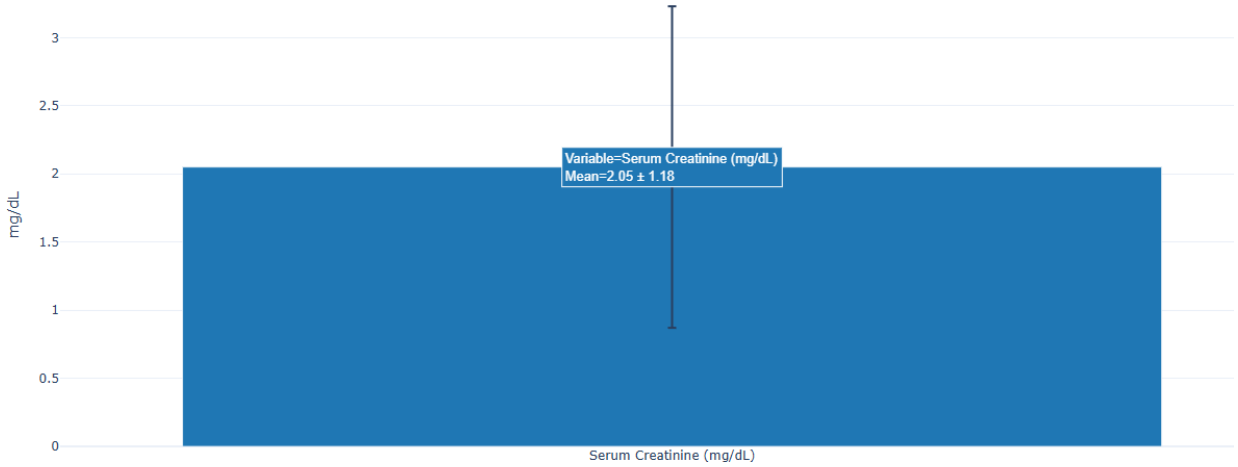

Figure 4.4 represent the average serum creatinine and standard deviation in the patients of the study. The elevated mean creatinine concentration indicates impaired kidney functioning in a significant percentage of patients.

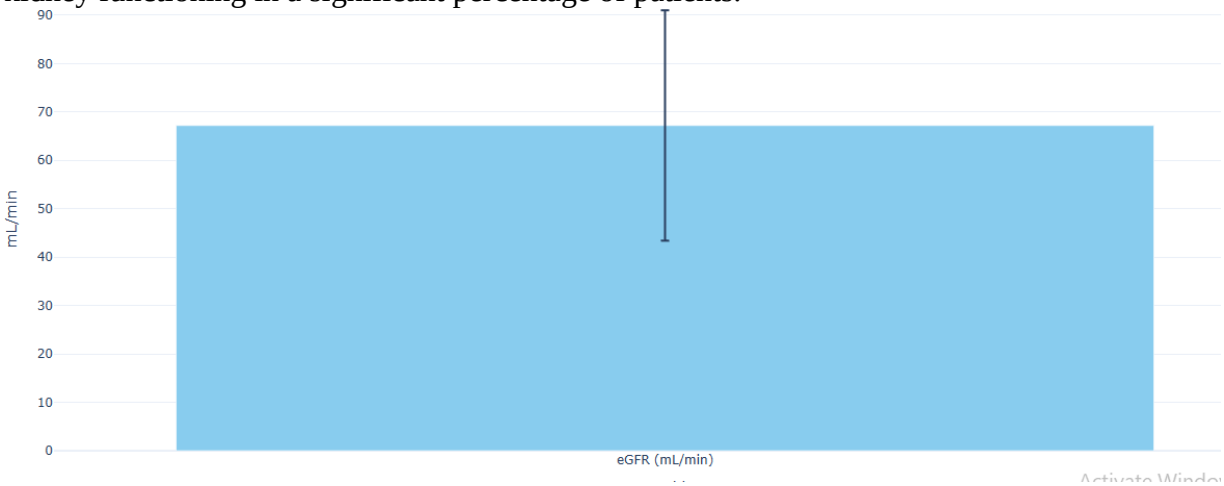

Figure 4.5 shows the mean standard deviation of eGFR. The lower mean of eGFR is evidence of deterioration of kidney activity, which confirms the existence of diabetic nephropathy in the sample under study.

Table 4.4: shows Albuminuria categories

Category	Frequency	Percentage (%)
Negative	7	17.5
1+	5	12.5
2+	9	22.5
3+	19	47.5

Table 4.4 shows the distribution of albuminuria in the patients.The most common category was severe albuminuria (3+) present in 19 patients (47.5%).9 patients (22.5%), and 5 patients (12.5%), respectively, had moderate albuminuria (2+) and mild

albuminuria (1+).Only 7 (17.5) patients did not have albuminuria.This distribution is indicative that most patients were already in the late stages of renal involvement since albuminuria is one of the main indicators of glomerular damage and progression of disease in diabetic nephropathy.

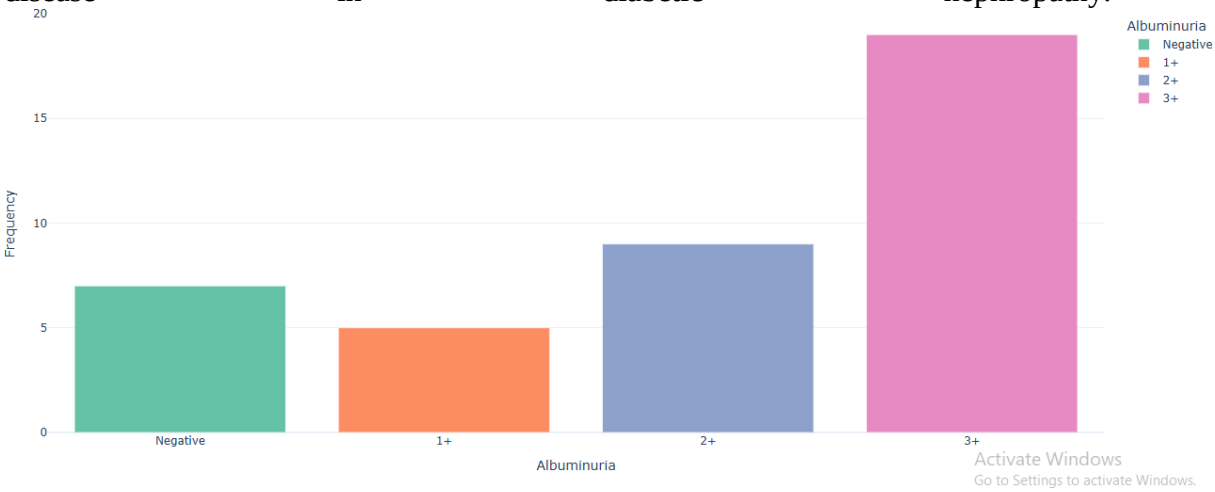

Figure 4.6 The graph below shows the distribution of negative negative, 1+, 2+, and 3+ categories of albuminuria.The most common category was severe albuminuria meaning that most patients were already in the advanced stages of renal involvement.

Table 4.5 Renal Resistive Index (RI) categories

RI Category	**Frequency**	**Percentage (%)**
Normal (≤0.70)	7	17.5
Borderline (0.71–0.80)	8	20.0
High (>0.80)	25	62.5

Table 4.5 shows the classification of the patients according to the values of renal resistive index.The most common category was high RI (>0.80) with 25 patients (62.5). Borderline RI (0.71–0.80) was present in 8 patients (20%), while normal RI (≤0.70) was observed in only 7 patients (17.5%). High RI values are predominant and also suggest that intrarenal vascular resistance is more in most patients and is linked to structural renal injury, including fibrosis, arteriosclerosis, and lack of vascular compliance.

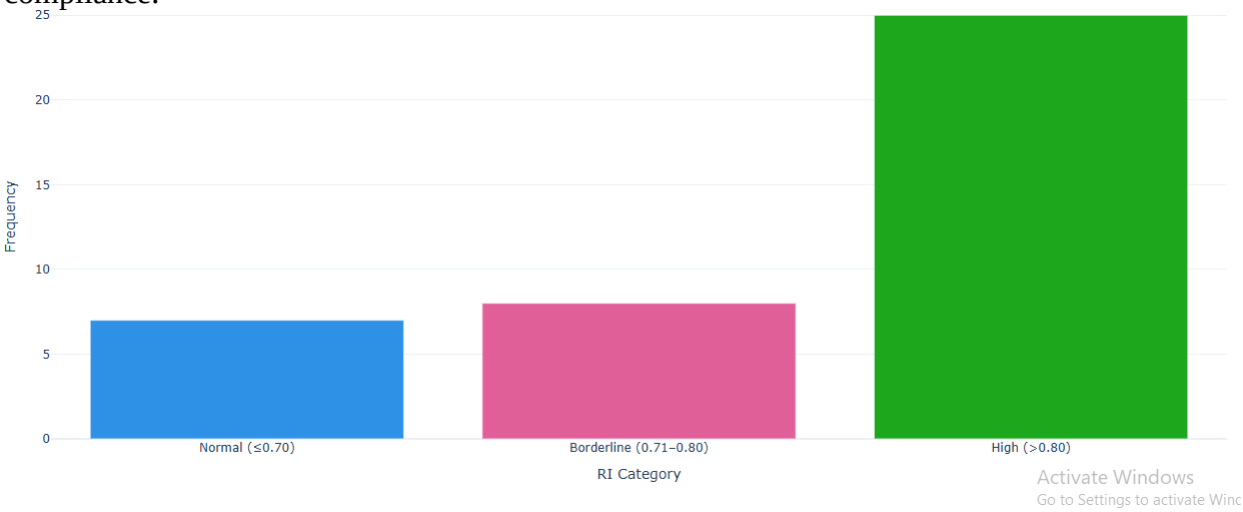

Figure 4.7 There are three groups of patients with normal, borderline, and high RI.The

most frequent values were quite large RI values indicating that intrarenal vascular resistance was higher in most cases.

Table 4.6 Descriptive statistics of Doppler parameters

Variable	Mean ± SD	Min	Max
RI	0.79 ± 0.11	0.60	0.93
PI	1.24 ± 0.36	1.00	2.73
PSV (cm/s)	95.2 ± 26.8	57	120
EDV (cm/s)	23.1 ± 6.5	13	35

Table 4.6 indicates the descriptive statistics of Doppler ultrasound parameters.Mean RI (0.79 +-0.11) is more than normal threshold, and it indicates elevated resistance of vascularity.The average pulsatility index (PI) stood at 1.24 +/- 0.36 which also pointed towards disturbed renal blood flow dynamics.The average peak systolic velocity (PSV) was 95.2 /26.8 cm/s and the average end diastolic velocity (EDV) was 23.1 /6.5 cm/s.The variation in these parameters indicates the difference in renal perfusion and vascular compliance between patients.

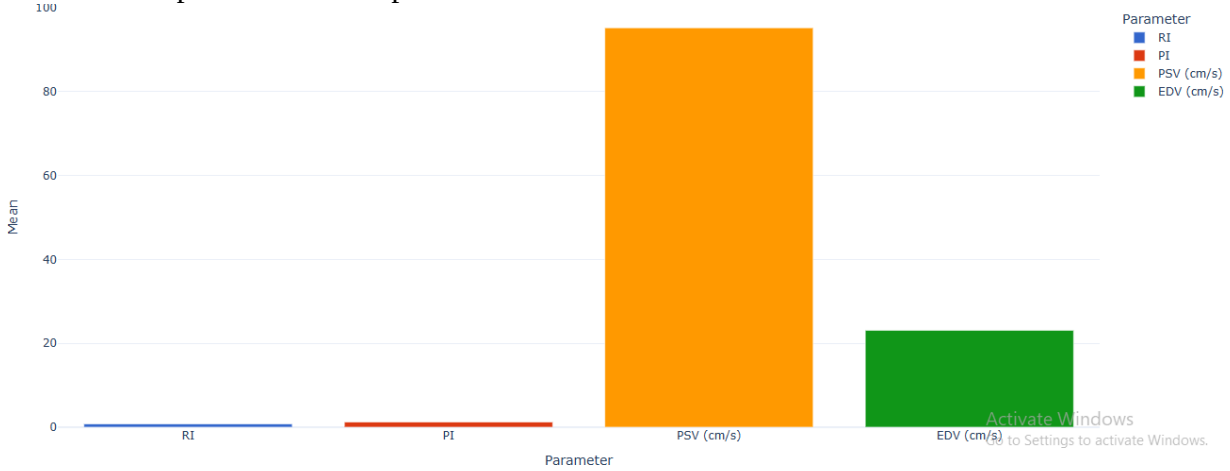

Figure 4.8 The graph is a comparison of the mean values of RI, PI, PSV, and EDV.The Doppler profile shows that there is a change in renal hemodynamics, where RI and PI are abnormally high in line with elevated vascular resistance.

Table 4.7: Cross-tabulation: RI vs Albuminuria

Albuminuria	Normal RI	Borderline RI	High RI	Total
Negative	5	2	0	7
1+	2	2	1	5
2+	0	3	6	9
3+	0	1	18	19

Table 4.7 shows the association between the categories of renal resistive index and the levels of albuminuria.Patients who had negative albuminuria were largely in the normal RI range, which shows that renal vascular resistance is normal.With rise in the severity of albuminuria, there was a distinct shift to the higher category of RI.High RI

group was mostly comprised of patients with moderate (2+) and severe (3+) albuminuria.Interestingly, nearly all patients who had 3+ albuminuria also had high RI values indicating a significant damage to the kidneys.This cross-tabulation shows that there is a strong relationship between RI and albuminuria, which means that RI indicates the magnitude of structural renal changes

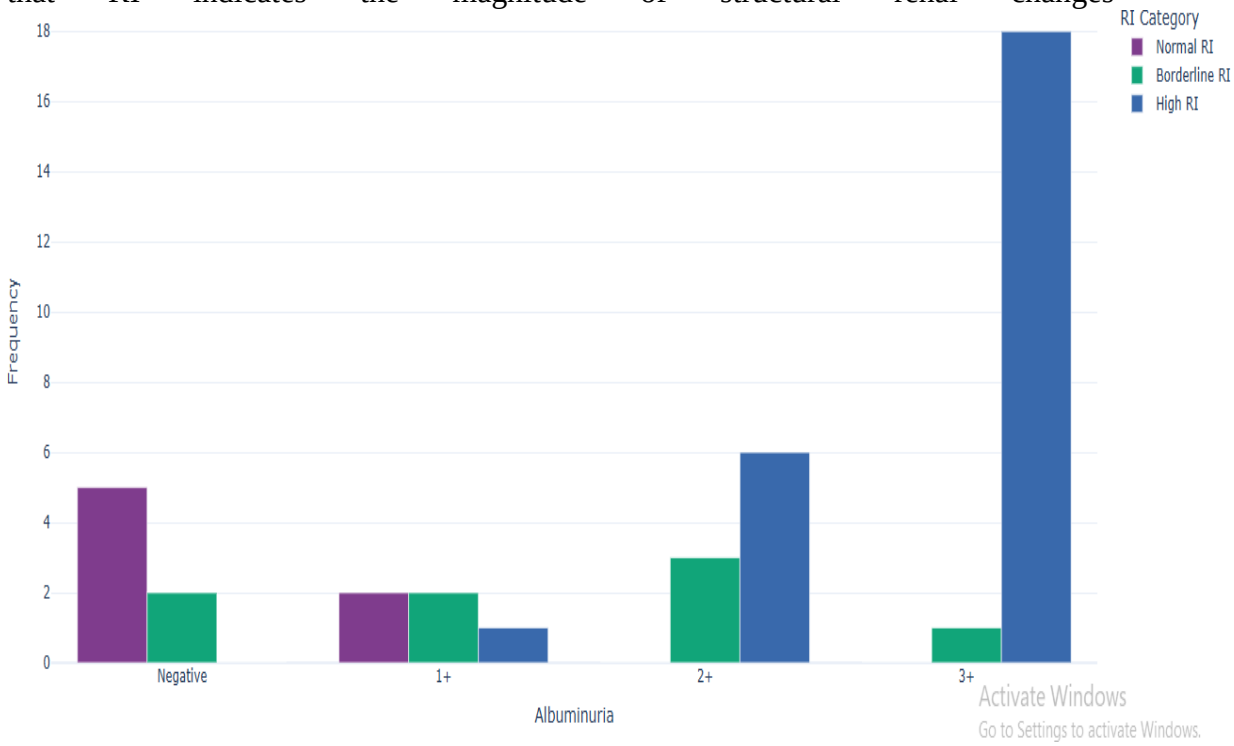

Figure 4.9 shows the plot of the categories of renal resistive index (RI) (normal, borderline, and high) at the various levels of albuminuria in patients with Type 2 Diabetes Mellitus.

Table 4.8 shows the Mean RI across albuminuria groups

Albuminuria	**Mean RI ± SD**
Negative	0.62 ± 0.02
1+	0.71 ± 0.03
2+	0.80 ± 0.04
3+	0.88 ± 0.05

ANOVA result: $p < 0.001$

Table 4.8 indicates that the mean RI values in various categories of albuminuria are different.The mean RI rose steadily between 0.62 in patients with negative albuminuria and 0.88 in patients with 3 + albuminuria.ANOVA indicated that there is a highly significant difference ($p < 0.001$) and thus the rise in RI between the categories of albuminuria did not occur by chance.This proves that RI is considerably linked with the disease severity.

