

# Comparison of Turkish Primary, Recurrent, and Non Stone-Forming Patients Using Hounsfield Unit Measurements: How Useful Is It?

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## Key Words

Hounsfield unit • Renal papillae • Urolithiasis

## Abstract

**Introduction:** To investigate renal papillae attenuation value differences between controls and stone-forming (SF) patients and to evaluate the impact of mean Hounsfield unit (HU) measurements on the predictivity of stone development. **Materials and Methods:** We compared papillae attenuation values in SF groups and a healthy stone-free control group. Metabolic evaluations were carried out on 88 primary and 98 recurrent SF patients, and 94 age-matched control patients were included. The papillae tip attenuation was measured using non-enhanced computed tomography scans in HU for an area with a mean size of 0.2 cm<sup>2</sup>. Inclusion criteria to the study were known stone composition (CaOx), unilaterality, and radiological examinations done in our center. **Results:** In this study, 186 patients who met the criteria and 94 age-matched control patients were divided into 3 groups: the primary SF (Group 1), the recurrent SF group (Group 2), and the control group (Group 3). Metabolic variables which were compared between primary and recurrent SF did not show any significant difference, except urinary volume and phosphorus. The median (interquartile range) value of papillae HU density for the control group was 26.23 (3.84), for primary SF group it was 26.50 (11.25), and for recurrent SF group it was 29 (13). A significant difference

in papilla HU levels for each group was found ( $p = 0.008$ ). **Conclusion:** This study implied that HU values reflect the severity of the stone disease, although they could not discriminate controls from primary stone formers whose stone forming risk is lower compared to recurrent stone formers.

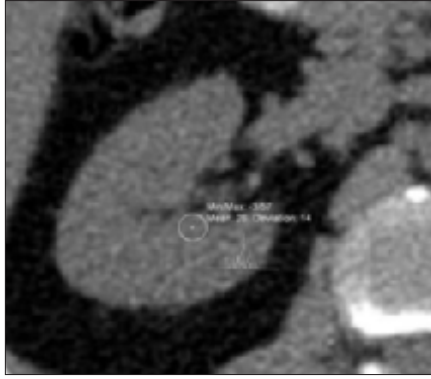
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## Introduction

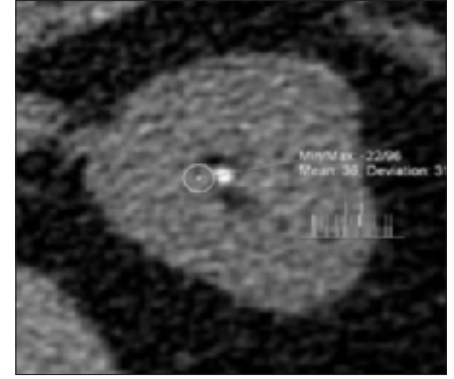
Eisner et al. [7] in 2008 indicated that renal papillae in stone-forming (SF) patients are more radiodense in comparison with non-SF patients in unenhanced computerized tomography (CT) evaluations.

This relationship between the “hyper-density” of the renal papillae as analyzed by unenhanced CT and the formation of calcium stones was subsequently reported by a few studies comparing SF patients with healthy (non-SF) patients [8–14]. Also, in some more recent retrospective studies, in view of the fact that there is a relationship between renal papilla Hounsfield unit (HU) values and recurrent stone formation, it was argued that new stone formation in patients with stones can be detected and followed-up using HU measurements [14–16].

In light of this information, the aim of our study was: 1. to analyze the relationship between renal stone formation with HU and recurrent stone formation, 2. to eval-



**Fig. 1.** Measuring density of papillae that have no stone in the kidney. Mean density was 26 HU.



**Fig. 2.** Measuring density of papillae that have a renal stone in the kidney. Mean density was 36 HU.

uate the usability of HU measurements as a stone predictor, and 3. to compare the HU values of primary and recurrent SF patients with plasma and urine metabolites which are thought to have an effect on stone formation mechanisms.

## Materials and Methods

### *Subjects and Data Collection*

Between January 2013 and January 2016 all the data of patients at our hospital who complained of renal colic or who were receiving treatment for kidney stones were collected. This study included 3 groups: Group 1 – the primary SF group, Group 2 – the recurrent SF group, and Group 3 – the control group. A total of 88 primary and 98 recurrent SF patients with unilateral stones whose metabolic evaluation had been carried out and 94 age-matched control participants, who underwent pre-transplant evaluation as potential living kidney donors in the last 10 years, were included to the study. Serum creatinine, calcium, uric acid, parathormone, 25(OH)-vitamin D; 24-hour urine volume, sodium, potassium, calcium, phosphorus, magnesium, oxalate, citrate, and biochemical stone analyzes were used as laboratory measurements for the evaluation in primary and recurrent SF patients.

