

Evaluation of resistance index (RI) values in patients with proteinuria: correlation of resistance index with biopsy findings.

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Abstract

Background: Duplex Doppler sonography has been recognized as a noninvasive method to evaluate hemodynamic features of renal blood in renal and intrarenal arteries in patients with various renal diseases. The significance of duplex Doppler sonography in the evaluation of renal vascular resistance in glomerular diseases has not yet been clearly determined. The present study was performed to evaluate renal vascular resistance in patients with proteinuria by measuring intrarenal arterial resistance (RI) and the aim of this study is to evaluate the correlation between RI and pathologic results.

Methods: RI was measured 24 hours before renal biopsy in 99 patient's admitted with proteinuria. Clinical and laboratory data were collected prospectively. We determined mean RI values in subtypes of disease according to the biopsy findings. Also correlation between RI with histopathological findings, age, gender, proteinuria level and serum creatinine level was evaluated.

Results: Among 99 patients with mean age of 45.92 ± 16.88 years, 61.61% were male. The mean RI was 0.65 ± 0.09 . The most common biopsy based diagnosis was focal segmental glomerulosclerosis. The mean of RI in this group was 0.72 ± 0.1 which was statistically significantly higher than in other groups of patients. RI significantly correlated with age ($P < 0.01$), serum creatinine ($P < 0.01$) and proteinuria ($P = 0.02$).

Conclusion: According to these findings, we recommended to evaluate RI in following patients with proteinuria, since the RI values could represent underlying disease injury.

Keywords: Doppler sonography, Vascular resistance, Renal paranchaimal disease, Glomerulonephritis, Pathologic findings.

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Introduction

Although color Doppler sonography is widely used in various renal diseases, its usefulness in medical renal diseases has been known to be really limited. This might be due to the conflicting results achieved in the previous researches or impossibility of differentiating between various renal diseases. Renal parenchymal resistance measured by Resistance Index indicates the general resistance at the tract through which blood enters the kidney. This resistance is caused by various parts of Parenchyma and Glomeruli [1]. It has been well confirmed today that only special renal diseases increase the resistance in inter-renal vessels. The increased level of Renal Index in Doppler sonography is associated with various diseases such as kidney obstruction, acute tubular necrosis, renal vein thrombosis, hemolytic uremic syndrome and primary hypertension. This modality is also widely utilized to diagnose renal vein narrowing. However, using color Doppler sonography to investigate the level of RI in renal parenchymal

and glomerular disease has not been properly studied and only a small number of researches have been done on this issue so far.

The present research is designed to study the resistance of renal veins among non-diabetic patients without primary hypertension who have proteinuria. The present research seeks to study the correlation between the level of RI and biopsy findings among these patients. Considering the accessibility and non-invasive nature of sonography, finding the correlation between levels of RI and biopsy results can help us estimate pre-awareness and study the procedure of responding to treatment. In a prospective research, Parabar et al. investigated the role of RI in predicting the confirmed tubulointerstitial waste in biopsy in patients with glomerular disease. In this research, 71 patients suffering from primary and secondary glomerular disease underwent color Doppler sonography right before renal biopsy and their RI rates were calculated. Then, the level of RI was compared against the histologic changes

available in biopsy sample. As the results indicated, an RI rate of 0.6 was an appropriate limit to show tubulointerstitial damages (a sensitivity level of 82.7% and a specialty of 92%). A significant correlation was also observed between old age, smoking cigarettes, rise of RI, low glomerular filtration level, high blood cholesterol and high blood pressure with tubulointerstitial damages. The researchers finally arrived at the conclusion that Doppler sonography can be used as a complementary diagnostic device to predict the intensity of tubulointerstitial damages in glomerular diseases [1].

Similar results were also achieved in the study conducted by Sugiura et al. on 60 patients suffering from primary and secondary glomerular disease [2]. In another research, Galesic et al. also studied the RI level of intra-renal veins among 50 patients suffering from glomerulonephritis and 60 patients in the control group. The average RI in glomerular disease group was 0.68 ± 0.09 which was significantly more than the average RI in control group (0.59 ± 0.03). In this research, the average RI rate among patients suffering from membranous glomerulonephritis (0.81 ± 0.62) was significantly more than other glomerulonephritis. There was also a significant correlation between RI and the Creatinine level of serum [3]. This correlation between RI and the level of Creatinine was also confirmed in the research conducted by Kim et al. [4]. In another research conducted by Sugiura et al., it became clear that a significant correlation existed between the level of RI and the tubulointerstitial damages [5]. Sanchez-Lozada et al. issued an article on the physiopathologic description of glomerular damage and the consequences of its effect on glomerular hemodynamics [6]. Turkmen et al. showed that a significant correlation existed between the level of RI and biopsy results such as the number of glomeruli in Stroma, density of glomerular level, the number of capillaries in glomeruli and arteriolar diameter [7].