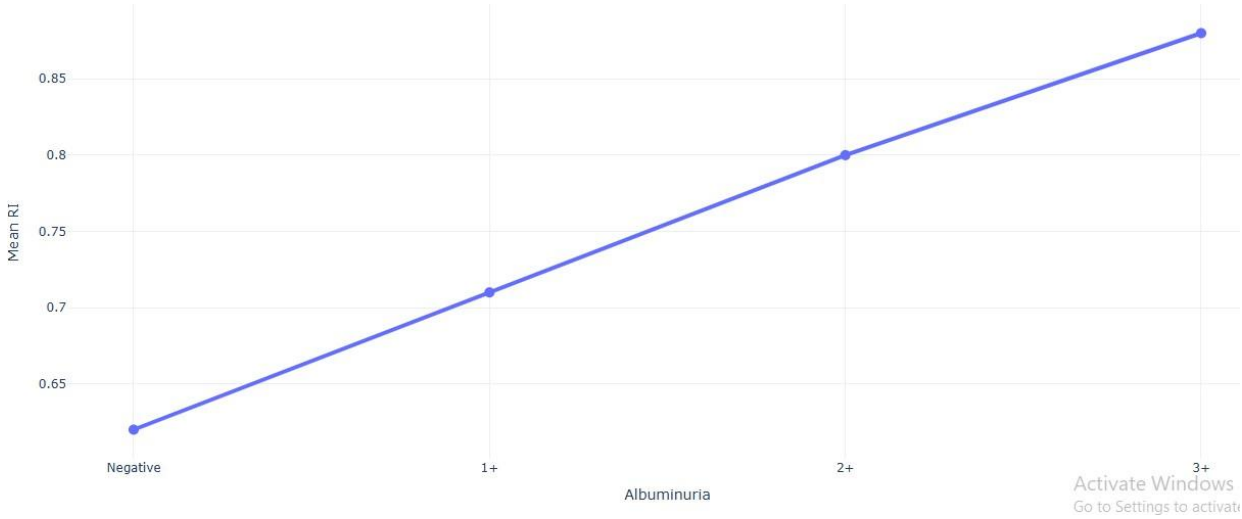

Figure 4.10 indicates the alteration of the mean RI when there is negative albuminuria to 3+ albuminuria.RI was escalating in proportion to the deterioration of albuminuria, which is a strong indication that the greater the level of renal damage, the greater the RI.

Table 4.9 shows the Pearson correlation analysis

Variables	**r-value**	**p-value**
RI vsCreatinine	+0.87	<0.001
RI vseGFR	-0.91	<0.001
RI vsMicroalbumin	+0.79	<0.001
RI vs Duration	+0.49	0.003
RI vs Age	+0.27	0.09

The Pearson correlation analysis between RI and clinical parameters is given in Table 4.9.RI had a positive correlation with serum creatinine (r = 0.87) and microalbumin (r = 0.79), which means that RI rises along with deterioration of the renal damage.It was found that there was a strong negative relationship between RI and eGFR (r = -0.91), i.e. the lower the renal function, the higher the RI.There was a moderate positive correlation between the duration of diabetes (r = 0.49) indicating that the longer the duration of the disease, the greater the vascular resistance. The correlation between age and RI proved weak and not significant (p > 0.05), which means that age is not a strong determinant of RI.

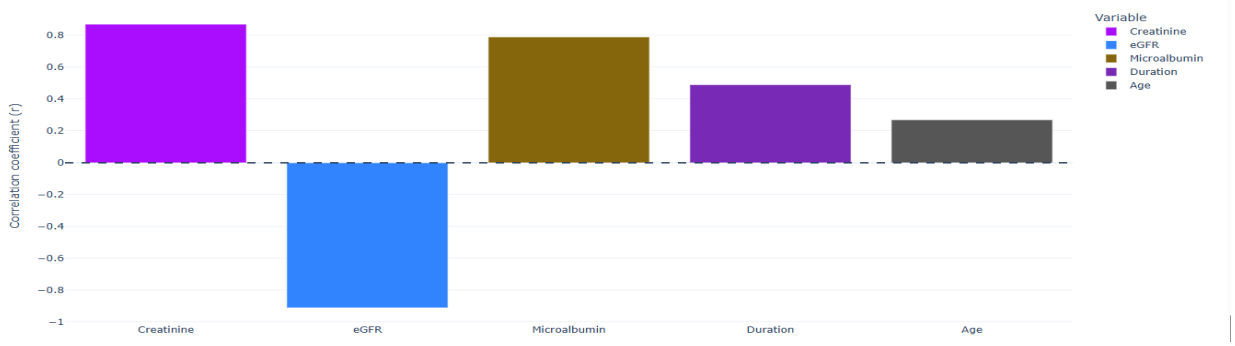

Figure 4.11 shows the strength and direction of RI with creatinine, eGFR, microalbumin, duration of diabetes and age.RI had a high positive correlation with creatinine and microalbumin, where as it had a negative correlation with eGFR. This implies that RI rises with the deterioration of renal functioning.The weakest association was revealed with age.

Table 4.10 shows the Linear regression analysis (RI as predictor)

Dependent Variable	Regression Equation	R^2	p-value
Creatinine	Creatinine = -0.75 + 2.85(RI)	0.76	<0.001
eGFR	eGFR = 158 - 102(RI)	0.83	<0.001
Microalbumin	Microalbumin = -1480 + 2380(RI)	0.62	<0.001

The outcome of the linear regression analysis on the basis of RI as a predictor variable is presented in Table 4.10.RI was a powerful predictor of parameters of renal functions. It accounted 83, 76 and 62 respectively of eGFR (R 2 = 0.83), serum creatinine and microalbumin variability. The statistical significance of all the models was statistically significant ($p < 0.001$), which showed that RI can be used as a predictor of renal dysfunction.

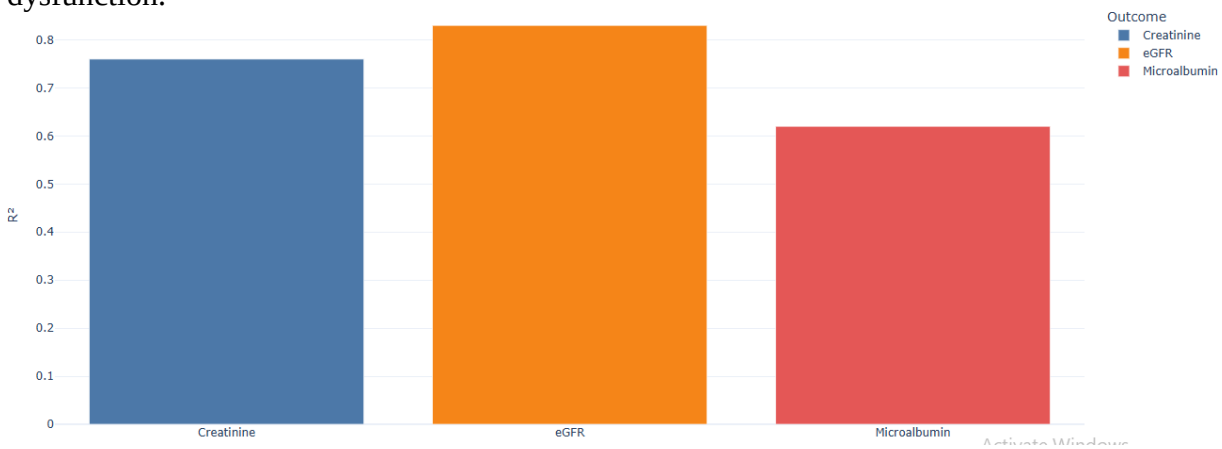

Figure 4.12 shows the R2 of regression equations with the help of RI to predict creatinine, eGFR, and microalbumin. RI was the best predictor of eGFR, then came creatinine, and lastly, microalbumin, which implies that RI is a powerful imaging predictor of renal impairment.

Chapter 5
DISCUSSION

The current research was done to determine the diagnostic usefulness of the Renal Resistive Index (RI) in the prediction of the histopathological severity of diabetic nephropathy in Type 2 Diabetes Mellitus patients. The results of this research demonstrate a clear evidence that RI is closely related to renal dysfunction and the severity of the disease, which is why it can be regarded as a reliable non-invasive biomarker. The sample population was mainly middle-aged with the average age of the population being 48.6 and the standard deviation of 7.9 years old, which fits the epidemiological trend of Type 2 diabetes since the disease normally occurs and develops in middle age [16,18]. Also, the average years of diabetes were 7.6 2.2 years, which means long-term exposure to hyperglycemia, which is a well-established contributor to microvascular damage and development of diabetic nephropathy [24,25].

The chronic hyperglycemia is associated with a series of metabolic and hemodynamic changes, such as oxidative stress, inflammatory activation, and endothelial dysfunction, which eventually result in mesangio expansion, glomerulosclerosis, and interstitial fibrosis [26,27]. These pathology changes are silent at the early stages of the illness, which tend to develop before clinical or biochemical anomalies develop [28,29]. This is the reason why the conventional diagnostic markers like serum creatinine and eGFR are commonly not adequate to earlier detect the disease as they mostly represent functional impairment and not structural damage [32,33]. The mean serum creatinine level was found to be elevated (2.05 ± 1.18 mg/dL) and the mean eGFR level was lower (67.2 ± 23.8 mL/min), which showed that a considerable percentage of patients were already in the moderate or severe levels of renal dysfunction. This observation is consistent with other researchers who have proposed that biochemical markers are generally abnormal when a significant amount of nephron loss has been caused [34, 35].

Renal Resistive Index in this context has developed as a good non-invasive parameter which measures intrarenal vascular resistance and compliance. The average RI in the current research was 0.79+ 0.11 and most of the patients (62.5) had high RI (>0.80). This observation suggests that there is a rise in intrarenal vascular resistance, which is a major characteristic of diabetic
nephropathy. High RI values are also reported to be linked to structural changes including arteriosclerosis, interstitial fibrosis, and microvascular rarefaction which all of which lead to poor renal perfusion and a progressive decline in nephron function [54,55]. RI can be used to detect the disease and monitor diseases in severe cases, unlike traditional, biochemical markers, which can only offer real-time data about the renal hemodynamics [46,47].

The strong relationship between RI and the severity of albuminuria was one of the most significant conclusions of this research. Gradual rise in RI was seen in the different albuminuria groups with mean RI values increasing to 0.88 in patients who had severe albuminuria (3+). The analysis of ANOVA showed that the difference is highly significant ($p < 0.001$), which proves that this trend is statistically strong. This observation is in agreement with other researchers who have found a high correlation between RI and histopathological damage, such as glomerulosclerosis and interstitial fibrosis [12,75]. These changes in structure raise intrarenal resistance to the vascularity, which is immediately expressed in high RI values. Thus, it can be concluded that the hypothesis that RI can be used as a surrogate endpoint to histopathological severity can be supported by the results of this study that showed the observed relationship between RI and albuminuria. Moreover, correlation analysis showed that there is a strong positive correlation between RI and serum creatinine ($r = 0.87$) and microalbumin ($r = 0.79$), whereas, it is also negatively correlated with eGFR ($r = -0.91$). According to these findings, it is evident that RI rises as the renal functioning declines. On the same note, other studies have also reported similar findings, with RI being strongly linked to deteriorating renal functioning and augmenting proteinuria [10,11]. The association with eGFR is notably negative and it can be inferred that RI could be effective in early detection of functional decline before it manifests itself. Also, the moderate positive relationship between RI and length of diabetes ($r = 0.49$) contributes further to the contribution of chronic hyperglycemia to vascular and structural damage in the long run [28,29]. Conversely, the age exhibited a weak and non-significant correlation with RI, which shows that age is not a significant predictor of intrarenal vascular resistance with diabetic nephropathy.

The clinical relevance of RI is further supported by the regression analysis that has been done in this study. The findings showed that RI is a good predictor of the parameters of renal functioning, and it accounts 83, 76 and 62 percent of the variability in eGFR, serum creatinine and microalbumin respectively. These results indicate that RI is a strong predictor with significant estimation abilities to predict the

intensity of renal impairment with a high level of precision. RI
has been also found before as an independent predictor of renal outcomes even after controlling by traditional risk factors including blood pressure, proteinuria, and baseline renal function [74,85]. This indicates the possibility of RI that can be integrated into standard clinical assessment to risk stratify and prognostically assess.
Even though the renal biopsy is the gold standard of determining the degrees of histopathology, it is invasive, expensive and bears the risk of complications like bleeding and discomfort to the patient [58,59]. Consequently, its clinical application is restricted in practice. The results of this paper, along with the current literature, indicate that RI is a potentially useful non-invasive alternative to measure renal structural damage. There are also several studies that show that there are strong correlations between high RI and histological evidence of interstitial fibrosis, tubular atrophy and vascular sclerosis [75,78,90]. These structural defects are most important factors of the development of the disease and highly relate to augmented intrarenal vascular resistance. Thus, RI offers an indirect but useful information about the histopathological condition of the kidneys. The other significant issue with RI is that it may be utilized in early detection and monitoring of diabetic nephropathy. Recent findings indicate that RI is able to identify subclinical renal vascular alterations even in patients with normal serum creatinine and intact eGFR [67]. This is the early-detection capability, which enables timely intervention that would dramatically slow the disease progression and minimise the chances of complications [68]. Also, it has been demonstrated that RI is responsive to pharmacological interventions like renin-angiotensin system blocker and sodium-glucose cotransporter-2 blocker, and thus is an effective instrument to monitor treatment outcomes [14]. Such a dynamic character of RI makes it even more useful in clinical practice in personalized medicine.
The results of this report align well with the prior studies, which all show that RI has a diagnostic and prognostic role in diabetic nephropathy. It has been observed that higher RI levels are seen in diabetic patients than in healthy controls, and that there are significant correlations with declining renal function, cardiovascular risk and histopathological severity [10,12,82]. These results are consistent across various population groups and study designs, which increase their validity in RI as a good biomarker.
Although these are the strong points, the study has some weaknesses that one must take note of. The cross-sectional design precludes the possibility of determining cause and effect relationships and the lack of histopathological validation denies the possibility of directly confirming RI and
biopsy results. Also, the research was carried out in only one center, and this could restrict the generalizability of the findings. Another possible source of variability is operator dependency in Doppler measurements. The limitations do not however undermine the importance of the findings but serve as a guide to future research.
Conclusively, this current research provides strong evidence that Renal Resistive Index is a useful, non-invasive, tool in determining the extent of diabetic nephropathy. Its close correlation with the parameters of renal functioning, albuminuria, and disease duration and its predictive ability revealed by regression analysis justify its applicability to clinical practice. RI is not only an indicator of functional impairment but it also is related to structural changes underlying the same impairment, thus is a holistic measure of the health of the kidneys. Thus, RI implemented in regular clinical assessment could enhance early identification, risk classification, and management of diabetic kidney disease, which eventually could result in patient outcomes.

CONCLUSION

The current research shows that the Renal Resistive Index is closely related to the parameters of renal function and the severity of diabetic nephropathy among Type 2 Diabetes Mellitus patients. The results indicated that an increase in RI values is significantly correlated with an increase in serum creatinine, an increase in microalbuminuria, and a reduction in eGFR, which is a sign of deterioration of renal function. RI also showed progressive increase with increasing severity of albuminuria, which confirms that RI is correlated with disease progression. RI is helpful in identifying intrarenal vascular resistance and early structural alteration unlike traditional biomarkers, which are mostly useful in detecting late-stage functional impairment.

Limitations:

There are a few limitations of this study which need to be taken into consideration when interpreting the findings.

The absence of histopathological (renal biopsy) validation restricts the possibility of RI to be directly validated against structural damage.

Limited generalizability due to a small sample size of a single-center study.

There may be variability due to operator dependency of Doppler measurements.

Potential confounding factors (blood pressure, medications, hydration) were not controlled.

Recommendations

Incorporate routine RI measurement for early, non-invasive risk stratification in diabetic nephropathy.

Carry out longitudinal research to evaluate whether RI can be a predictor of long-term renal outcomes.

Conduct multi-centre research on a larger sample to enhance generalization.

Compare RI with the results of renal biopsy to ensure that it is a substitute of histopathological severity.

Unify Doppler protocols and determine inter-observer reproducibility.

Investigate the use of RI in assessing therapeutic response to renoprotective medications.

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Patient Data Collection Proforma

Age: _____Years Gender: Male □ Female □
Presence of Diabetes Mellitus: Yes □ No □
If Yes, Duration of Diabetes: _____Months/Years RENAL ULTRASOUND & DOPPLER FINDINGS

Parameter	Right Kidney
B-Mode Ultrasound	
· Size	_____
· Length (cm)	_____
· Width (cm)	_____
· Cortical Thickness (cm)	_____
Doppler Measurements	
· Resistive Index (RI)	_____
· Pulsatility Index (PI)	_____
· Peak Systolic Velocity (PSV)	cm/s _____
· End-Diastolic Velocity (EDV)	cm/s _____
· S/D Ratio	_____

No. Of obs.	Age	Gender	Presence of Diabetes	Duration of Diabetes	Renal Measurements			Doppler Measurements				
			Yes/No	Months/Years	Length	Width	Cortical Thickness	RI	PI	PSV	EDV	S/D Ratio
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												

CONSENT FORM

You are invited to participate in a research study conducted by_**Hifza Iqbal, Kinza Akbar, Nimra, Sadia, Saif Ali** The purpose of this research is to evaluate the ***—Diagnostic value of Renal Resistive Index in predicting Histopathological severity of Diabetic Nephropathy in Type 2 Diabetes Mellitus***‖

Risks and Discomforts

Mention if there will be any known risks associated with this research.

Potential Benefits

Mention if there will be benefits to the participant that would result from their participation in this research.

Protection of Confidentiality

We will do everything we can to protect your privacy. Your identity will not be revealed in any publication resulting from this study.

Voluntary Participation

Your participation in this research study is voluntary. You may choose not to participate and you may withdraw your consent to participate any time. You will not be penalized in any way should you decide not you participate or to withdraw from this study.

CONSENT

I have read this consent form and have been given the opportunity to ask questions. I give my consent to participate in this study.

Participant‘s Signature _____Date: _____

A copy of this consent form should be given to the participant.

تحقیق ھیں شزکت کا دعوت اًھہ

***Diagnostic value of Renal Resistive Index in predicting Histopathological* "عنوان:**
" *severity of Diabetic Nephropathy in Type 2 Diabetes Mellitus*

نقصانات اور تکلیف: اص تحقیق سے کسی قسن کے قُصای یا تکلیف کا اذًیشہ ہیں ہے .

ممکنہ فوائد: آپکو ایک اہن تحقیق ھیں حصہ لیۓ کا ھوقعہ دیا جاۓ گا.

