SONOGRAPHIC GRADING OF RENAL CORTICAL ECHOGENICITY AND RAISED SERUM CREATININE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

BACKGROUND
Chronic Kidney Disease (CKD) is a worldwide public health problem and the world’s 12th commonest cause of mortality and 17th cause of morbidity. The approximate prevalence of CKD in India is 800 with an incidence of about 150-200 per million population. The most common cause of CKD is diabetic nephropathy.

PURPOSE OF STUDY
The purpose was to study various renal sonographic changes in patients with chronic kidney disease and to correlate renal length, parenchymal thickness, cortical thickness and echogenicity of the kidney with serum creatinine levels.

MATERIAL AND METHODS
The study was conducted on hundred patients in the Department of Radiodiagnosis and Imaging, Government Medical College, Amritsar, from August 2013 to October 2015. Patients were subjected to sonographic examination on Philips Envisor C Ultrasound machine/Toshiba ultrasound machine model–SSA 510A/Esato ultrasound machines using curvilinear probe of 3.5 MHz - 5 MHz or linear high frequency probe 7-12 MHz. Ultrasound of kidneys for renal length, parenchymal thickness, cortical thickness and cortical echogenicity was performed. The mean values of both kidneys were calculated from length, parenchymal thickness and cortical echogenicity. These parameters were compared with serum creatinine. Statistical analysis was performed using one-way ANOVA.

RESULTS AND CONCLUSIONS
The grade of renal disease was determined by cortical echogenicity with Grade 1 mild form, Grade 2 moderate and Grade 3 severe form and Grade 4 as end-stage renal disease. The mean serum creatinine was 2.87 mg/dL for Grade 1, 3.27 mg/dL for Grade 2, 4.3 mg/dL for Grade 3 and 5.8 mg/dL for Grade 4. No correlation was observed between renal length, parenchymal thickness and cortical thickness with serum creatinine levels. The grading of renal echogenicity on sonography correlated well with serum creatinine in CKD than any other sonographic parameters with a statistically significant positive correlation (P <0.001).

KEYWORDS
Chronic Kidney Disease, Renal Cortical Echogenicity, Serum Creatinine.
2. To make a decision about a possible renal biopsy in cases where US fails to define the CKD etiology.
3. To obtain renal measurements as a prognostic factor. Such measurements are important since in most cases CKD leads to a common final-stage condition characterized by small kidneys, cortical and parenchymal thinning (indicating atrophy) and hyperechogenicity indicating sclerosis and fibrosis (small, dense, echogenic kidneys); such findings indicate disease irreversibility and poor prognosis.6

The measurement of serum creatinine has been the traditional approach to assessing CKD. eGFR derived from formulas such as the Modification of Diet in Renal Disease (MDRD) equation is superior to serum creatinine alone in the diagnosis of CKD. However, busy clinicians are unlikely to routinely calculate eGFR from serum creatinine for all of their older patients.7

MATERIAL AND METHODS

Hundred patients, clinically diagnosed with chronic kidney disease (GFR <60/mL/min calculated by using Cockcroft-Gault equation, for three months or more) above the age of 18 years, referred to the Department of Radiodiagnosis and Imaging, Government Medical College, Amritsar, from August 2013 to October 2015. The patient was made to lie supine on the examination table.

The ultrasound coupling gel was applied to the abdomen so as to remove air between the abdominal skin and the transducer. Patients were subjected to sonographic examination on Philips Envisor C ultrasound machine/Toshiba ultrasound machine model-SSA. 510A/Esaote ultrasound machines using curvilinear probe of 3.5 MHz - 5 MHz or linear high frequency probe 7-12 MHz. Longitudinal, transverse and oblique views were taken.

The exclusion criteria were the patients on haemodialysis, peritoneal dialysis, renal transplant patients, patients with hepatic diseases diagnosed on ultrasonography and renal tumours (Both Primary and Secondaries).