Material and Method

The present research was conducted according to the principles of cross-sectional studies in order to study the correlation between the RI index in renal veins' Doppler and the biopsy results of the patients with Proteinuria. Our target society consisted of patients hospitalized in Hashemi Kejad Hospital in order to undergo biopsy following Proteinuria. The present research was conducted in 2012 in Shahid Hashemi Nejad Hospital of Tehran. All those patients hospitalized for biopsy due to Proteinuria were investigated over the course of research. The patients resorted to the sonography unit 24 hours before biopsy in order to measure the level of RI. The required information was extracted from patients' files and entered into a special form designed for this purpose. Having conducted the necessary researches in pathology unit, the results of pathology report were also extracted.

As many as 99 patients were studied in this research. SPSS 17 was used to analyze the data. Mean and standard deviation were used to investigate the quantitative data, while frequency was used to represent the qualitative data. T-test, Chi square,

and One Way Anova were used to compare the two groups. The level of significance was set to 0.05.

Results

This was a cross sectional research and the required information was extracted from patients' files in Hasheminejad Hospital. Mean and standard deviation were used to investigate the quantitative data, while frequency was used to represent the qualitative data. T-test, Chi square, and One Way Anova were used to compare the two groups. The level of significance was set to 0.05. Based on our results, the average age of patients suffering from Proteinuria who underwent Doppler sonography with an age range of 17 to 77 years old was 42.92 ± 16.88 . The gender distribution in this research indicated the superiority of males (62%) to females (38%). The average RI level among the patients with a high limit of 0.94 and a low limit of 0.53 was equal to 0.6570 ± 0.09 . In our research, out of the 99 patients suffering from proteinuria, 32 patients (32.32%) had an RI level above 0.7, while 67 had an RI level below 0.7. The average creatinine level with a range of 0.7 to 7.1 millig per milliliter was 2.42 ± 1.888 , while the average proteinuria level with a range of 500 to 24284 millig per a day was 4756.53 ± 5011.69 . The relative frequency of pathologic diagnosis among the patients we studied is represented in Table 1. The level of Chronicity of this disease in this research was divided to mild, moderate to severe, and severe levels based on pathologic results. 70.7% of all the patients in this research were suffering from chronicity based upon pathologic findings 58.58% of whom were in the mild category. The frequency of interstitial nephritis in this research was 47.47.

Table 1. Correlation between RI and biopsy results in the population studied.

Pathologic diagnosis	Frequency	Average RI \pm SD	P-value
Acute Tubulo-interstitial Nephritis	14	0.04 ± 0.688	
Primary Amyloidosis	4	0.12 ± 0.727	
Focal segmental glomerulo sclerosis (FSGS)	28	0.10 ± 0.72	
IgA nephropathy	8	0.01 ± 0.537	
Lupus nephritis	6	0.04 ± 0.626	<0.01
MGN	25	0.05 ± 0.625	
Pos-tinfectious glomerulonephritis	2	0.07 ± 0.63	
Minimal change disease	10	0.00 ± 0.602	
Secondary amyloidosis	2	0.00 ± 0.67	
total	99	0.09 ± 0.65	

A significant correlation was observed between the age and RI among patients we studied ($P=0.000$). This issue points to the fact that as people grow older, the RI level also increases. In studying the correlation between the level of proteinuria and creatinine with RI, a significant difference was observed between the level of proteinuria and RI in the population we

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studied ($P=0.02$). Meanwhile, Creatinine Serum has a significant correlation with higher levels of RI ($P=0.000$). No significant difference was observed while studying the correlation between gender and RI using T-test methodology in this research ($P=0.12$). Based on T-test analysis, the correlation between interstitial nephritis and RI was studied among the patients but our results found no significant correlation between these 2 results ($P=0.66$). Based on the results of our research, a significant correlation was observed between RI and results of biopsy based on one way anova. The correlation between RI and chronicity was assessed and studied among the patients using one way anova. Accordingly, a significant correlation was observed between RI and Chronicity ($P=0.036$). Concerning the correlation between serum's creatinine and the level of Chronicity, no significant correlation was found ($P\text{-Value}=0.01$) (Table 1).