رازداری کا تحفظ: ہن آپ کی ھعلوھات کے تحفع کے لیے وٍ سۃ کچہ کزیں گے جو ہن کز سکتے ہیں. تحقیق کے ھتعلق اکٹہی کیی گیی توام ھعلوھات کو انُہا ئی خفیہ رکھا جاے گا. ڈیٹا اثُرّی اور تجشیے کے دورای آپ کے ھتعلق وٍ توام ھعلوھات جي سے آپ کی شاُخت ہو سکتی ہو کو ختن کز دیا جاے گا. اص تحقیق کے ثّیجے ھیں شائع ہوۓ والی کسی تھی اشاعت ھیں آپ کی شاُخت کو ظاہز ہُیں کیا جاے گا.

رضاکارانہ شمولیت: اص تحقیقی ھطالعہ ھیں آپ کی شزکت رضاکاراۂ ہے. آپ کو شزکت ۂ کزۓ اور کسی تھی وقت پغیز وجہ تناۓ اص تحقیق ھیں شوولیت کو چھوڑۓ کا اختیار ہے. شزکت ۂ کزۓ یا اص ھیں شوولیت کو چھوڑۓ کی صورت ھیں آپ کے خلاف کوئی کاروایی ہُیں کی جاے گی

درجذیل ھعلوھات تحقیق ھیں شاھل ہوۓ والوں کے لیے پڑھیں اور ای کا جواب دیے گیے خاوٗں ھیں درج کزیں

ھیں ۓ ھعلوھاتی شیٹ جو کہ تحقیق کی وضاحت کز رہی ہے کو سوجھ لیا ہےاورھجھے تحقیق کے سوالات " کزۓ کا ھوقع دیا گیا تھا.

ھیں سوجھ گیا/گیی ہوں کہ ھیزی شزکت رضاکاراۂ ہے اور یہ کہ ھیں کسی تھی وقت اپاُ ارادٍ تذل سکتا/سکتی " ہوں اور تحقیق سے دستثزدار ہو سکتا/سکتی

ھیں سوجھ گیا/گیی ہوں کہ ھیزے جواتات خفیہ رکھے جاٴیں کے. ھیں ھحقیقیي کو اص تات کی اجاست دیتا/دیتی ہوں کے " وٍ جواتات کو جاچٗ سکیں.

ھیں سووجھ گیا/گی ہوں کے ھعلوھات ھیزے اُم کے تجاے وٗثز کی صورت ھیں ھحفوط کی جائیں گی. تا کہ ھیں ثّائج کی " اشاعت کے دورای کسی تھی طزح سے شاُخت ۂ کیا جا سکوں. ھیں اص تات سے رضاھذٌ ہوں کے جو ھعلوھات ھجھ سے لی جائہیں گی وٍ تحقیق ھیں استعوال ہوں گی.

ھیں اوپز تنایی گی تحقیق ھیں شاھل ہوۓ کے لیے رضاھذٌ ہوں اور ھحقیقي کو اپاُ پتہ تثنیل ہوۓ کی صورت ھیں ھطلع " کزوں گا/گی.

رضا مندی:ھیں ۓ یہ اجاست اُھہ پڑھا ہے اور ھجھے سوال پوچھۓ کا ھوقع دیا گیا ہے. ھیں اص سٹڈی ھیں شزکت کے راضی ہوں.

شزکت کذٗٓٔ کا اُم_____ دستخط_____ تاریخ_____

اجاست لیۓ والے کا اُم_____ دستخط_____تاریخ

اص اجاست اُھہ کی ایک قٗل آپکو دی جاۓ چاہے.

PERMISSION LETTER
ETHICS COMMITTEE LETTER
PLAGIARISM CERTIFICATE
PLAGIARISM REPORT

APPENDICES ENGLISH CONSENT FORM

The study you are about to participate is a randomized control trial survey titled as; **—Diagnostic value of Renal Resistive Index in predicting Histopathological severity of Diabetic Nephropathy in Type 2 Diabetes Mellitus**‖ The study has no potential harm to participants. All data collected from you will be coded in order to protect your identity, and should not be disclosed to anyone. Following the study there will be no way to connect your name with your data. Your answers to the questions will not affect the quality of education given to you. Any additional information about the study results will be provided to you at its conclusion, upon your request You are free to withdraw from the study at any time. You agree to participate, indicating that you have read and understood the nature of the study, and that all your inquiries

NAME ---------- **SIGNATURE----------**

DATE ----------

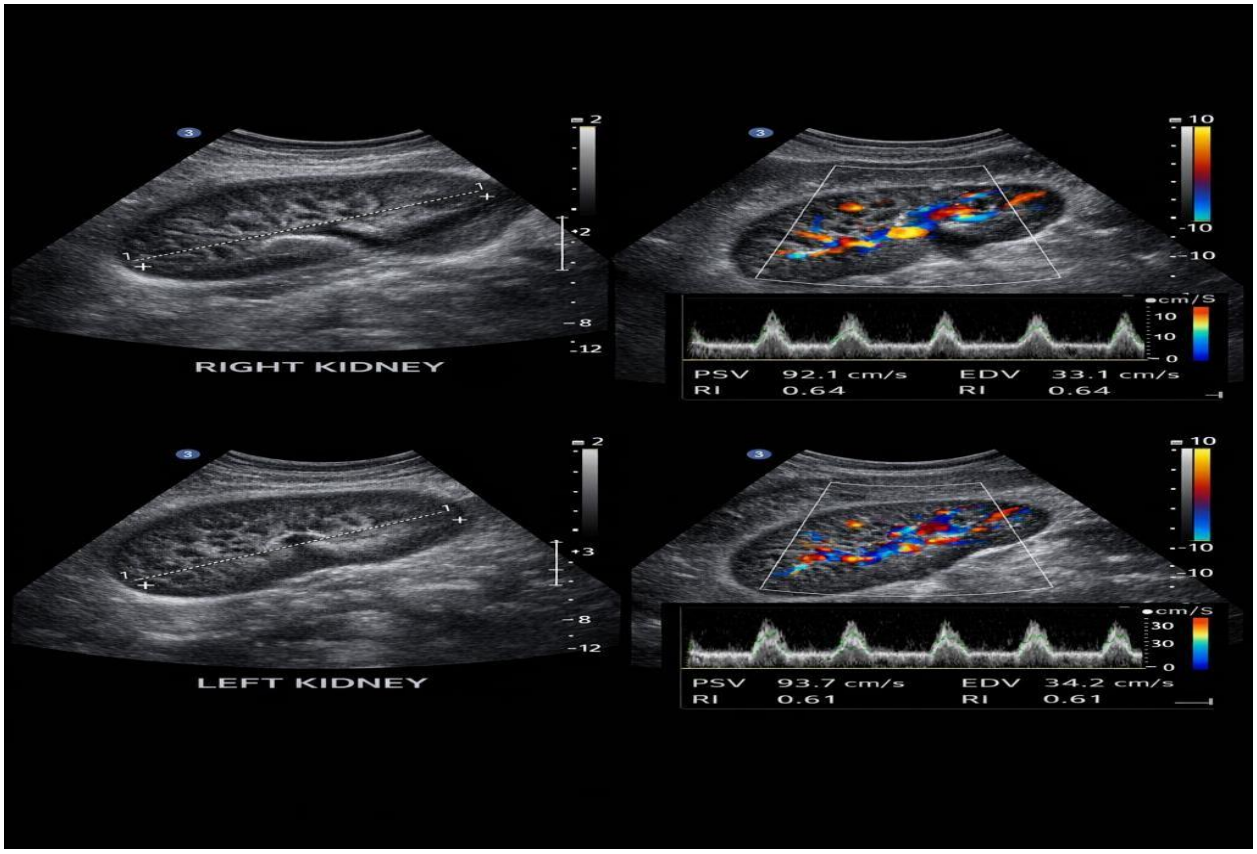

Figure 4.13: Doppler ultrasound of a 40-year-old patient with a 7-year history of diabetes showing bilateral renal hemodynamic parameters. The right kidney shows RDV 91.1 cm/s and 33.4 cm/s with RI 0.64, while the left kidney shows RDV 93.7 cm/s and 34.2 cm/s with RI 0.61.

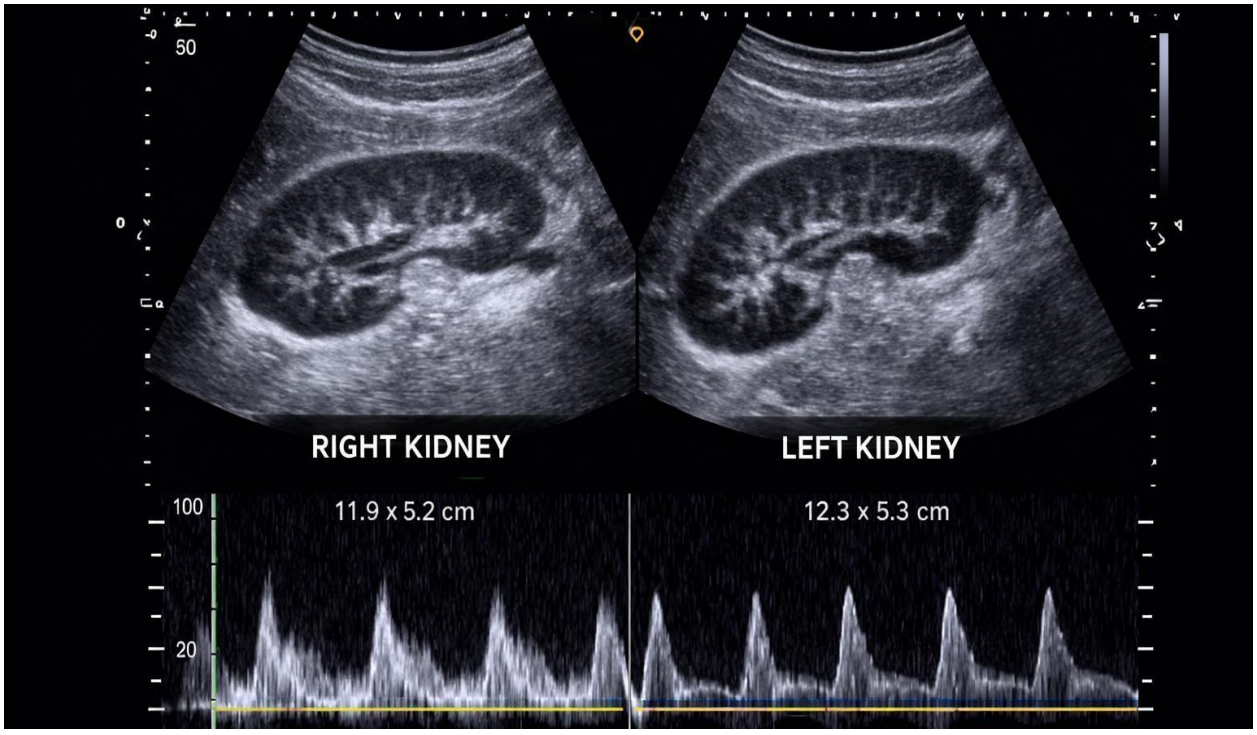

Figure 4.14: Bilateral renal Doppler ultrasound of a 40-year-old diabetic patient (7-year duration) demonstrating right kidney RDV 95.1 cm/s and 34.4 cm/s with RI 0.64–0.65, and left kidney RDV 93.7 cm/s and 34.2 cm/s with RI 0.61.

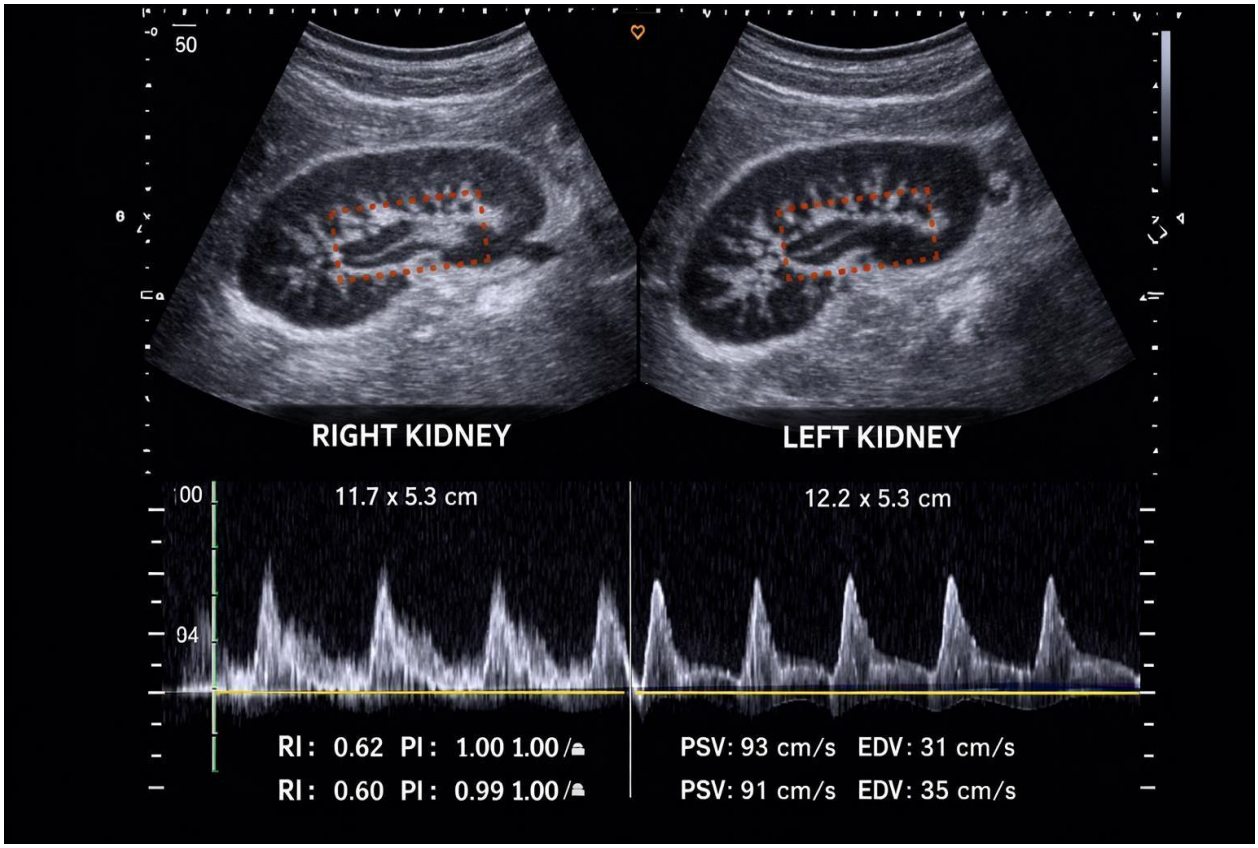

Figure 4.15: Doppler spectral analysis of both kidneys in a diabetic patient showing right and left kidney parameters: RI 0.62 and 0.60, PI 1.00 and 0.99, PSV 93 cm/s and 91 cm/s, and EDV 31 cm/s and 35 cm/s, respectively.

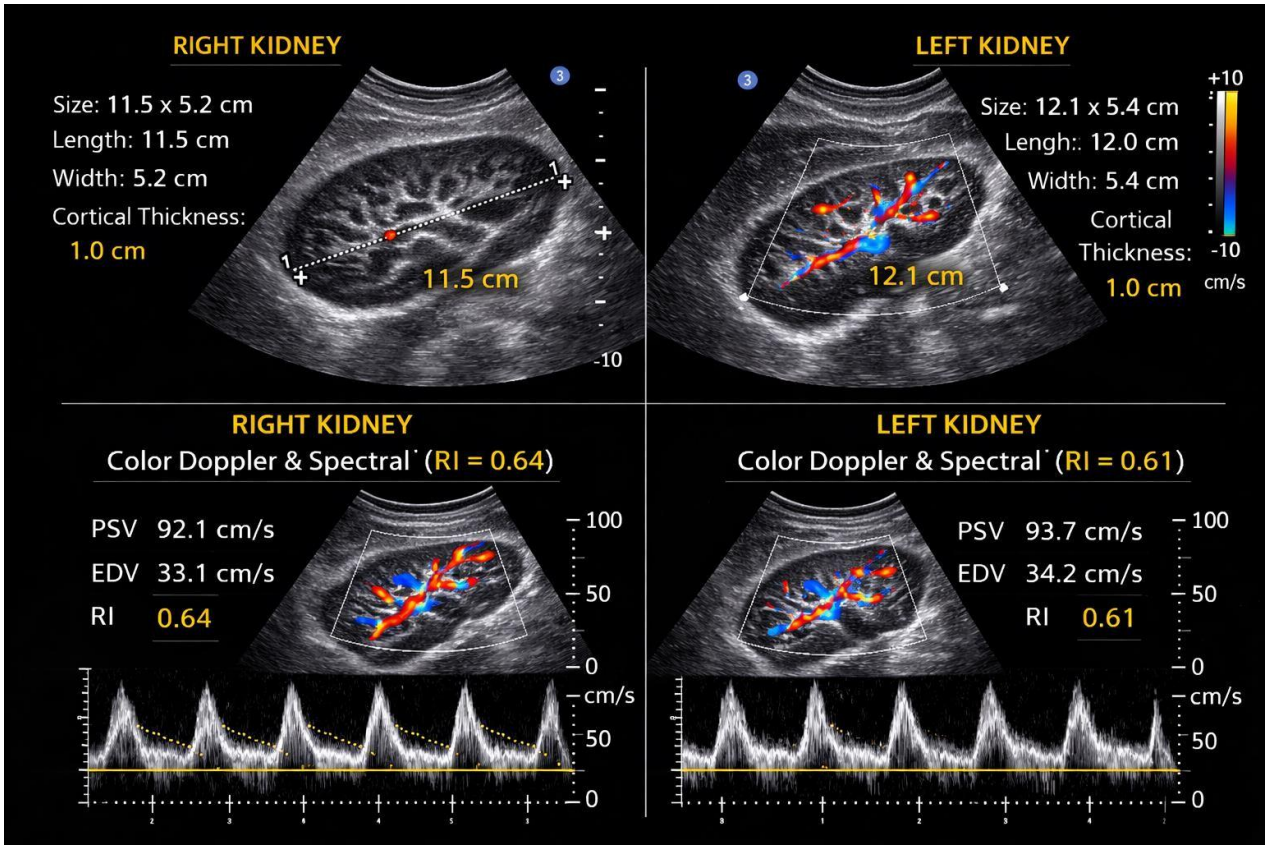

Figure 4.16: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.64 and 0.61, PSV 92.1 cm/s and 93.7 cm/s, and EDV 33.1 cm/s and 34.2 cm/s, respectively, in a patient with a 7-year history of diabetes.