The detailed history from patients regarding age, duration of diabetes mellitus if diabetic, duration of hypertension if hypertensive, other causes of chronic renal failure and treatment history. The most recent serum creatinine values were noted. After taking the informed consent of the patient for investigation, each patient was subjected to ultrasound of the abdomen for kidneys and liver. Low tissue harmonic imaging was applied to visualize the liver and kidney echogenicities. A manual method of adjusting the gain and Time Gain Compensation (TGC) was used.

Renal lengths were measured as the greatest pole to pole distance in the sagittal plane (Figure 5). Renal parenchymal thickness was measured from the renal hilum to the maximum convex border of the lateral renal margin (Figure 6). Renal cortical thickness was measured over a medullary pyramid, perpendicular to the capsule as the shortest distance from the base of the medullary pyramid to renal capsule (Figure 7). In every case, the mean values of the right and left renal longitudinal size, parenchymal thickness and cortical thickness were calculated.

Renal cortical echogenicity and cortico-medullary differentiation was evaluated. Renal cortical echogenicity was compared and graded with the echogenicity of the liver and renal medulla with Grade 0: Normal echogenicity less than that of the liver with maintained cortico-medullary differentiation.

Grade 1: Echogenicity the same as that of the liver with maintained cortico-medullary differentiation (Figure 8).
Grade 2: Echogenicity greater than that of the liver with maintained cortico-medullary differentiation (Figure 9).
Grade 3: Echogenicity greater than that of the liver with poorly maintained cortico-medullary differentiation (Figure 10). Grade 4: Echogenicity greater than that of the liver with a loss of cortico-medullary differentiation (Figure 11).

The data were entered and stored in a spreadsheet (Excel, Microsoft). Statistical analysis was performed between the ultrasonographic renal parameters and serum creatinine levels with the aid of SPSS statistical software (version 17.0). Analysis was done using one way ANOVA and Pearson’s correlation coefficient.

RESULTS

The age range of the patients was 19-85 yrs. with mean age of the patients was 54.32 years (Table I). There were 58% male cases and 46% were females with male:female ratio of 1.38:1 (Table II). The most common known cause of CKD in these patients was diabetes mellitus seen in 32 cases (32%) followed by hypertension in 18 cases (18%), diabetes and hypertension together in 5% of the cases. In 2% of cases, the cause was HIV associated nephropathy. No provisional cause was made in 43 cases (43%) at the time of scanning (Table III).

The kidneys were small in size in 35% of the cases, the difference in size between right and left kidneys was more than 2 cm in 4% of the cases and the kidneys were enlarged in 3% of the cases. In 62% of cases, the kidneys were of normal size. The average kidney length measured in the present study was 8.69 cm (Range, 6.6-15.45 cm; SD=1.35 cm).

The average parenchymal thickness of 1.7 cm was seen in 75% of the cases, reduced in 18% of the cases and in 7% of the cases the cortico-medullary differentiation was lost. Cortical thickness could not be assessed in 16 patients, as the renal pyramids could not be identified on USG (Table IV). The mean parenchymal thickness obtained in the present study was 1.77 cm (Range 1 - 2.35 cm; SD=0.3 cm). The mean cortical thickness in our study was found to be 0.5 mm (Range 0.2 mm - 1.28 mm; SD = 0.63 mm) (Table IV).

The increased renal cortical echogenicity was reported in all the patients with CKD. Grade 1 increased echogenicity in 35 (35%) cases, Grade 2 in 42 (42%) cases; Grade 3 in 16 (16%) cases and Grade 4 in 7 (7%) cases. Corticomedullary differentiation was maintained in 77% of the cases, poorly maintained in 16% of the cases and it was lost in 7% of the cases (Table V). The mean serum creatinine values were 2.87 mg/dL for Grade 1 echogenicity (Range 1.8 - 5.6 mg/dL; SD=0.81), 3.26 mg/dL for Grade 2 echogenicity (Range 1.6 - 6.1 mg/dL; SD=1.09), 4.3 mg/dL for Grade 3 echogenicity (Range 2.7 - 7.5 mg/dL; SD=1.58) and 5.81 mg/dL for Grade 4 echogenicity (Range 3.6 - 9.5 mg/dL; SD=5.81) (Table VI).