Inclusion criteria for the study were: known stone composition (CaOx stones), unilaterality, and radiological examination done in our radiological department. Biochemical examination of the stone composition was done by infrared spectrometry and polarizing microscopy in another center. Additionally, solitary kidney, ureteral calculi, renal hypoplasia, kidney cyst, staghorn stone, stone found in more than 1 calyx, renal anomaly, and urinary system tumor existence were reasons for exclusion from the study.

### *CT Scanning*

All patients underwent unenhanced CT examination with the same device (Philips Brilliance 40-detector row, Philips Medical

Systems Eindhoven, The Netherlands) in our hospital, with slices of 0.7 mm and reconstructions of 3 mm being included in the study. No oral or intravenous contrast was administered. Patients were placed in the supine position with a full urinary bladder and the scan length stretched from the diaphragm to the pubic symphysis.

### *Image Analysis*

The CT images were retrospectively reviewed by 1 radiologist experienced in abdominal imaging. The analysis was done on the Picture Archiving and Communication System (PACS version 4.0, Agfa, Richmond, VA). The renal papillary HU density was measured by placing region of interests (mean size 0.2 cm<sup>2</sup>) in the region of renal papilla and the attenuation measurements were recorded (fig. 1, 2). The images were magnified 5× to prevent contamination of the region of interest with fat in the renal sinus. The densities of one upper, middle, and lower pole renal papillae were separately measured in both kidneys including the papillae in the region of calculi in patients with nephrolithiasis. The attenuation value of the stone bearing calyx in SF, and the attenuation value of the calyx with the highest measurement in control participants were taken into account. Coronal reformatted images were used for better definition of the papillary anatomy and the density measurements were obtained on axial and/or coronal images.

### *Definitions of Urinary Metabolic Abnormalities in SF Patients*

Hypercalciuria was defined as urine calcium excretion > 300 mg/d. Hyperoxaluria was defined as urinary oxalate excretion > 45 mg/d. Hyperphosphaturia was defined as urinary phosphorus excretion > 1,300 mg/d. Hypocitraturia was defined as urinary citrate excretion < 300 mg/d.

### *Statistical Analysis*

Statistical analyses were performed using R Statistical Software (www.r-project.org), a free software environment for statistical computing and graphics [17]. All data are presented as median and interquartile range (IQR), minimum, and maximum values.

Continuous variables were compared using the Mann-Whitney U test for primary versus recurrent groups and the Kruskal-Wallis

**Table 1.** Patients characteristics and Mann Whitney U test results

|              | Primary (n = 88) |            | Recurrent (n = 98) |             | p      |
|--------------|------------------|------------|--------------------|-------------|--------|
|              | Median (IQR)     | Range      | Median (IQR)       | Range       |        |
| Age, years   | 34 (10)          | 21–60      | 37 (12)            | 21–67       | 0.278  |
| Papillae HU  | 26.5 (11.25)     | 12–56      | 29 (13)            | 12–60       | 0.025* |
| Plasma       |                  |            |                    |             |        |
| Calcium      | 9.5 (0.953)      | 8.38–11.20 | 9.75 (1.143)       | 8.60–12.12  | 0.099  |
| Creatinine   | 0.895 (0.345)    | 0.30–2.07  | 0.900 (0.345)      | 0.48–2.20   | 0.913  |
| Parathormone | 40.4 (14.03)     | 17–166     | 43.05 (16.10)      | 20.30–156.7 | 0.152  |
| Vitamin D    | 23 (16)          | 5–56       | 23.5 (21)          | 7.05–160    | 0.590  |
| Urinary      |                  |            |                    |             |        |
| Volume       | 1,810 (770)      | 680–4,700  | 1,565 (835)        | 205–4,500   | 0.044* |
| Calcium      | 0.24 (0.293)     | 0.10–1.10  | 0.25 (0.14)        | 0.10–0.90   | 0.712  |
| Oxalate      | 24.9 (16)        | 0.34–76    | 25.2 (17)          | 9–54        | 0.7901 |
| Citrate      | 347.5 (309)      | 151–1,325  | 356.5 (282)        | 136–1,693   | 0.285  |
| Sodium       | 135 (28.98)      | 115–220    | 145.5 (43.85)      | 105–230     | 0.205  |
| Potassium    | 36.75 (14.85)    | 22–62      | 37 (12)            | 17–65       | 0.55   |
| Magnesium    | 1(0.7)           | 0.09–2.20  | 1 (0.5)            | 0.05–2.10   | 0.257  |
| Phosphate    | 0.825 (0.330)    | 0.16–2     | 0.98 (0.363)       | 0.3–2       | 0.011* |
| Phosphorus   | 6 (1.93)         | 3.70–8     | 6 (1.93)           | 4–9.90      | 0.082  |

\*p &lt; 0.05.

test for primary, recurrent, and control groups as the data did not follow a normal distribution. The significant difference was then followed by a post-hoc test [18].