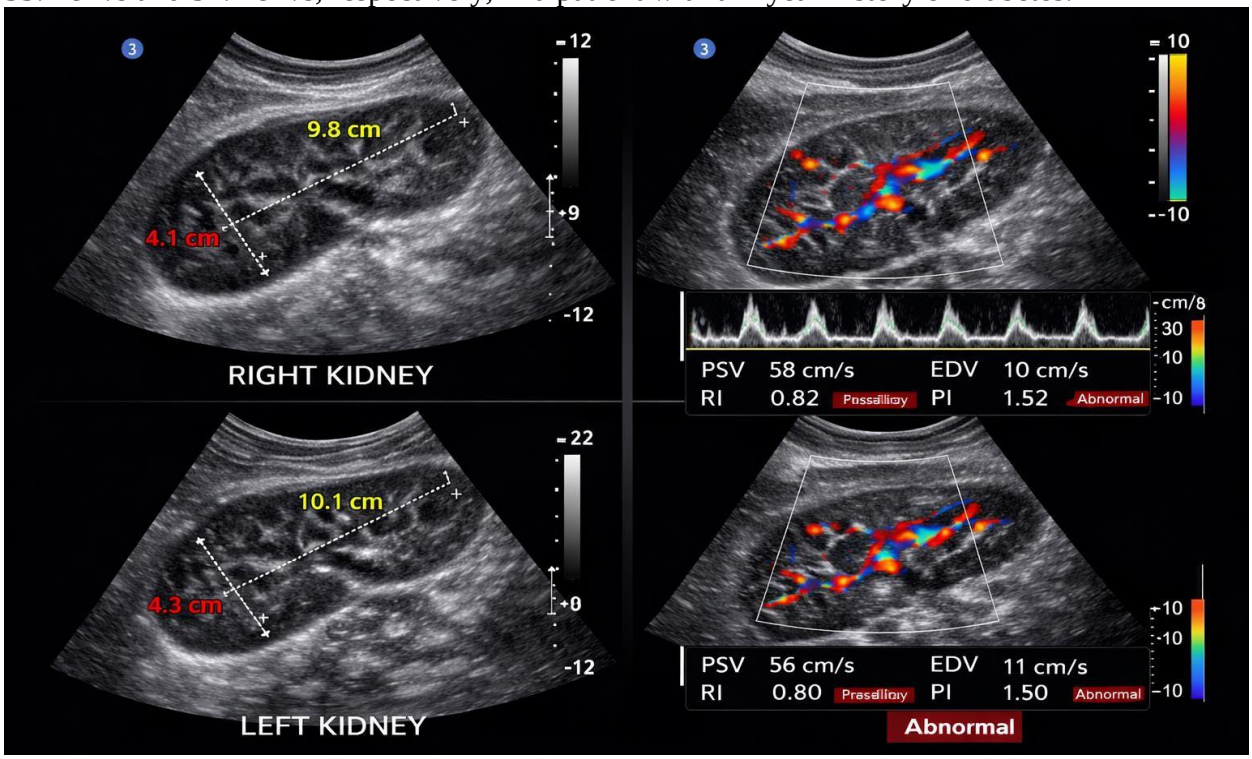

Figure 4.17: shows that a 40 year patient who had diabetes 7 year under went bilateral renal ultrasound and Right kidney and Left kidney shows RI 0. 82, RI 0.61, PSV 92.1 cm/s, PVS 93.7 cm/s, EDV 10.1 cm/s and EDV 11.0 cm/s rescectively.

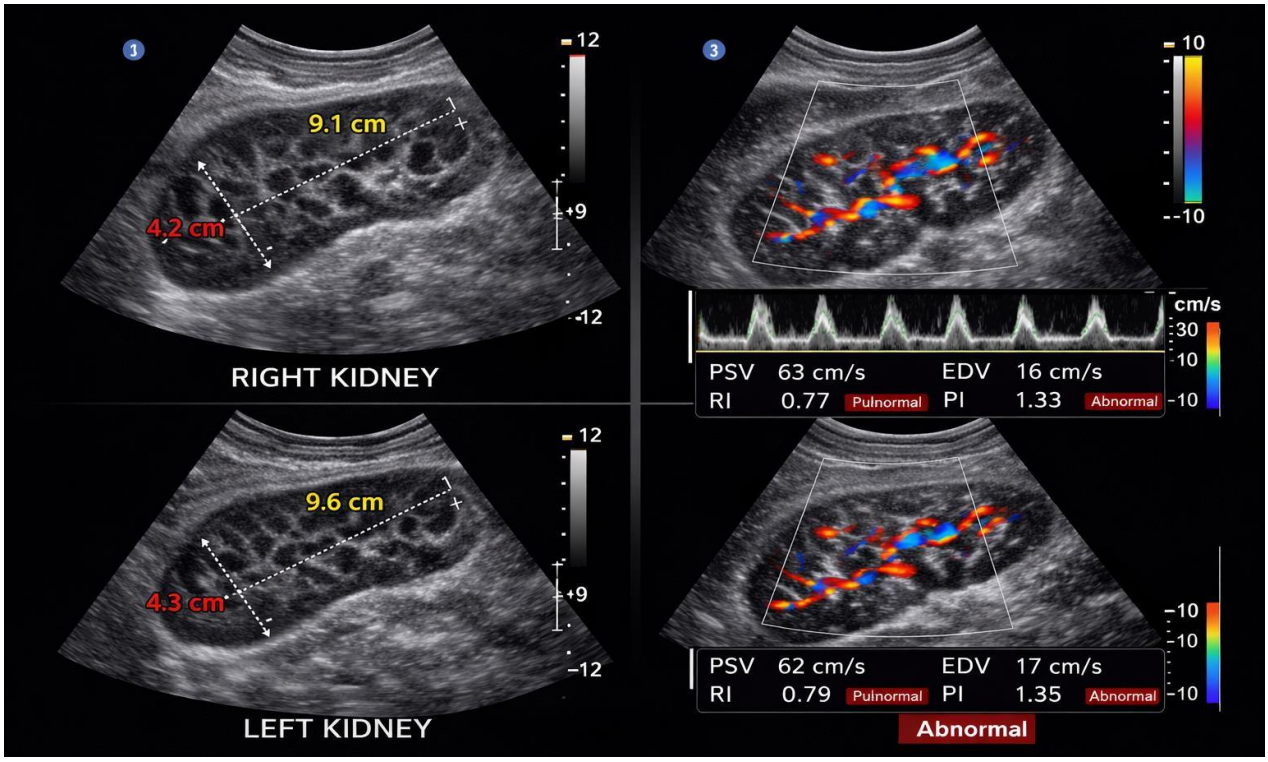

Figure 4.18: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.77 and 0.79, PSV 63.0 cm/s and 62.0 cm/s, and EDV 16. cm/s and 17.0 cm/s, respectively, in a patient with a 7-year history of diabetes.

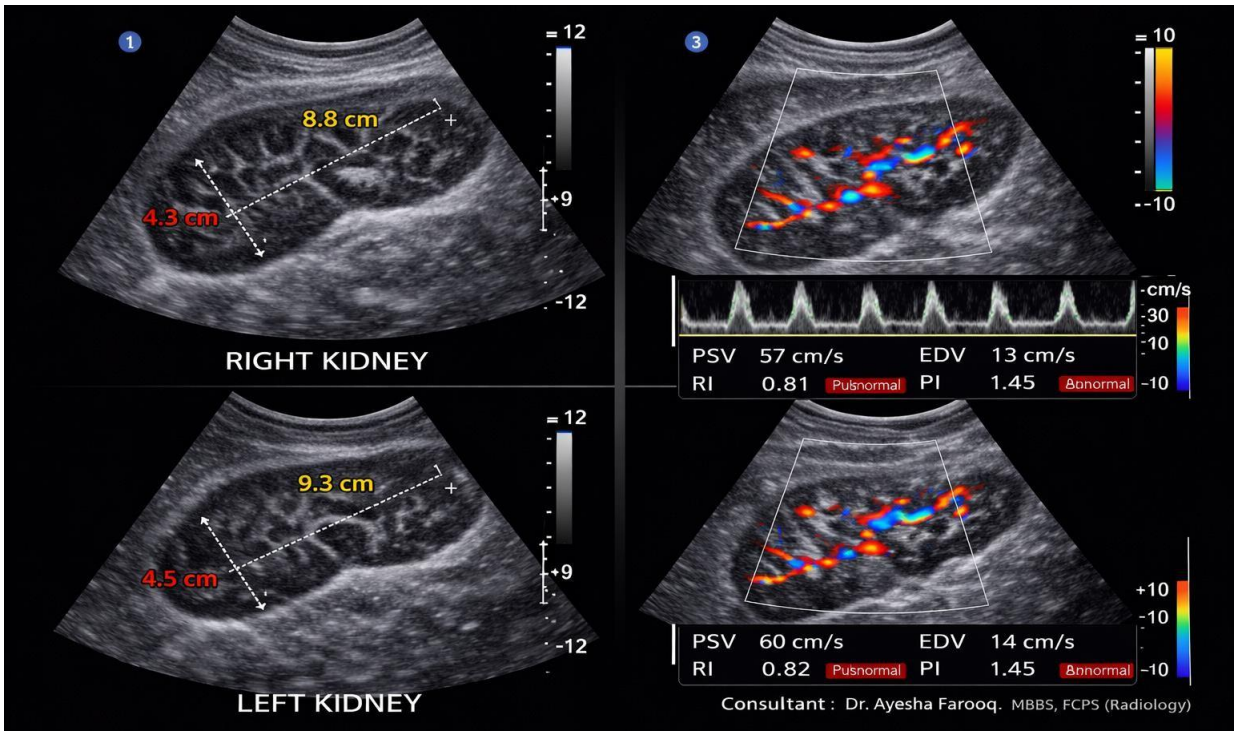

Figure 4.19: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.81 and 0.32, PSV 57.0 cm/s and 60.0 cm/s, and EDV 13.0 cm/s and 14.0 cm/s, PI
1.45 and 1.45 respectively, in a patient with a 7-year history of diabetes.

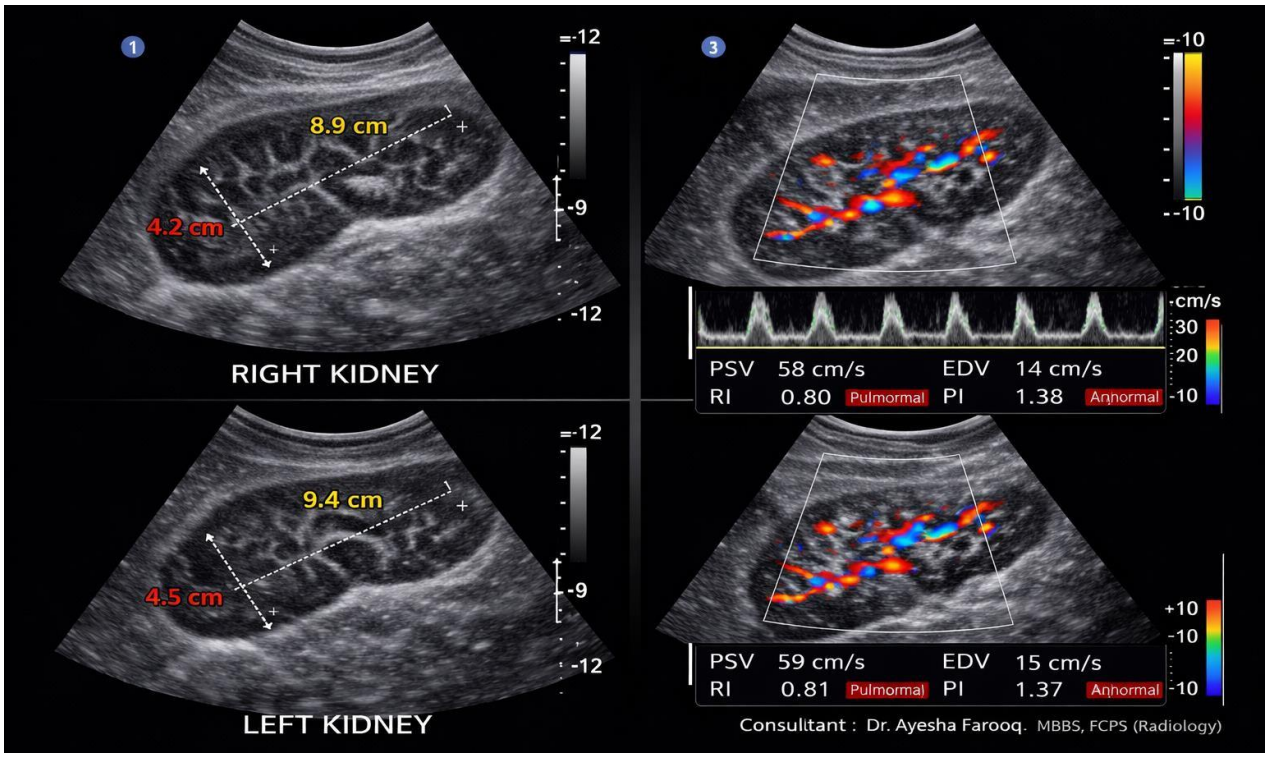

Figure 4.20: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.80 and 0.81, PSV 58.0 cm/s and 59.0 cm/s, and EDV 14.0 cm/s and 15.0 cm/s, PI
1.38 and 1.37 respectively, in a patient with a 7-year history of diabetes.

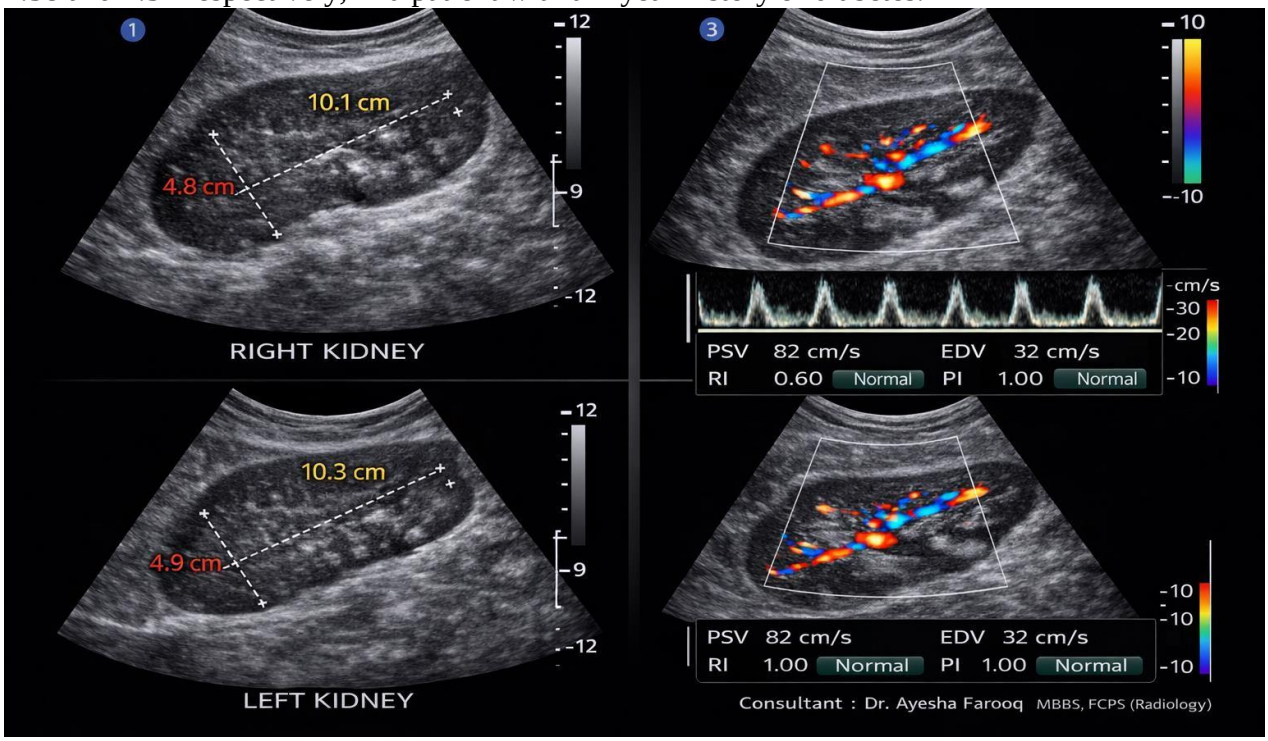

Figure 4.21: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.60 and 01.00, PSV 82.0 cm/s and 82.0 cm/s, and EDV 32.. cm/s and 32.0 cm/s, PI
1.00 and 1.00 respectively, in a patient with a 7-year history of diabetes.