The present study showed a statistically significant correlation between serum creatinine and the grade of echogenicity (p=<0.001). (Table VI, Figure 1). The present
study did not show any statistically significant correlation between serum creatinine values and renal length \( (r=0.096; \ p=0.343) \), parenchymal thickness \( (r=-0.048; \ p=0.649) \) or cortical thickness \( (r=0.059; \ p=0.577) \).

(Table VII, Figures 2, 3, 4). Most common associated findings included renal cysts \( (99\%) \) followed by pleural effusion \( (88\%) \), renal calculi with or without hydronephrosis \( (77\%) \) and ascites \( (55\%) \). (Table VIII).
Table 1: Shows that the most frequent age group of patients with CKD was 51-60 yrs. (33%) followed by 41-50 yrs. (31%) with age group 81-90 years (1%) of the cases. The mean age was 54.32±12.25 years.

<table>
<thead>
<tr>
<th>Age Range (In Years)</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>03</td>
<td>03%</td>
</tr>
<tr>
<td>31-40</td>
<td>08</td>
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<tr>
<td>41-50</td>
<td>31</td>
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<td>51-60</td>
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<td>33%</td>
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<td>61-70</td>
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<td>81-90</td>
<td>01</td>
<td>01%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 1: Age Distribution of Cases with Chronic Kidney Disease

Table 2: Shows that males were more commonly affected by chronic renal disease, 58% cases as compared to females with 42% cases. The male:female ratio was 1.38.

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>58</td>
<td>58%</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>42%</td>
</tr>
</tbody>
</table>

Table 2: Gender Distribution of Cases with Chronic Kidney Disease

Table 3: Shows that in 43% of cases, no underlying cause of CKD was established. The single most common cause of CKD clinically was diabetes alone in 33% cases followed by hypertension alone in 17% cases, 5% cases had co-existing diabetes and hypertension combined and in 2% cases had HIV associated nephropathy.

<table>
<thead>
<tr>
<th>Cause of CKD</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Underlying cause of CKD not established</td>
<td>43</td>
<td>43%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32</td>
<td>32%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>18%</td>
</tr>
<tr>
<td>Diabetes and Hypertension Combined</td>
<td>05</td>
<td>05%</td>
</tr>
<tr>
<td>HIV</td>
<td>02</td>
<td>02%</td>
</tr>
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</table>

Table 3: Provisional Clinical Causes of Chronic Kidney Disease

Table 4: Shows that there was a significant difference in size of right and left kidneys in 96% cases and only 4% cases showed difference in size >2 cm. Bilateral renal size was reduced in 35% cases, enlarged in 3% cases with normal sized kidneys in 53% cases. The average parenchymal thickness was 75% of the cases, which was normal while it was reduced in 18% of the cases. However, in 7% cases it could not be assessed as the cortico-medullary differentiation was lost. Cortical thickness was reduced in 84% patients and in 16% cases could not be assessed as the renal pyramids could not be identified on sonography.

<table>
<thead>
<tr>
<th>Sonography Renal Findings</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Size Difference (Right vs. Left)</td>
<td>Not Significant (&lt;2 cm)</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Significant (&gt;2 cm)</td>
<td>04</td>
</tr>
<tr>
<td>Average Renal Length (8.69 cm)</td>
<td>Enlarged (&gt;12 cm)</td>
<td>03</td>
</tr>
<tr>
<td></td>
<td>Normal (8-12 cm)</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Small (&lt;8 cm)</td>
<td>35</td>
</tr>
</tbody>
</table>
Table 4: USG Findings of Renal Size Parameters with Chronic Kidney Disease

Table 5: Shows that 35 cases had Grade 1 increased echogenicity (35%), 42 cases had Grade 2 increased echogenicity (42%), 16 cases had Grade 3 increased echogenicity (16%) and 7 cases had Grade 4 increased echogenicity (7%). (In case of difference in the echogenicity, higher grade of the kidney was taken into account). Corticomedullary differentiation was maintained in 77% of the cases, poorly maintained in 16% of the cases and it was lost with 7% of the cases.