Discussion

Although the applicability of Doppler Sonography in renal medical diseases is not certain, but this method seems to be quite useful in assessing the various renal pathologic disorders in both transplanted and non-transplanted kidneys. By illustrating the blood flow of kidney, Color Doppler Sonography displays the structural performance of the kidney [8]. One reason that many doctors do not rely on these methods is probably due to great differences observed in sonographic reports issued by sonographers [9]. RI as an index of vein resistance is usually influenced by changes in the vascular system, especially pre-glomerular veins [3]. However, the Parenchymal resistance of kidney can be assessed using RI and it indicates various parenchymal and structural vascular disorders, particularly about vascular interstitial compartment and changes in this part result in certain rise of RI. However, it is not clear yet whether glomerular damages have the same level of influence on RI or not [1].

It is certain that assessing RI helps us estimate the normality or damage caused to the structure of kidney. It also helps us predict the possibility of renal disease progress to a sort of failure [8,10,11]. Various researches have been conducted to study the assessment power of color Doppler sonography in various renal disease. The present research seeks to investigate the correlation between RI and results of biopsy to see if it is possible to delay prognosis of renal disease by studying RI before conducting biopsy. In our research with an age range of 17 to 77 years old for patients who had resorted to Shahid Hasheminejad Hospital in 2012, the average age was around 42.992 years old. The majority of population consisted of male patients (62%). Compared to other researches that have studied the renal disease, these statistical results of ours do not exhibit much difference [1,3,8]. The results of our research with a range of 0.53 to 0.94 and an average of 0.65 ± 0.09 showed the level of RI for the population we studied. No significant difference is observed with regards to these results with previous studies.

For instance, the study conducted by Prabahar et al. published in 2008 that studied the doppler sonography in diagnosing

tubulointerstitial damages among 71 patients suffering from glomerular disorders in a comparison with biopsy reported an average RI level of 0.64 ± 0.08 among patients. In another similar conducted by Galestic et al. [3], the average RI level among patients was 0.68 ± 0.09 . In this research, the average RI among the group of patients was significantly more than control group. A difference of 0.41 between the low and high limit of RI in the group we studied indicates the high difference of RI in various renal disease. All these differences will finally manifest themselves in para-clinical proteinurial findings. This fact also hold true about creatinine and urinary protein in the population we studied. There is no significant difference between these results and other similar results [12,13].

In the statistical analysis of relative frequency of all types of pathologic diagnosis in the population of our research (patients with proteinuria hospitalized in Shahid Hasheminejad Hospital of biopsy in 2012), Membranous glomerulonephritis had the highest percentage and this was quite in line with the results of previous studies [1,3]. No significant difference was observed between occurrence of interstitial damage and RI ($P\text{-value}=0.667$). However, similar studies have pointed to a significant correlation between these 2 factors. For instance, the study conducted by Prabahar et al. [1] published in 2008 that studied doppler sonography in diagnosing tubulointerstitial damages among 71 patients suffering from glomerular disorders and compared it against biopsy reported a significant correlation between rise of RI and interstitial involvement ($P\text{-value}=0.001$). In another research conducted by Galesice et al. on 50 patients suffering from glomerular diseases, RI was significantly more than what was observed in 60 patients of the control group: 0.68 ± 0.09 compared to 0.59 ± 0.03 . These researchers observed a significantly higher level of RI among patients suffering from membranoproliferative nephropathy compared to other Glomerulonephritis (0.81 ± 0.62). These researchers also reported a significant correlation between higher RI and high levels of creatinine serum and clearance creatinine. This is in line with the results of our research.

Other researches such as Patriquin et al. [14], Mostbeck et al. [15], Platt et al. [10] and Brkljacic et al. [16] reported no significant results from findings of Doppler sonography in glomerular findings of kidney and Glomerulonephritis. Although our results also showed no significant correlation between rise of RI in doppler sonography and the level of kidney's interstitial involvement, this correlation cannot be denied with high certainty. It is possible to arrive at more precise radiologic results using a greater sample size. A significant correlation was observed between the level of proteinuria and RI ($P\text{-value}=0.02$). One of the bad prognosis factors in glomerular diseases used to predict the occurrence of ESRD is the higher level of proteinuria. Various researches have pointed to the fact that a proteinuria level above 1 g a day is the most important negative prognostic factor in Glomerulonephritis: Bogneschuetz et al. [17], and Okada et al. [18]. In a research conducted by Bige et al. in France [19], RI was measured in 58 patients suffering from various renal diseases 48 hours before conducting biopsy. The majority of

these patients were suffering from glomerular diseases (82%). As it turned out in this research, high RI was significantly correlated with less renal functioning in future (P-value=0.000015). According to the results of these researches, a significant correlation was observed between the level of RI and the level of proteinuria (P-value=0.04).