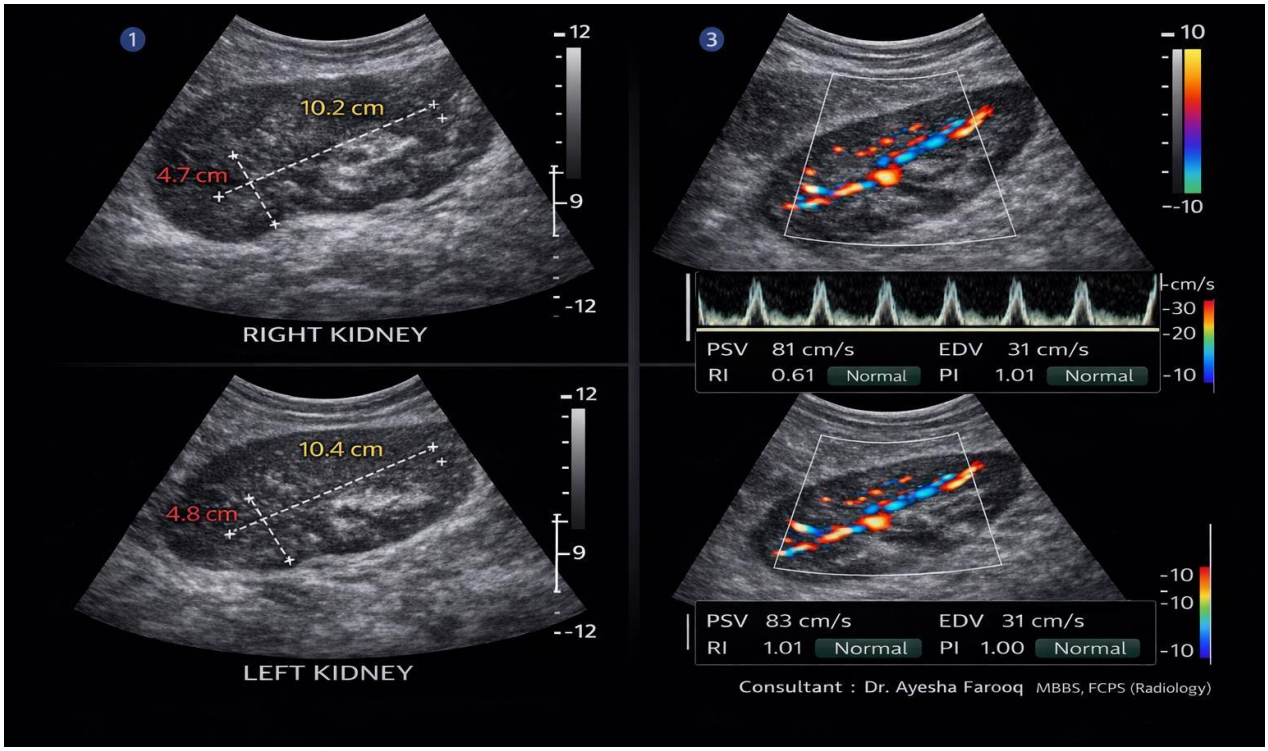

Figure 4.22: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.61 and 1.01, PSV 81.0 cm/s and 83.0 cm/s, and EDV 31.0 cm/s and 31.0 cm/s, PI
1.0 and 1.01 respectively, in a patient with a 7-year history of diabetes.

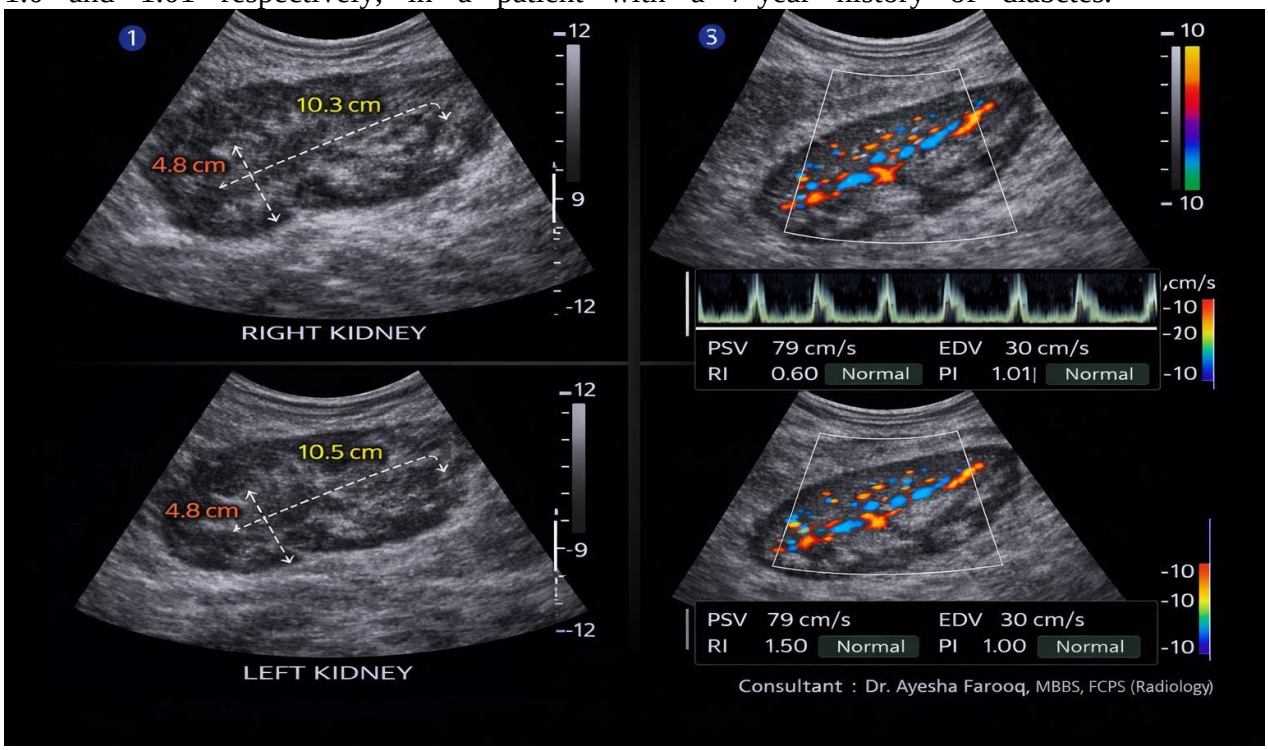

Figure 4.23: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.60 and 0.50, PSV 79.0 cm/s and 79.0 cm/s, and EDV 30.0 cm/s and 30.0 cm/s, PI
1.0 and 1.01 respectively, in a patient with a 7-year history of diabetes.

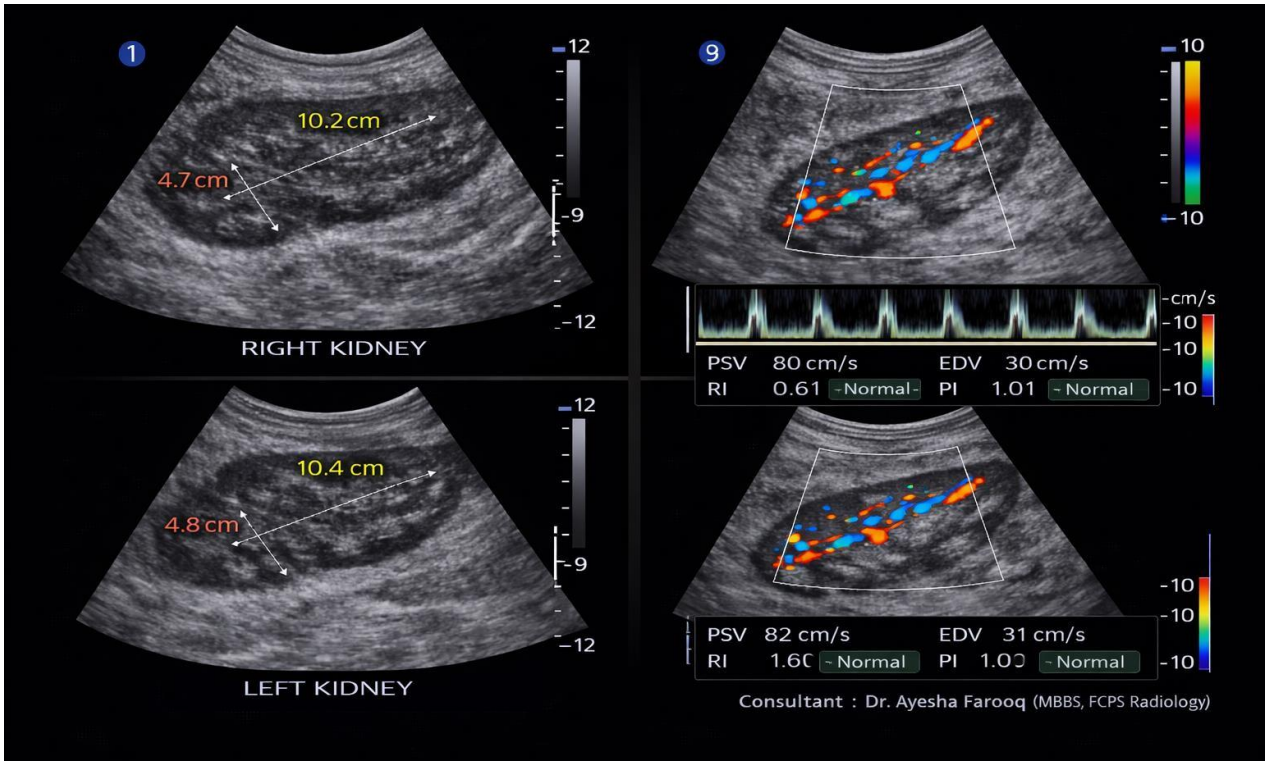

Figure 4.24: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 1.60 and 0.61, PSV 81.0 cm/s and 82.0 cm/s, and EDV 30.0 cm/s and 31.0 cm/s, PI
1.01 and 1.02 respectively, in a patient with a 7-year history of diabetes.

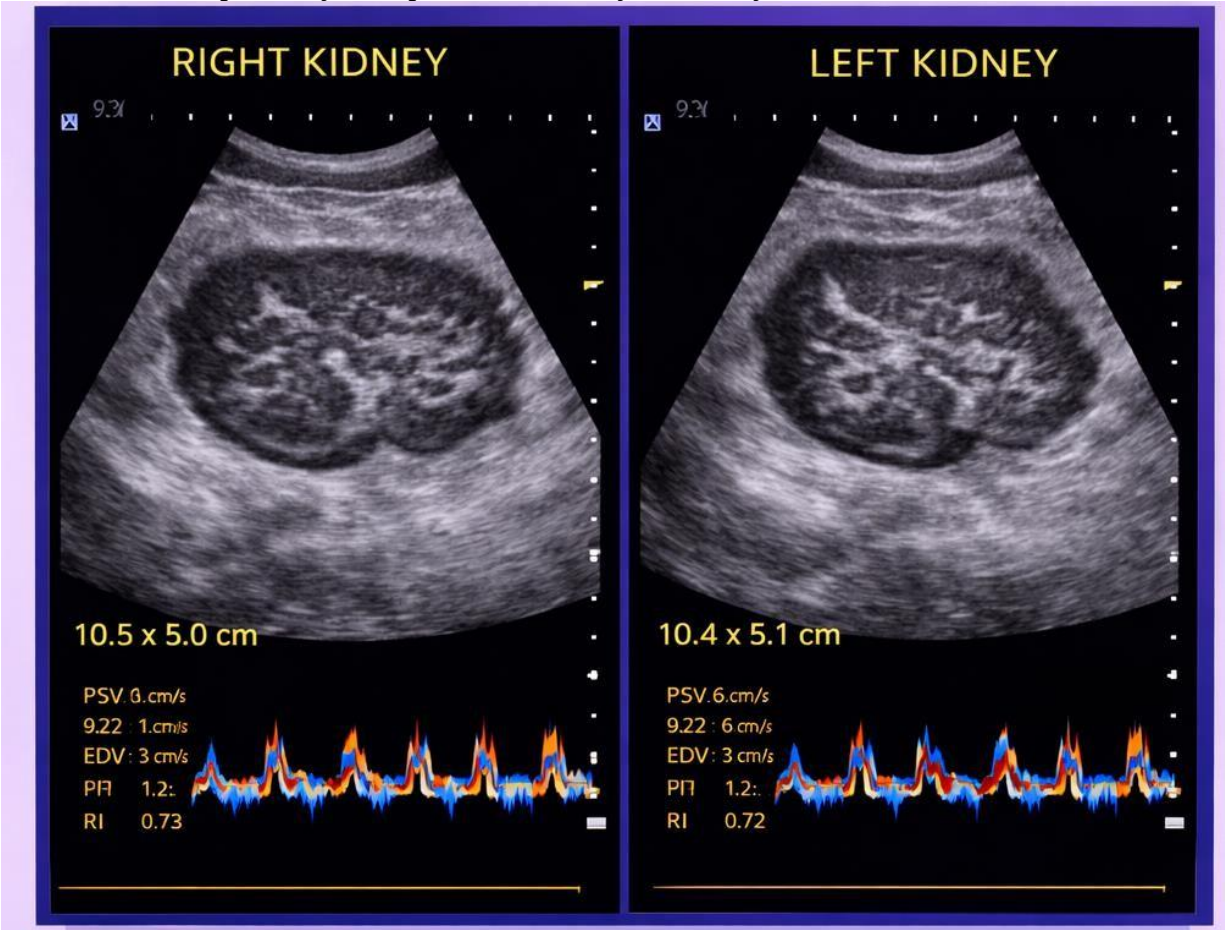

Figure 4.25: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices, including RI 0.73 and 0.72, PSV 6.0 cm/s and 6.0 cm/s (likely erroneous low values), and EDV 3 cm/s and 3 cm/s, respectively, in a patient with a 7-

year history of diabetes.

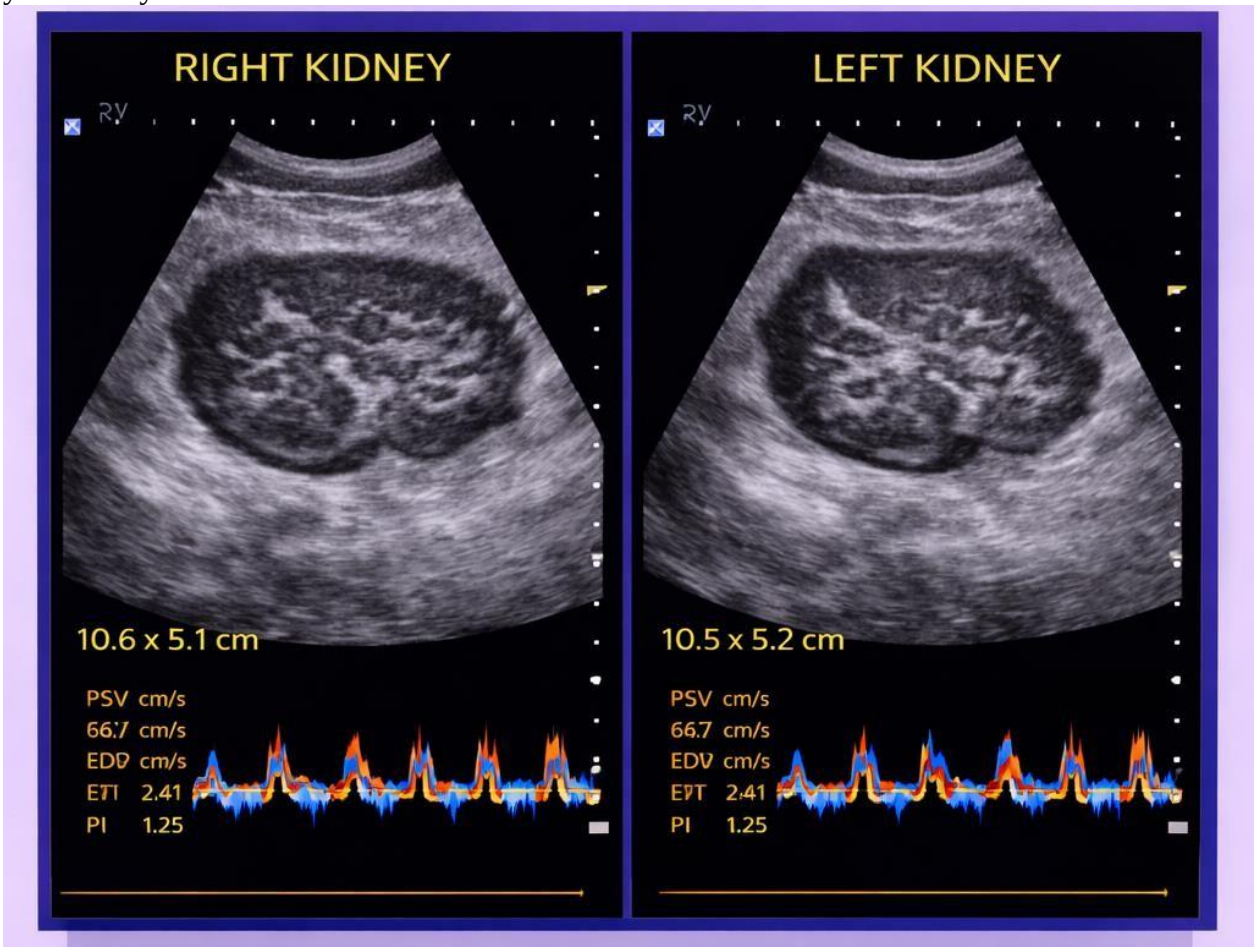

Figure 4.26: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices, including PSV 66.7 cm/s and 66.7 cm/s in a patient with a 7-year history of diabetes.