Table 6: Shows that the mean serum creatinine values in the present study were 2.87 mg/dL for Grade 1 echogenicity (range 1.8-5.6 mg/dL; SD=0.81), 3.26 mg/dL for Grade 2 echogenicity (range 1.6-6.1 mg/dL; SD=1.09), 4.3 mg/dL for Grade 3 echogenicity (range 2.7-7.5 mg/dL; SD=1.58) and 5.81 mg/dL for Grade 4 echogenicity (range, 3.6-9.5 mg/dL; SD=2.11). A statistically significant correlation between serum creatinine and the grade of echogenicity (p<0.001) was observed.

Table 7: Associated Findings on Ultrasound with Chronic Kidney Disease (N=100)

Table 8: Associated Findings on Ultrasound with Chronic Kidney Disease (N=100)
DISCUSSION
The burden of CRF has increased exponentially and is consuming the resources of both developed and developing economies and efforts to reduce the cost of managing this dreadful disease are always welcomed. This study was geared towards looking for a simpler method of determining the functional capacity of the kidneys in CKD and eliminating (If possible) the need for double determination of GFR using serum biochemistry, particularly in resource-poor settings. The ultrasound machine is quite cheaply and widely available and provides real-time information on the renal measurements and echogenicity particularly in resource poor settings.

Renal length is measured as the longest diameter obtained on a posterior oblique image with a lower limit of normality generally indicated as 9 cm. According to Fiorini and Barozzi, renal length under 8 cm is definitely reduced and should be attributed to chronic renal failure, whereas a length between 8 and 9 cm should always be correlated to the patient’s phenotype, particularly the height. Hence, a lower limit of 8 cm was selected for the present study. According to O’Neill, the useful upper limit of the normal range for kidney length is said to be 12 cm. Also, a threshold of 2 cm is considered reasonable for diagnosing pathological size discrepancy between the two kidneys. Kidneys measuring more than 12 cm in length were considered enlarged in the present study.

Kidney length was affected in 39% of the patients – the kidneys were small in size in 35% of the cases and the kidneys were enlarged in 3% of the cases. In the remaining 62% of cases, the kidneys were of normal size. The pathological discrepancy in size (>2 cm) was seen in 4% of the cases in the present study. Of the 3 cases having enlarged kidney sizes, 2 cases were diabetic and 1 case had Adult Polycystic Kidney Disease (APKD), thus explaining the enlarged kidney sizes in CKD, as nephromegaly is common in both DM and APKD.

Of the 4 cases having size discrepancies 1 case had unilateral hydronephrosis, 1 case was hypertensive with unilateral small kidney with the clinical suspicion of renal artery stenosis, 1 case had clinical suspicion and sonographic features of pyelonephritis in a diabetic and the remaining case had adult polycystic kidney disease having irregular enlargement of the two kidneys due to numerous cysts, thus explaining the difference in the sizes. In the study conducted by Moccia et al, the kidney size was affected in 57% of the cases having chronic renal disease, of which 7 cases had size discrepancy. The mean renal length measured in the present study was 8.69 cm (Range 6.6 - 15.45 cm; SD=1.35 cm). This correlated well with the findings of Yamashita et al, in which the average renal length was 9.5 cm in CKD patients (Range 6.99 – 13 cm; SD = 1.25 cm).