However, Galesic et al. observed no significant correlation between the level of proteinuria and the level of RI. We observed a significant correlation between age and level of RI (P-value<0.01). Similar results were also achieved in the study conducted by Bige et al. [19]. According to these researchers, the reason for rise of RI is probably increased prevalence of Arteriosclerosis and fibrosis and intensity of chronicity of disease as the patient grows older. This correlation was not observed in the similar study conducted by Galesic et al. [3] and P-value was not significant. In our research, a significant correlation was also observed between the level of creatinine serum and the RI (P-value<0.01). Similar results were also observed in the study conducted by Bige et al. According to this research, a significant correlation was observed between higher levels of RI and creatinine serum and reduction of GFR during biopsy (P-value=0.05). The same discoveries have also been made in the study of Galesic et al. [3]. These researches have reported a significant correlation between RI and the level of creatinine serum (P-value<0.01). These results are also confirmed in the study conducted by Turkmen et al. [7].

Our results indicated a significant difference between the rise of RI and the results of biopsy in our population (P-value<0.01). This fact indicates the effect of renal structural disorders on the rise of RI in doppler sonography. In a similar research conducted by Galesic et al. [3] on 50 patients suffering from glomerular diseases using Anova, RI's of different groups of glomerular diseases were compared with one another and a significant correlation was observed between them. Other studies such as Patriquim et al. [14] and Mostbeck et al. [15] did not report any significant results from doppler sonography results in glomerular involvements of kidney and Glomerulonephritis. However, studying a more precise research population with various diseases of renal structural diseases is valuable to determine the level of this correlation in diagnosing and determining the type of treatment.

Proteinuria is a major marker of renal diseases. As most renal diseases with glomerular pathology can become chronic and progressive, the main emphasis of the guidelines of National Kidney Foundation is placed on the early diagnosis of proteinuria and early commencement of treatments that play a major role in preserving the performance of kidneys. Diagnosing the type of background disease that result in proteinuria is also an important factor in selecting exclusive treatments and this factor plays a major role in the final prognosis of patients. Biopsy of kidneys needs to be taken into consideration among mature patients with a stable proteinuria. The majority of nephritic syndrome cases among kids caused by Minimal Change are sensitive to Corticosteroid. In such cases, an experimental treatment seems suitable and biopsy is undertaken in the cases that are resistant to treatment.

However, statistical studies among the matured have pointed to the fact that those matured patients who have an isolated proteinuria level below 1 g a day and have no indicator of renal diseases had a good prognosis and the necessity of an exclusive treatment seems improbable. Most nephrologists observed these patients with non-exclusive scales and treat them with non-exclusive treatments and biopsy only takes place in increasing the level of proteinuria or progressive reduction of renal functioning.

On the other hand, different studies conducted on chronic renal diseases have pointed to the major contribution of RI. Some researchers have even introduced an RI of 0.08 or more as an independent factor for bad prognosis and death caused by chronic renal disease. In this research, we studied RI among patients suffering from proteinuria and compared the average RI in different subtypes of disease. As the results indicated, the average level of RI in certain subtypes was more than others. This difference was significant in some cases and this could indicate a less favorable prognosis in these subtypes. Furthermore, a significant correlation was observed between the level of proteinuria and RI. One bad prognosis factor in glomerular diseases which is used to predict the occurrence of ESRD is the higher level of proteinuria. According to different researches, a proteinuria level above 1 g a day is the most important negative prognostic factor in Glomerulonephritis. Our other result was the correlation between RI and patient's age. We can justify it by saying that the possibility of Atherosclerosis and formation of renal parenchymal fibrosis as the patient grows older and the disease gets longer and longer. The results of our research also indicate the correlation between the level of creatinine serum and chronicity found in pathological slides which indicate the effect of chronic diseases on vascularity and parenchyma of kidney and point to rise of vascular resistance and rise of RI. The applied value of these results in clinics can be really important. In following up patients suffering from proteinuria, progress and development in laboratory disorders is an indicator for more invasive treatments. Many patients with pure daily proteinuria less than 1 g a day with no clue of background renal disease are followed without biopsy. In this process of follow-up, investigating the level of RI can be really helpful. High RI or rise of it in following up the patient can act as an indicator to conduct biopsy and also consider a more invasive treatment.

Conclusion

According to the results of our research, as patients grow older and their level of proteinuria and creatinine serum goes up and changes take place in the structure of kidney and veins, significant changes will also be observed in results of Doppler sonography and RI.

Based on the results of our research, we recommend conducting renal RI in following up patients with proteinuria. However, investigating the unnatural cut off for RI among patients with proteinuria requires more researches with a focus on this issue.

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