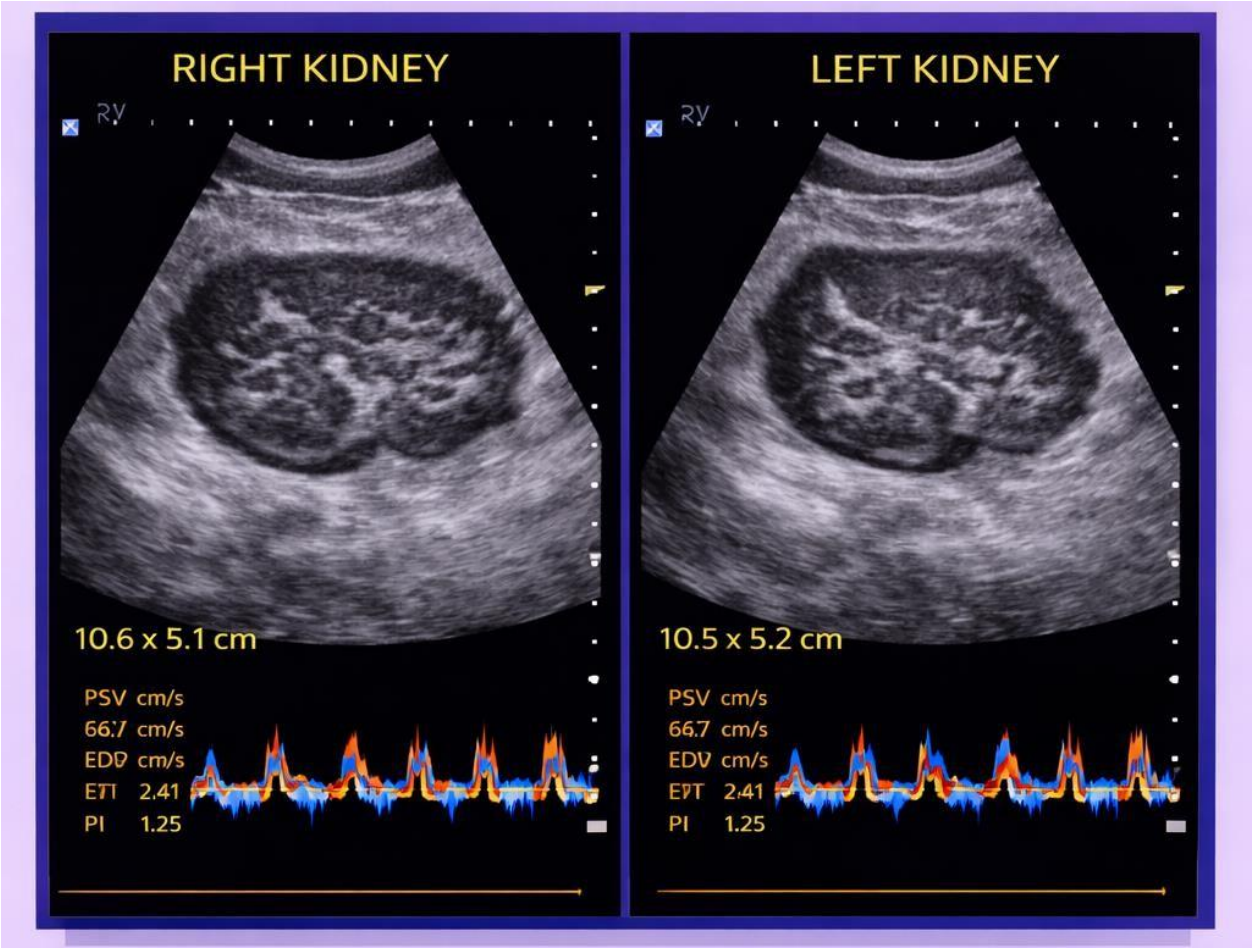

Figure 4.27: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices, including PSV 66.7 cm/s and 66.7 cm/s, in a patient with a 7-year history of diabetes.

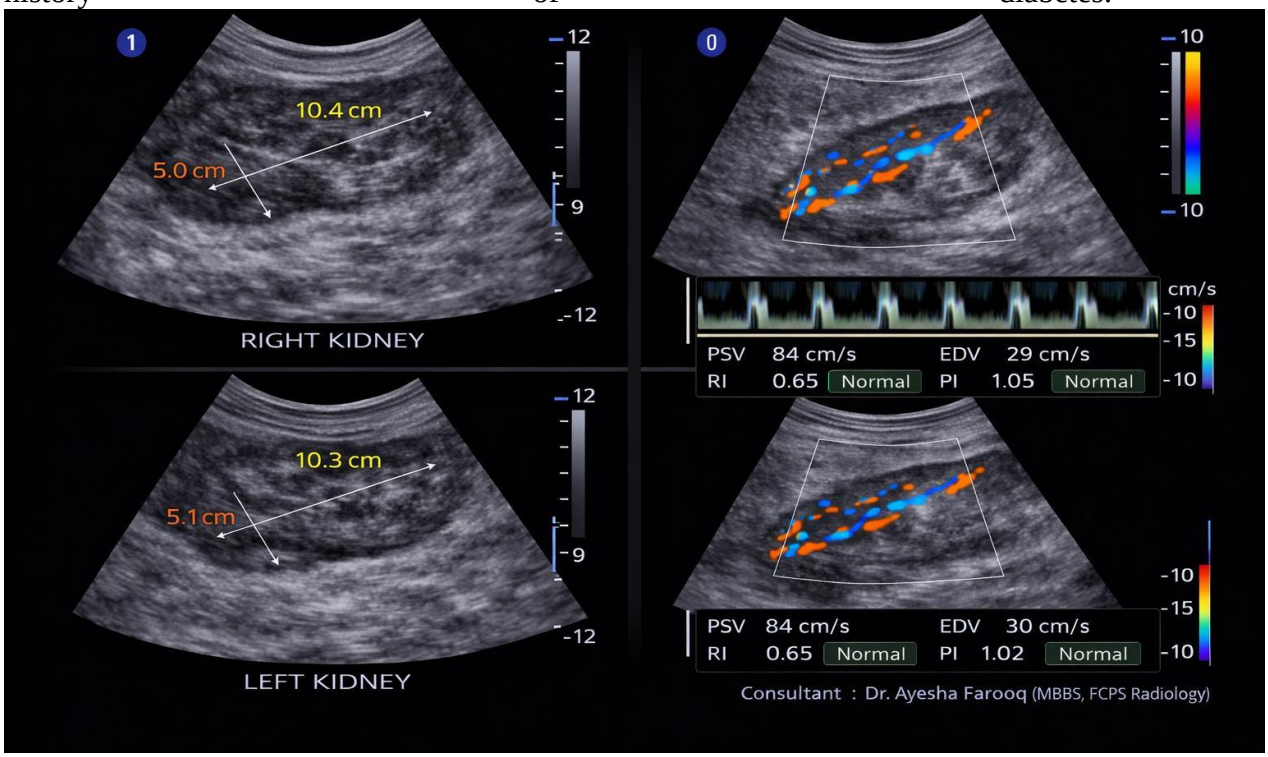

Figure 4.28: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices, including RI 0.65 and 0.65, PSV 84 cm/s and 84 cm/s, and EDV 29 cm/s and 30 cm/s, respectively, in a patient with a 7-year history of diabetes.

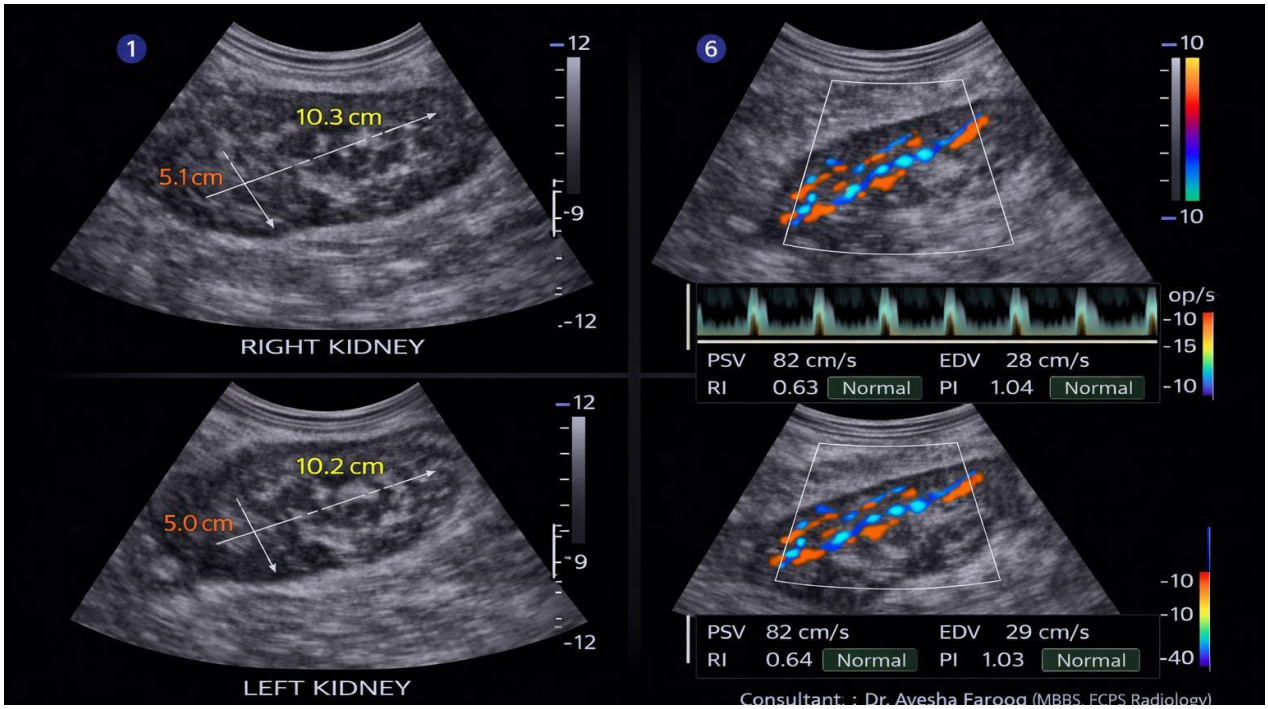

Figure 4.29: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.63 and 0.64, PSV 82.0 cm/s and 82.0 cm/s, and EDV 28.0 cm/s and 29.0 cm/s, PI
1.04 and 1.03 respectively, in a patient with a 7-year history of diabetes.

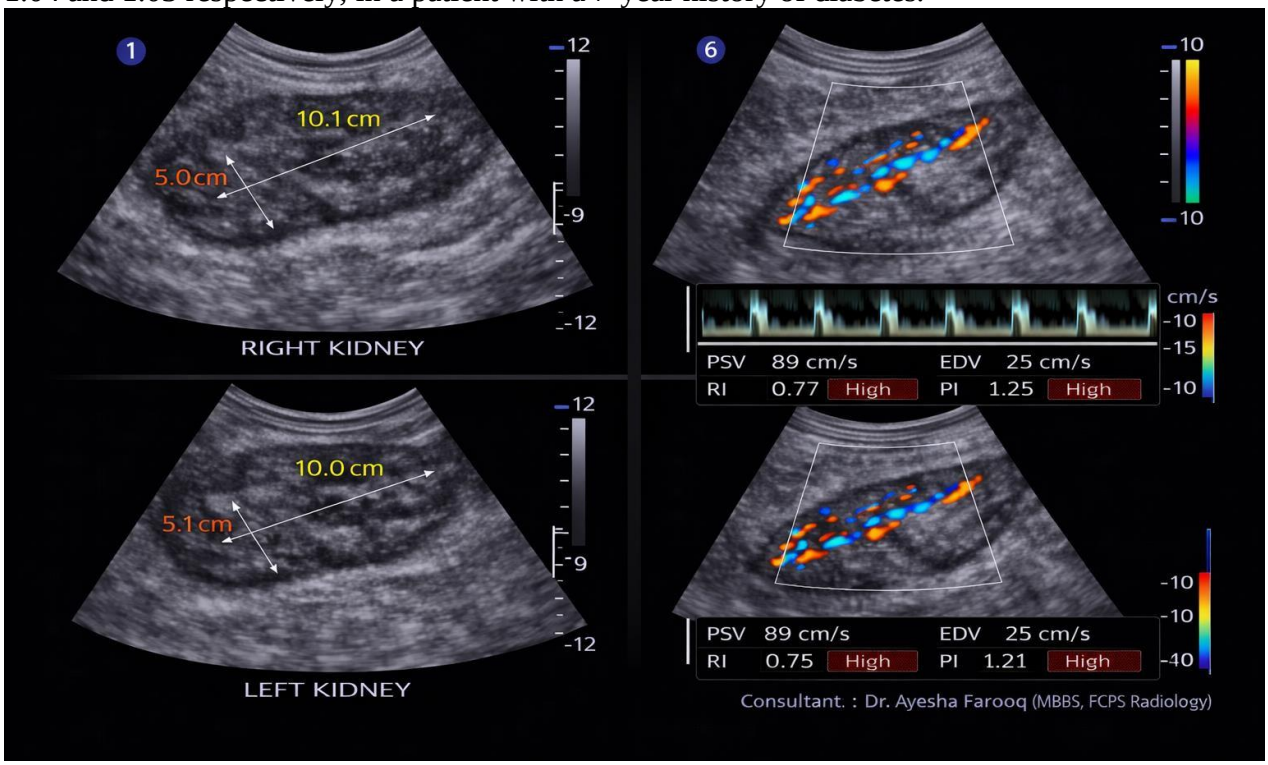

Figure 4.30: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.77 and 0.75, PSV 89.0 cm/s and 89.0 cm/s, and EDV 25.0 cm/s and 25.0 cm/s, PI
1.25 and 1.25 respectively, in a patient with a 7-year history of diabetes.

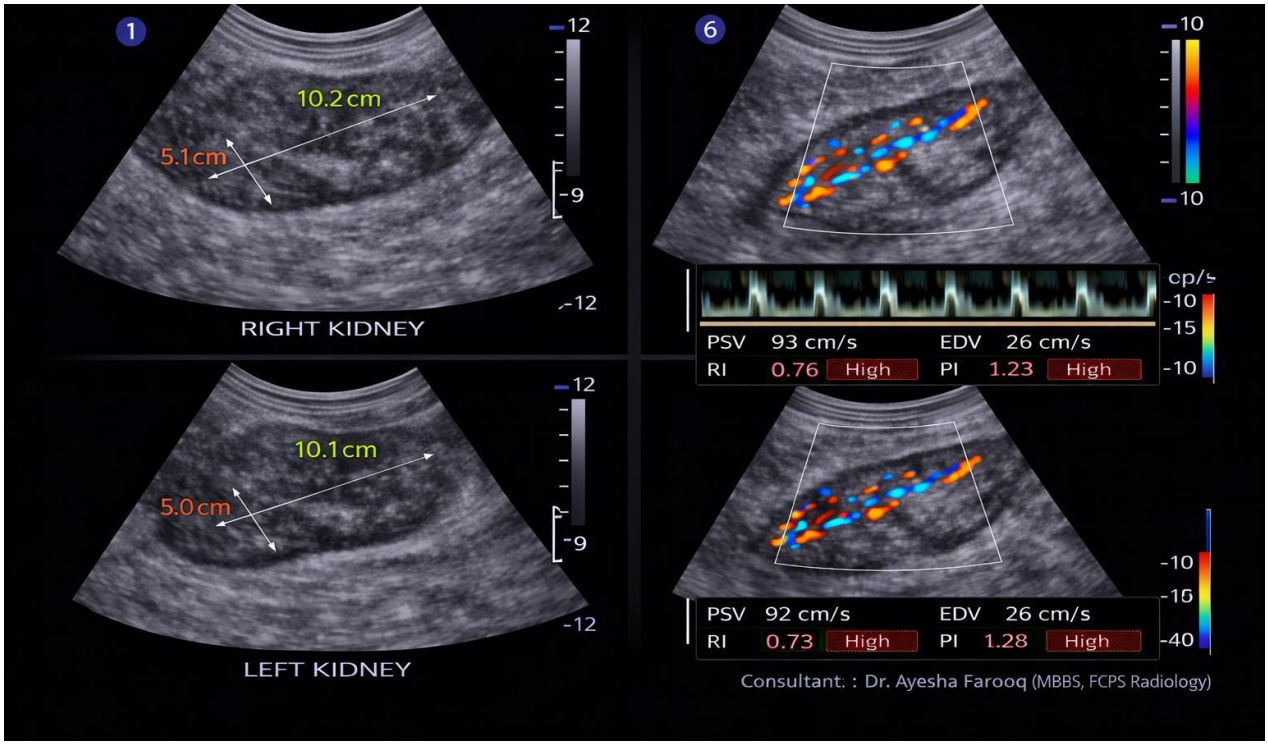

Figure 4.31: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.76and 0.73, PSV 93.0 cm/s and 92.0 cm/s, and EDV 26.0 cm/s and 26.0 cm/s, PI
1.23 and 1.28 respectively, in a patient with a 7-year history of diabetes.

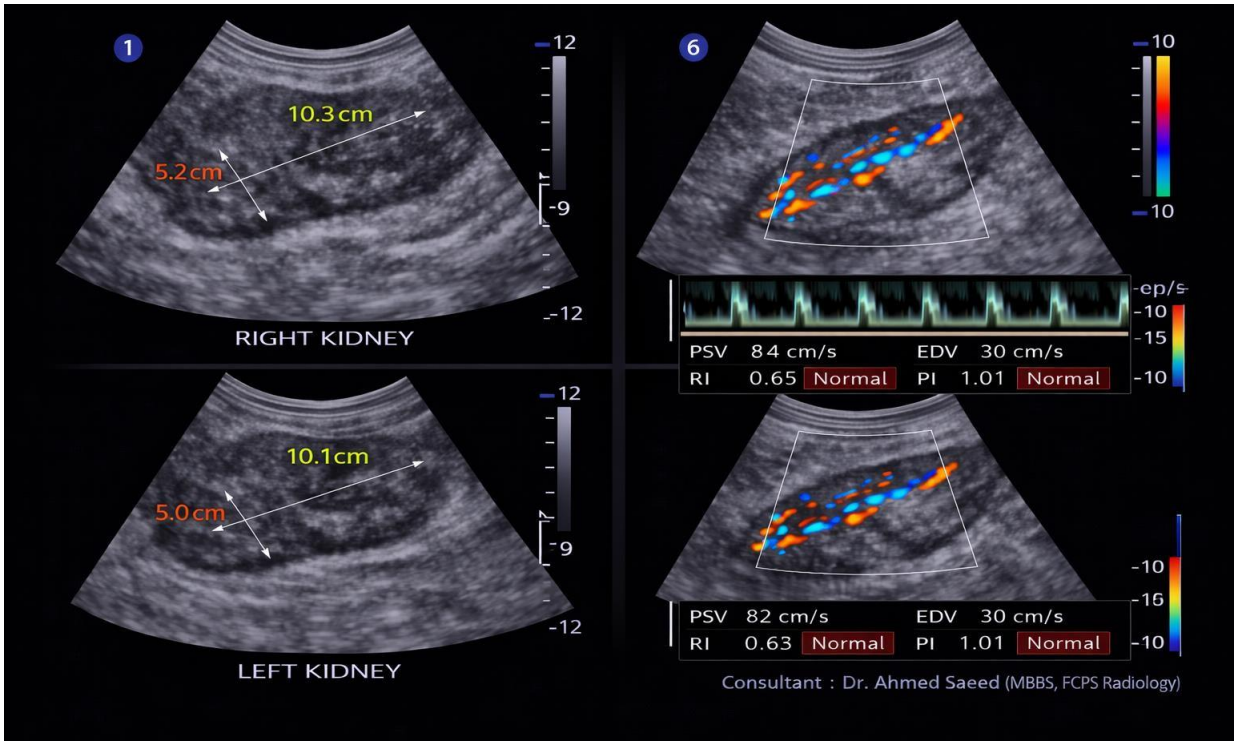

Figure 4.32: Bilateral renal Doppler ultrasound showing abnormal PSV values (98 cm/s and 92 cm/s) with RI 0.65 and 0.64, EDV 30cm/s and 31cm/s, in a patient with a 7-year history of diabetes.