Normal parenchymal thickness ranges from 1.5 - 2 cm. The mean parenchymal thickness obtained in the present study was 1.77 cm (Range 1 - 2.35 cms; SD=0.3 cm). The average parenchymal thickness was normal in 75% of the cases. In 18% of the cases it was reduced and in 7% of the cases it could not be assessed as the cortico-medullary differentiation was lost. These findings correlated well with those of Moghaz et al who found the mean parenchymal thickness to be 1.71 cm (Range, 0.7 - 3.3 cm).

There is no established normal range of cortical thickness. A normal range of 8 to 11.5 mm was reported in a small study of transplant donors by Raj et al. However, El-Reshaid et al stated that cortical thickness values up to 6 mm are also considered to be normal. The mean cortical thickness in our study was found to be 8.5 mm (Range 5.2 mm - 12.8 mm; SD=1.63 mm). Cortical thickness could not be assessed in 16 patients as the renal pyramids could not be identified on USG. The findings were closely consistent with those of Yamashita et al who found the mean cortical thickness to be 7.1 mm in their cases. Beland et al reported a mean cortical thickness of 5.9 mm in CKD patients in their study.

Raised renal cortical echogenicity was reported in all the patients with CKD in this present study. Only 4 cases had difference in the echogenicities of the two kidneys, remaining 96 cases had similar echogenicity changes in both the kidneys suggesting that echogenicity changes occur in CKD patients bilaterally and symmetrically. Paivansalo et al also reported that an echogenic cortex was the most common abnormality detected. In the present study, echogenicity was further graded according to the classification proposed by Siddappa et al. 35 cases had Grade 1 echogenicity (35%), 42 cases had Grade 2 echogenicity (42%), 16 cases had Grade 3 echogenicity (16%) and 7 cases had Grade 4 echogenicity (7%). Thus, Grade 2 echogenicity had maximum number of cases. These findings were slightly different from those of Siddappa et al, who found Grade 1 echogenicity to be the largest group with 48.3% of the cases in it. Also, in the present study, cortico-medullary differentiation was maintained in 77% of the cases, poorly maintained in 16% of the cases and it was lost in 7% of the cases. This finding closely correlated well with those of Siddappa et al, who had 83.3% of cases with maintained cortico-medullary differentiation, 11.7% with poorly maintained cortico-medullary differentiation and in 5% of the cases the cortico-medullary differentiation was lost.

The mean serum creatinine values in the present study were 2.87 mg/dL for Grade 1 echogenicity (Range 1.8 - 5.6 mg/dL; SD=0.81), 3.26 mg/dL for Grade 2 echogenicity (Range 1.6 - 6.1 mg/dL; SD=1.09), 4.3 mg/dL for Grade 3 echogenicity (Range 2.7 - 7.5 mg/dL; SD=1.58) and 5.81 mg/dL for Grade 4 echogenicity (Range 3.6 - 9.5 mg/dL; SD=2.11). The present study showed a statistically significant correlation between serum creatinine and the grade of echogenicity (p<0.001). This finding was consistent with the findings of Siddappa et al who also noted a statistically significant correlation between these two parameters (p=0.004). Iliniaye et al had a similar finding (r=0.9).

This correlation can be explained by the research findings of Rosenfield and Siegel, who documented that the echogenicity of the kidneys had a good correlation with the severity of the interstitial disease on biopsy. Focal interstitial changes tend to produce a minimal increase in cortical echogenicity, while diffuse scarring produces a greater increase in echogenicity. Moghaz et al also supported this finding by stating that renal echogenicity had the strongest correlation with histological parameters (Glomerular Sclerosis, Tubular Atrophy, Interstitial Fibrosis and Interstitial Inflammation). Hricak et al showed a statistically significant positive correlation between cortical echogenicity and the severity of global sclerosis, focal tubular atrophy, the
number of hyaline casts per glomerulus and focal leucocytic infiltration.22

Renal length has traditionally been considered a surrogate marker of renal function.8 In the present study; the renal length did not show statistically significant correlation with the serum creatinine values (r=0.096; p=0.343). In this context, our finding was consistent with those of Mocci et al, who also did not find any significant correlation between renal length and serum creatinine levels.13 This finding is further supported by the research of Van Den Noortgate et al who confirmed that renal length has a low specificity in predicting renal impairment. In clinical practice, serum creatinine and calculated creatinine clearance is most useful in predicting renal impairment. They also mentioned that a normal renal length in the elderly, however, can help exclude renal impairment.23 Our study contradicted this finding, as we did have elderly patients with normal renal length having impaired renal functions.