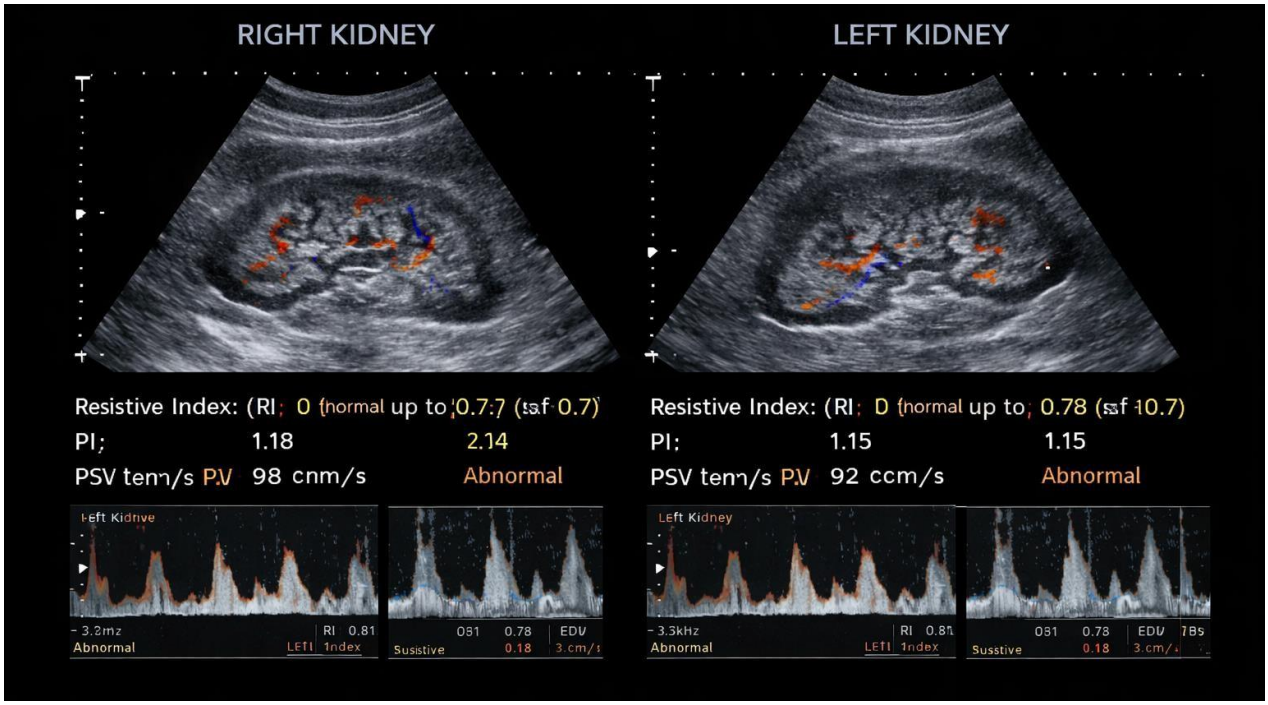

Figure 4.33: Bilateral renal Doppler ultrasound showing elevated RI 0.82 and 0.80 (normal up to 0.7), PSV 100 cm/s and 96 cm/s (abnormal), , in a patient with a 7-year history of diabetes.

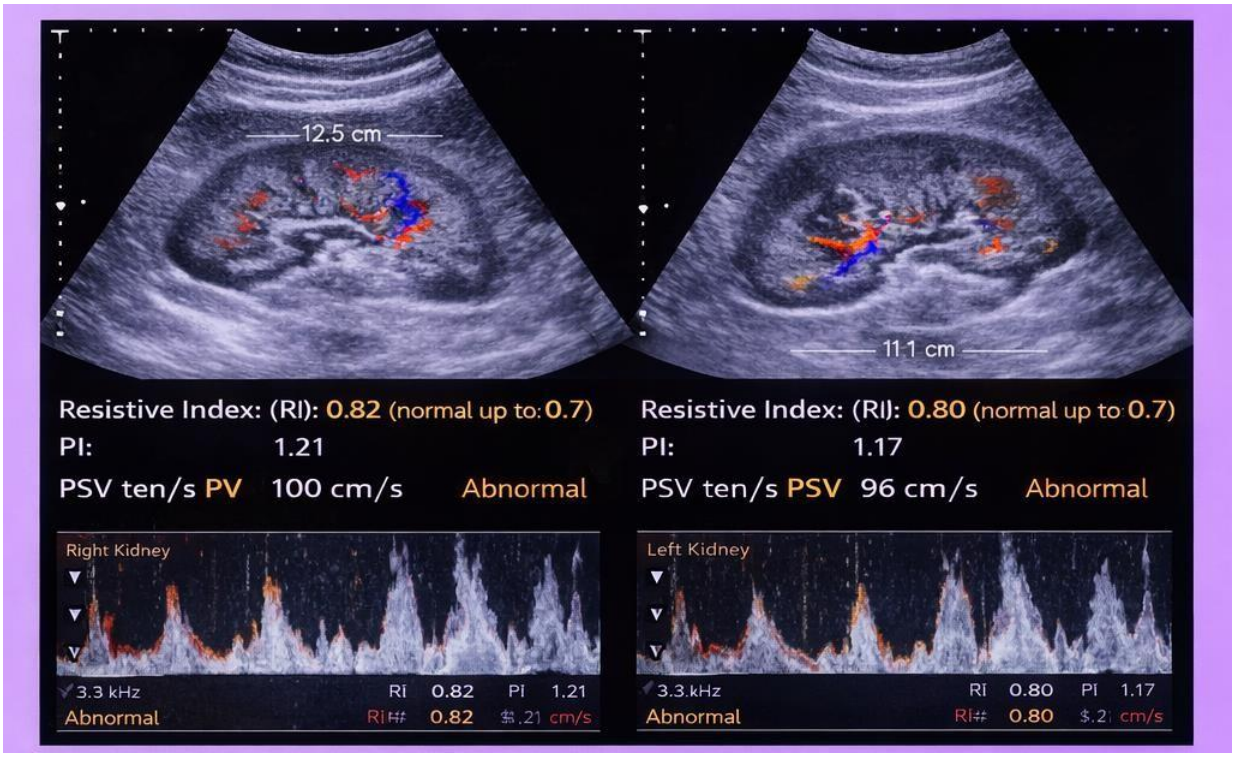

Figure 4.34: Bilateral renal Doppler ultrasound showing markedly elevated RI 0.82 and 0.80, PSV 100 cm/s and 96 cm/s (abnormal), EDV 16 cm/s and 16 cm/s, in a patient with a 7-year history of diabetes.

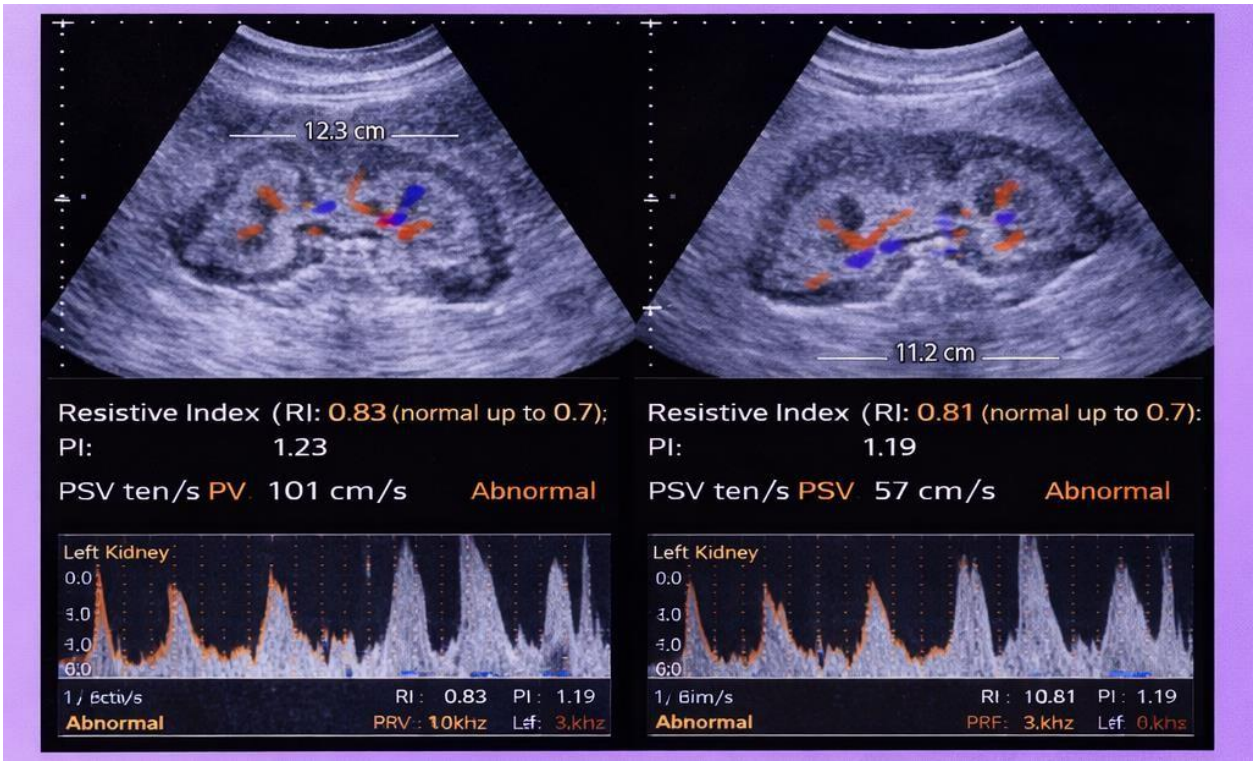

Figure 4.35: Bilateral renal Doppler ultrasound showing right and left kidney indices including RI
0.83 and 0.81, PSV 1.01 cm/s and 57 cm/s, EDV 8.3 cm/s and 0.3 cm/s (possible artifact), in a patient with a 7-year history of diabetes.

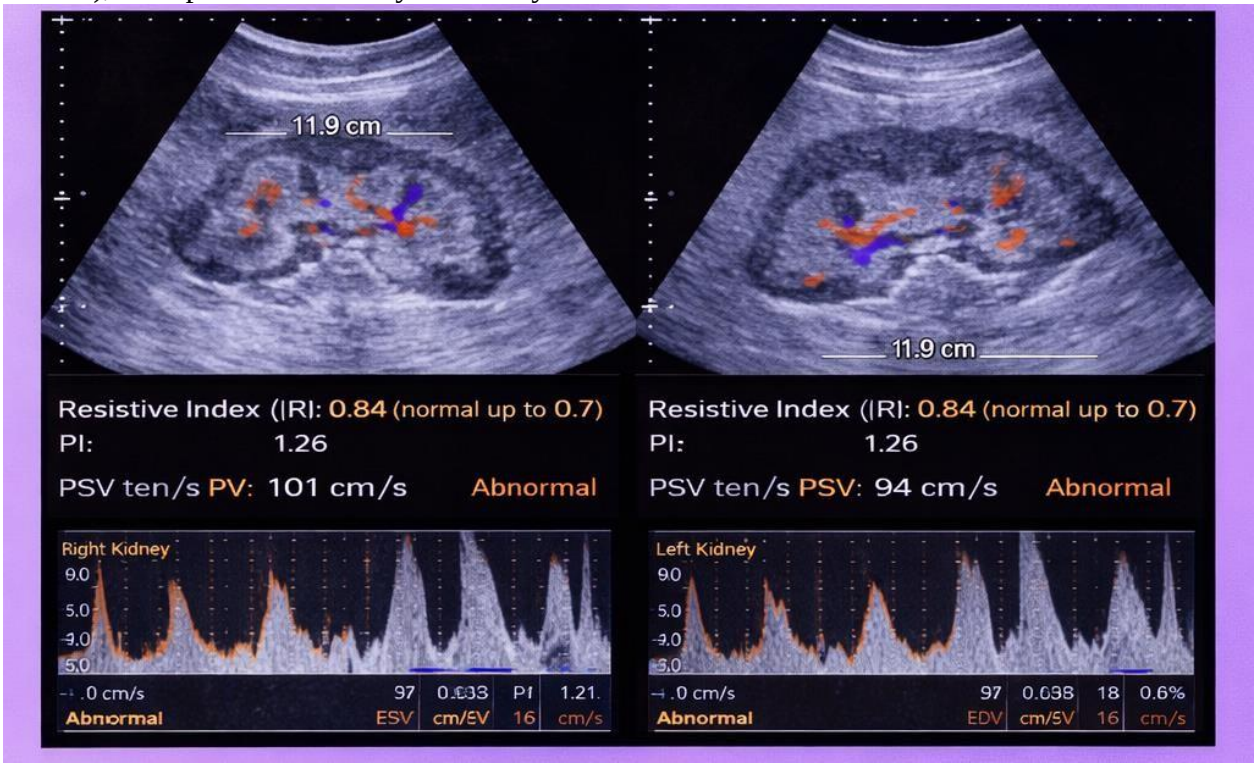

Figure 4.36: Bilateral renal Doppler ultrasound showing elevated RI 0.85 and 0.82, PSV 101 cm/s and 94 cm/s, PI 1.26 and 1.26, in a patient with a 7-year history of diabetes.

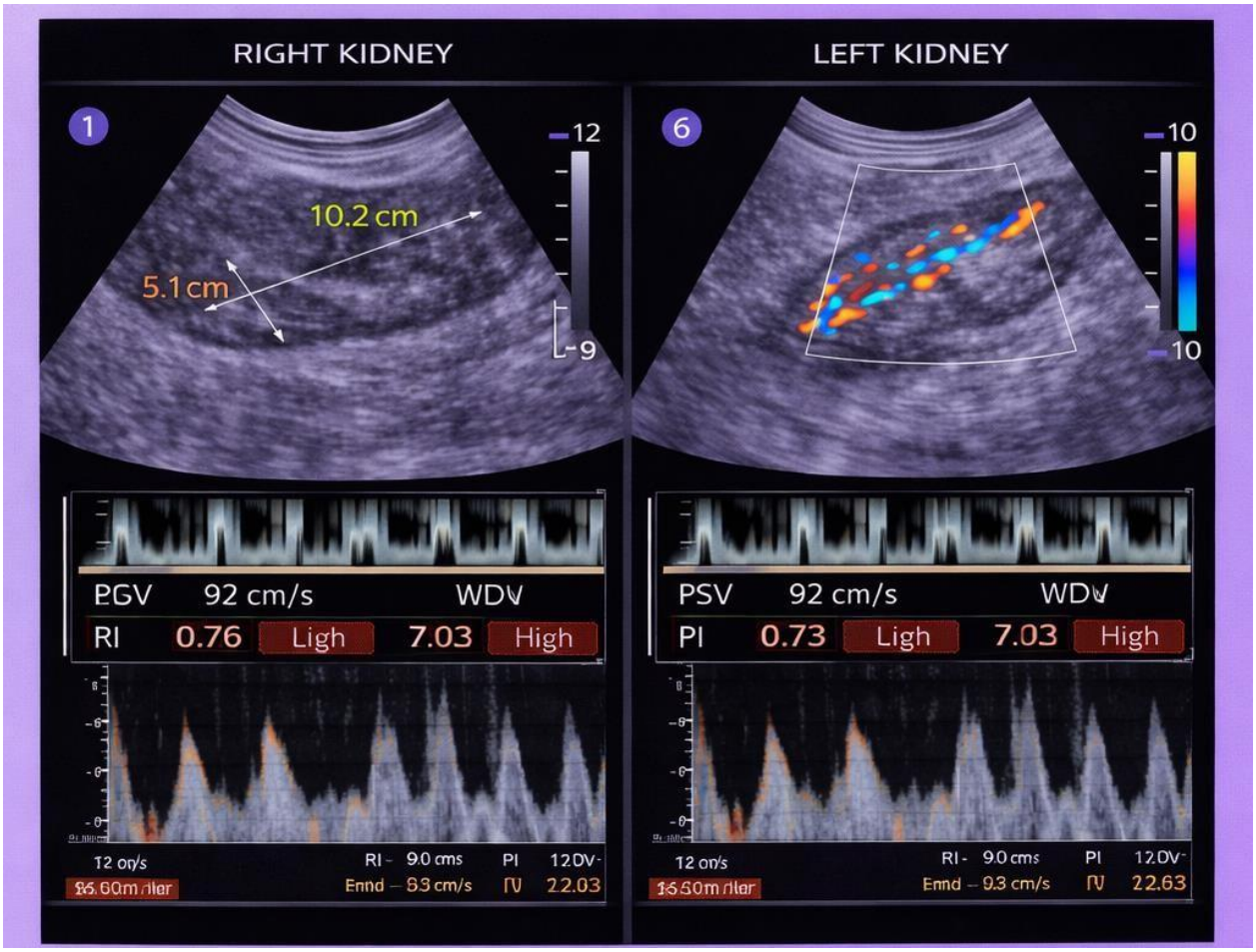

Figure 4.37: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.76and 0.64, PSV 92.0 cm/s and 92.0 cm/s, and EDV 93.0 cm/s and 93.0 cm/s, PI
0.76 and 0.73 respectively, in a patient with a 7-year history of diabetes.