In the present study, the parenchymal thickness did not show statistically significant correlation with the serum creatinine values (r=0.048; p=0.649). This finding was consistent with those of Yamashita et al, who found that parenchymal thickness had non-significant correlation with the renal function impairment. They also stated that the measurement of the thickness of the renal parenchyma, which is still widely used in the clinical practice to infer some chronic nephropathies should be discouraged, since it showed no statistical correlation with renal function impairment and therefore it is useless in this context.6 Our present study further confirmed this finding.

In the present study, the cortical thickness did not show statistically significant correlation with the serum creatinine values (r=0.059; p=0.577). In this context, our finding was consistent with those of Siddappa et al who did not find a statistically significant correlation between cortical thickness and serum creatinine levels and reported a p value of 0.656 for these two parameters.19

In this context, our finding contradicted those of Beland et al20 and Yamashita et al16 who reported that cortical thickness had statistically significant correlation with renal function impairment. Moghazy et al had also shown that cortical thickness had no significant correlation with the histological parameters like glomerular sclerosis, tubular atrophy, interstitial fibrosis and interstitial inflammation.15

The statistically insignificant correlations of renal measurements with serum creatinine levels in the present study can also be related by the facts that kidney length varies with body height in both adults and children.10 The renal length has also been showed to vary with weight and BMI of the person.10 Although ischaemic nephropathy causes cortical thinning, renal hypertrophy in diabetic nephropathy affects all components, so that the kidney maintains its shape and architecture in the early phase. Due to the incipient nephromegaly, the diabetic kidney often looks bigger and ‘Better’ than the kidney with the same level of chronic, irreversible renal failure caused by other chronic diseases such as other glomerular diseases, hypertensive nephropathy or tubulointerstitial diseases.

Consequently, in the case of diabetic nephropathy, it is often difficult to predict the irreversibility of renal failure solely on the basis of renal length or thickness of the parenchyma. Even in the phase of end-stage renal disease, the diabetic kidney can retain the size of a normal kidney.11 In the present study, ultrasound was able to diagnose the cause of chronic renal impairment due to renal calculi or polycystic kidney disease with certainty in all the 8 cases that were studied. In this context our study supports the findings of Mocci et al, stated that the exclusion of obstructive uropathy or polycystic disease as the cause of renal failure had been always possible with USG. An ultrasound is usually performed in renal failure to exclude the obstructive uropathy.13

This study had a few limitations. Serum creatinine levels were used as a marker of renal function in the present study. Serum creatinine concentration is widely interpreted as a measure of the Glomerular Filtration Rate (GFR) and is used as an index of renal function in clinical practice.24 It is the most widely used index of renal function.23 However, estimates of GFR measured by either CG or MDRD equations are the best overall indices of the level of kidney function.25 More studies relating these ultrasonographic parameters to the estimates of GFR should be welcomed. Also, since ultrasonography is an operator dependent modality, measurements like cortical thickness has been shown to have inter-observer and intra-observer variations with poor reproducibility when comparing repeated measurements.

Despite its limitations, the present study has shown a good correlation of renal cortical echogenicity with serum creatinine levels. The renal cortical echogenicity has its advantages of being irreversible compared to serum creatinine levels, which improve with renal replacement therapies like haemodialysis and peritoneal dialysis.24 Also, quantification of echogenicity of the renal cortex relative to that of the liver has been shown to be reproducible with only little variability between different scanners and probes in previous studies.26

REFERENCES