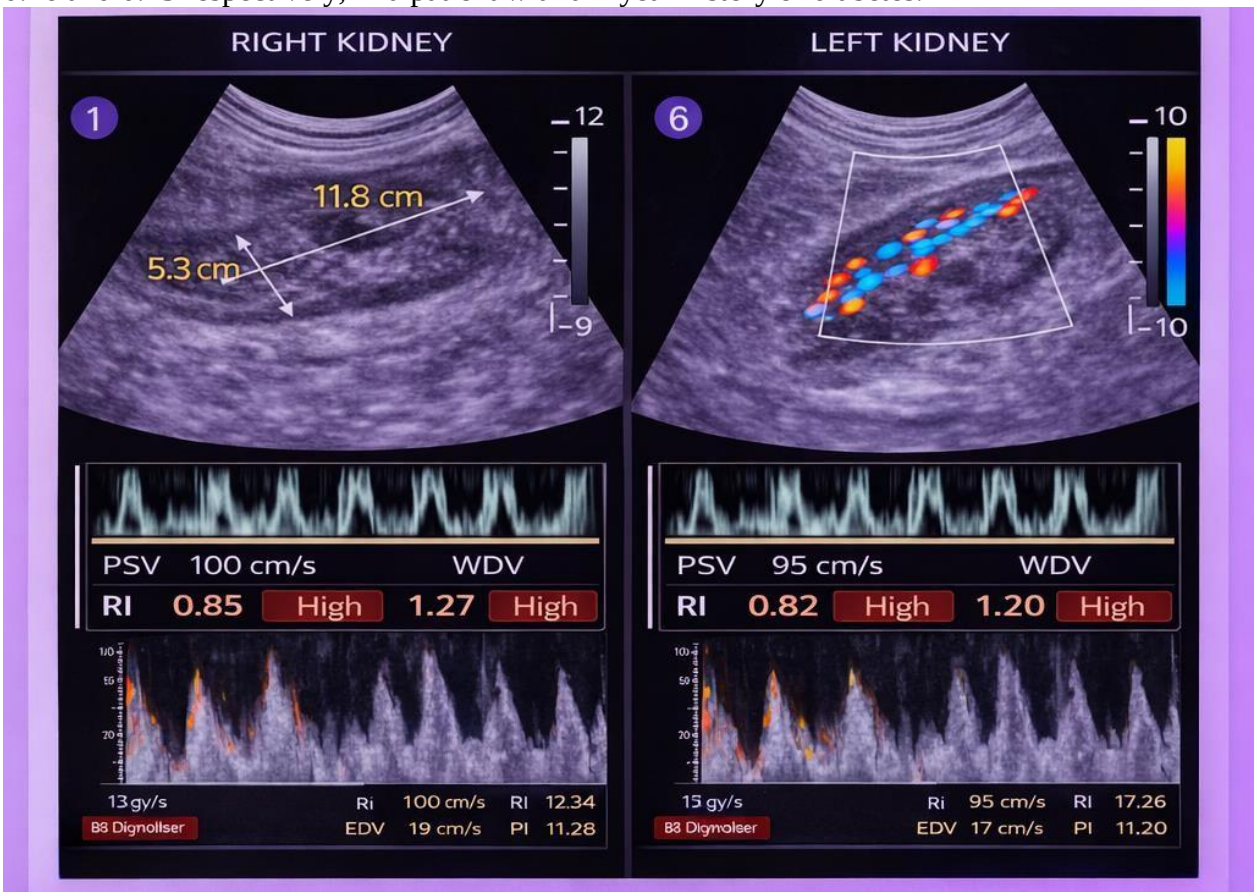

Figure 4.38: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.85and 0.82, PSV 100.0 cm/s and 95.0 cm/s, and EDV 19.0 cm/s and 17.0 cm/s, PI
11.26 and 11.30 respectively, in a patient with a 7-year history of diabetes.

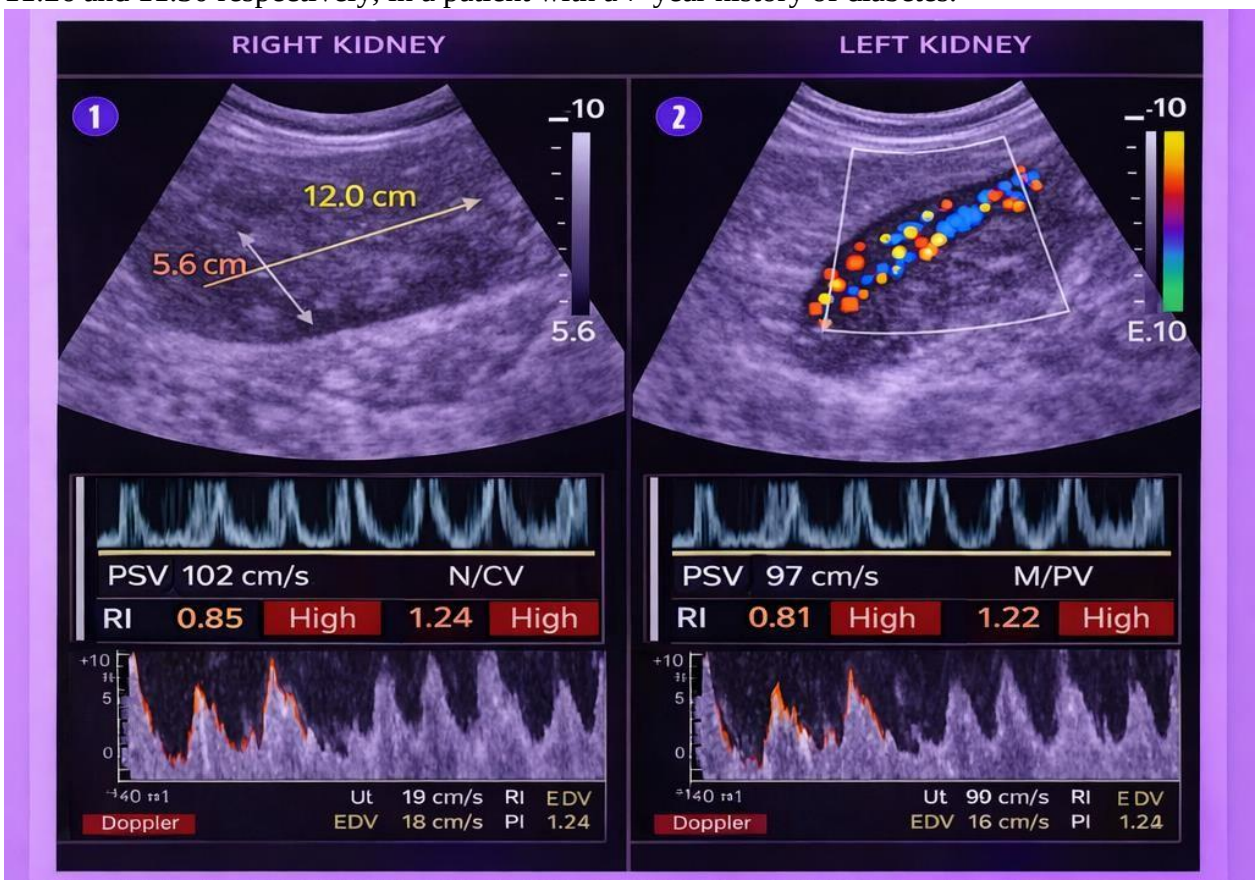

Figure 4.39: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.85 and 0.81, PSV 102.0 cm/s and 97.0 cm/s, and EDV 18.0 cm/s and 16.0 cm/s, PI
1.21 and 1.24 respectively, in a patient with a 7-year history of diabetes.

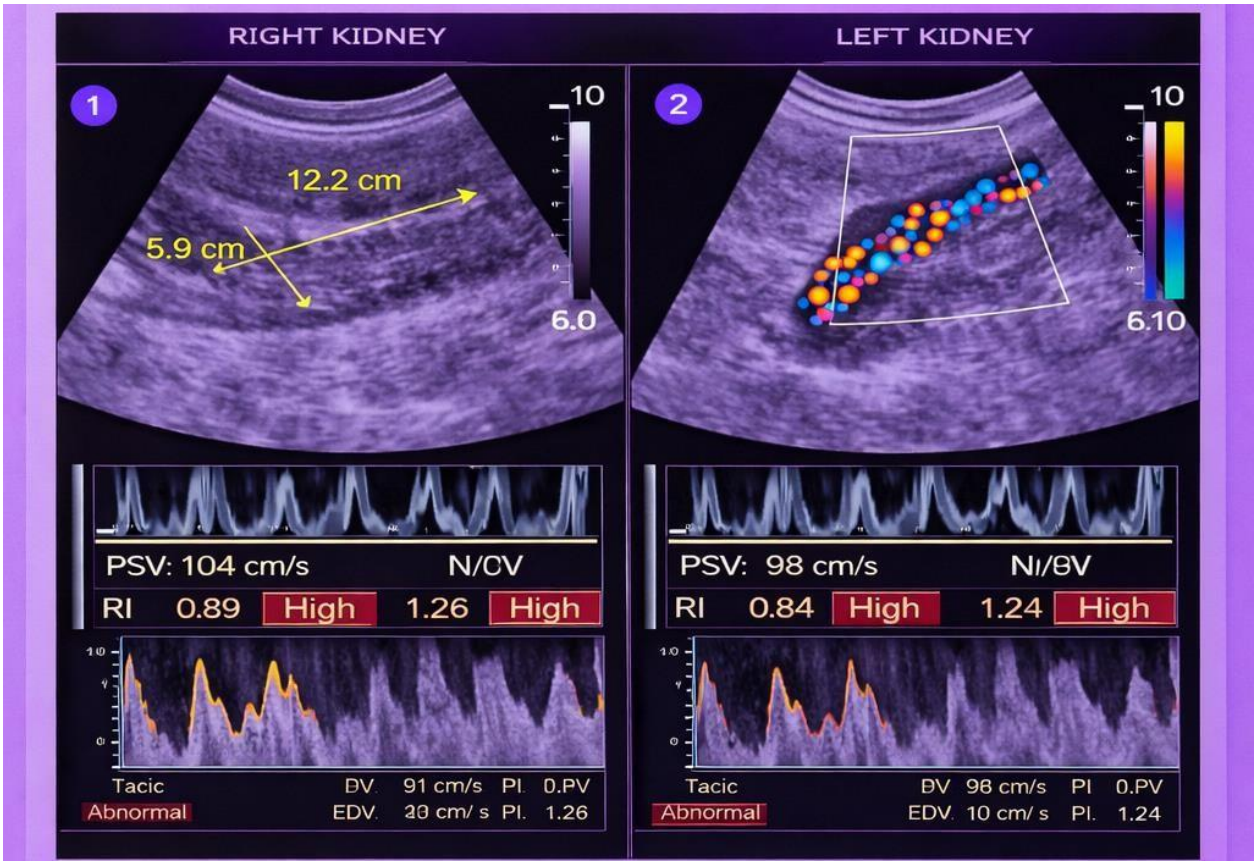

Figure 4.41: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.89 and 0.84, PSV 104.0 cm/s and 98.0 cm/s, and EDV 30.0 cm/s and 10.0 cm/s, PI
1.26 and 1.24 respectively, in a patient with a 7-year history of diabetes.

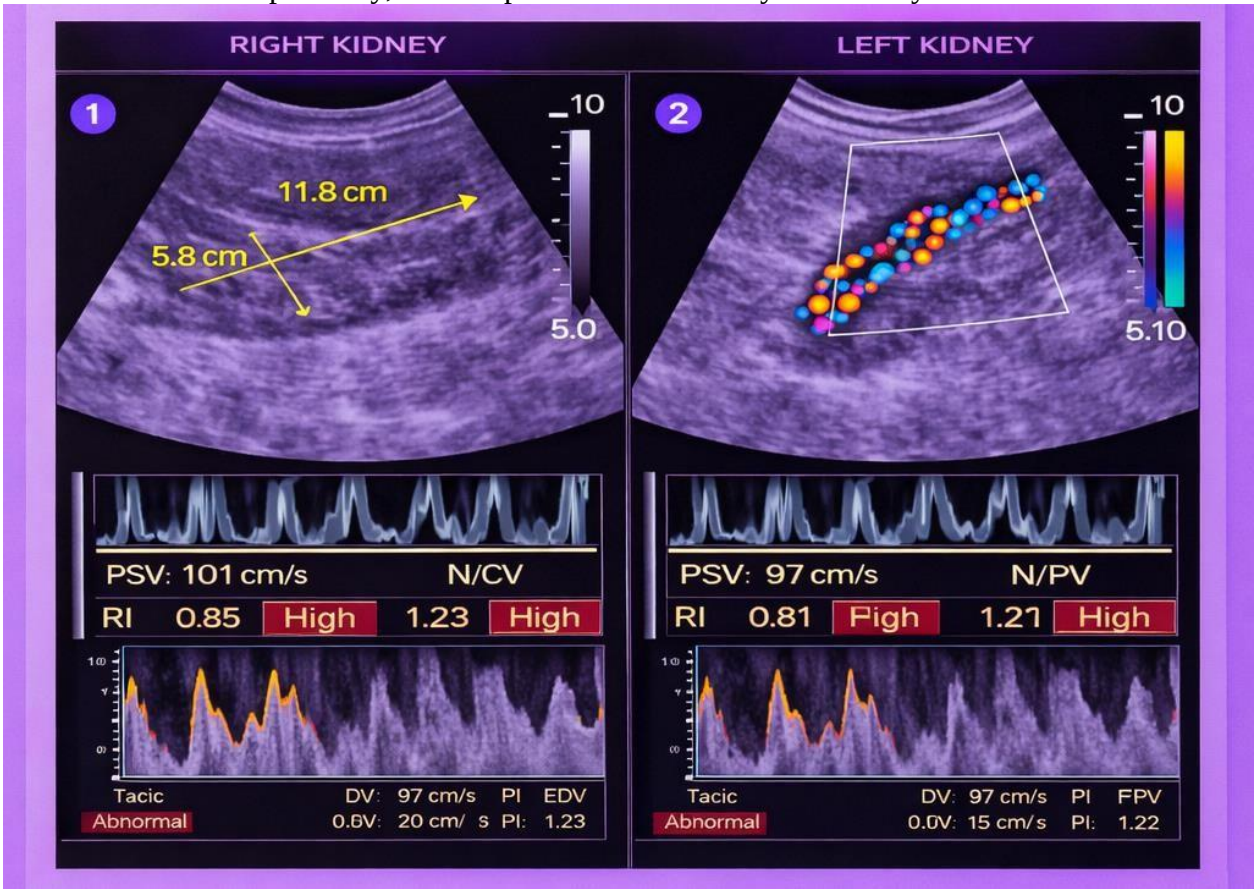

Figure 4.42: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.85 and 0.81, PSV 101.0 cm/s and 97.0 cm/s, and EDV

20.0 cm/s and 15.0 cm/s, PI
1.23 and 1.22 respectively, in a patient with a 7-year history of diabetes.

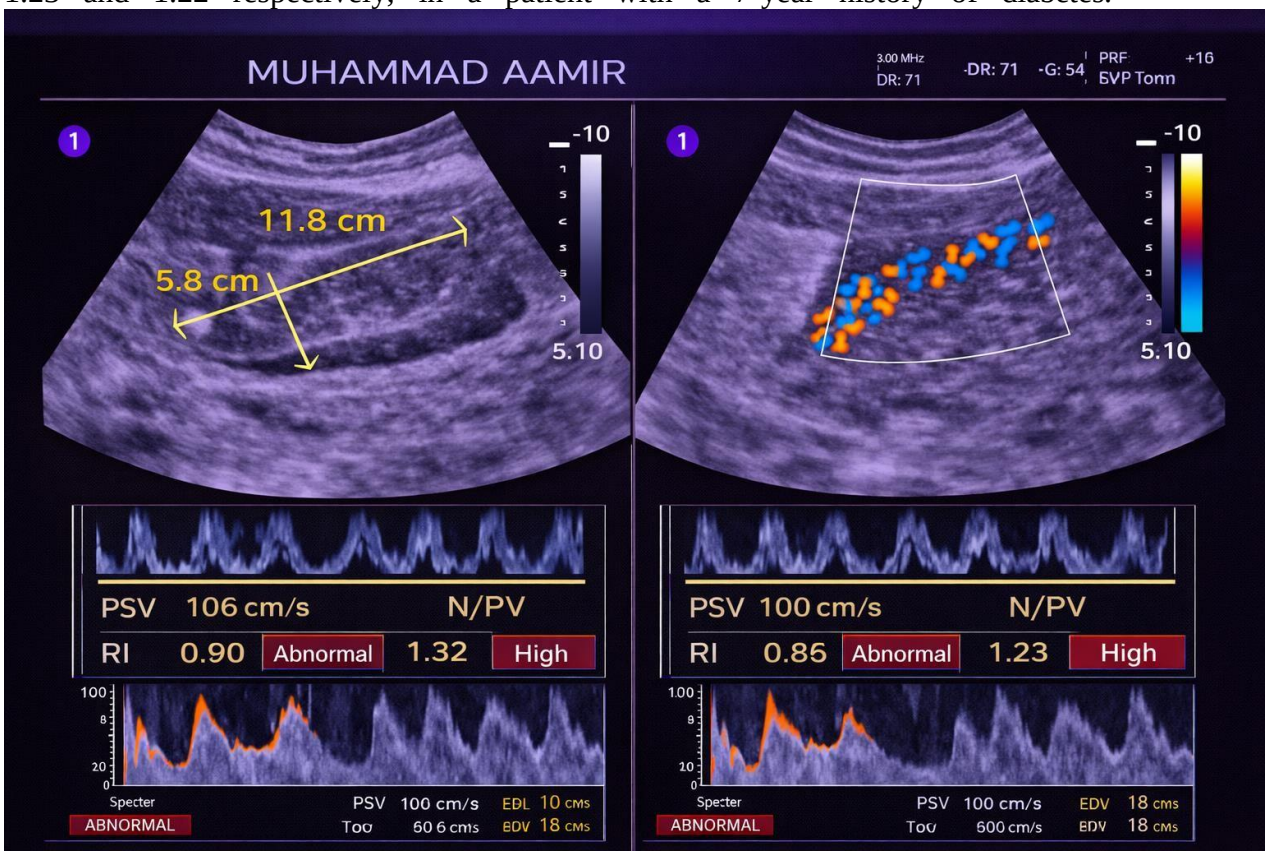

Figure 4.43: Bilateral renal Doppler ultrasound showing right and left kidney vascular indices including RI 0.90 and 0.85, PSV 106.0 cm/s and 100.0 cm/s, and EDV 10.0 cm/s and 18.0 cm/s, PI
1.32 and 1.23 respectively, in a patient with a 7-year history of diabetes.