Youden's index, which is the maximum of (sensitivity + specificity – 1) was used as an optimization criterion for cut-off values [19]. All tests were two tailed, and the significance was set at 5%.

## Results

The 186 SF patients who met the criteria and 94 age-matched control participants were divided into 3 groups: the primary SF (Group 1), the recurrent SF group (Group 2), and the control group (Group 3). Metabolic variables, which were compared between primary and recurrent SF did not show any significant difference, except for urinary volume and phosphorus (table 1). The median, IQR, minimum, and maximum values for each variable within each group (primary or recurrent) were determined. The 2 groups were compared with the Mann-Whitney U test and the corresponding p values are also shown in table 1. Median and IQR value of the papillae HU density for the control group was 26.23 (3.84), for the primary SF group it was 26.50 (11.25), and for the recurrent SF group it was 29 [13]. A significant difference in papillae HU levels for each group was found (p = 0.008) (table 2).

The Kruskal-Wallis test was significant and thus it was followed by a post-hoc test. Cohen's f effect size for the Kruskal-Wallis test was calculated as 0.198 which

refers to a medium effect size [20]. Pairwise comparisons from the post-hoc test showed that there was a significant difference between the HU values of the control versus the recurrent SF group and the primary SF versus the recurrent SF group (table 3). The pairwise effect sizes were 0.024, 0.232, and 0.165 for the control versus the primary, the control versus the recurrent, and the primary versus the recurrent group, respectively [21]. The effect size of the control versus the primary group was small and thus was not interpreted. There is a 23.2% chance that the number of papillae HU in the recurrent group will be greater than that in the control group. There is a 16.5% chance that the number of papillae HU of the recurrent group will be greater than that in the primary group. In addition, association between urinary parameters and HU values of renal papillae were investigated. The Spearman rank correlation ( $\rho$ ) and the associated p-value between HU and volume are in table 4. The associations were not significant.

A receiver operating characteristic (ROC) curve was constructed to see how predictive papillae HU were for kidney stone formation, which is given in figure 3. The area under the curve (AUC) was 0.596. The cut-off point for papillae HU density was about 30 units to pass from the primary to the recurrent stage. If papilla HU density is about or over 30 units, a high risk for kidney stone recurrence in primary SF could be suspected. At this optimal cut-off point, the positive predictive value (PPV) was

**Table 2.** Amount of papillae HU for each group

| Group     | n  | Median | IQR (Q1–Q3)        | Range       | p      | $\chi^2$ | $\eta^2$ | f     |
|-----------|----|--------|--------------------|-------------|--------|----------|----------|-------|
| Control   | 94 | 26.32  | 3.84 (24.28–28.12) | 21.26–32.56 | 0.008* | 9.7      | 0.038    | 0.198 |
| Primary   | 88 | 26.50  | 11.25 (21.75–33)   | 12–56       |        |          |          |       |
| Recurrent | 98 | 29.00  | 13.00 (24–37)      | 12–60       |        |          |          |       |

Q1 = 1<sup>st</sup> quartile; Q3 = 3<sup>rd</sup> quartile;  $\chi^2$ : Kruskal Wallis test statistic;  $\eta^2$ : Etasquared effect size; f: Cohen's f effect size.

**Table 3.** Pairwise comparisons of amount of papillae HU for each group

| Groups                | Observed difference | Critical difference | Significance | r     |
|-----------------------|---------------------|---------------------|--------------|-------|
| Control vs. primary   | 6.175               | 28.388              | false        | 0.024 |
| Control vs. recurrent | 32.775              | 27.729              | true         | 0.232 |
| Primary vs. recurrent | 26.600              | 26.236              | true         | 0.165 |

r: Effect size [21].

**Table 4.** Spearman rank correlations between urinary parameters and HU value of renal papillae

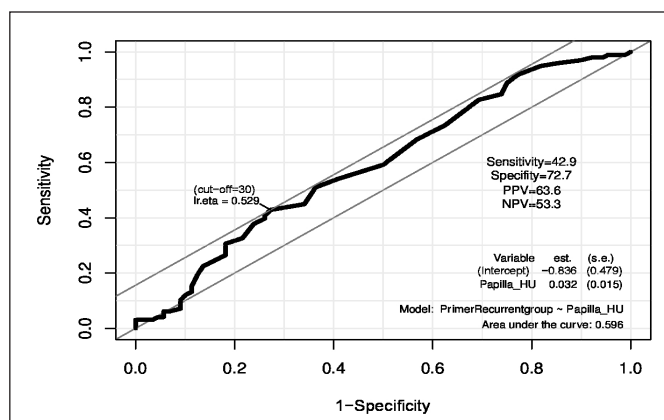
| Urinary parameters | Correlation | p     |
|--------------------|-------------|-------|
| Volume             | 0.072       | 0.334 |
| Calcium            | 0.113       | 0.128 |
| Oxalate            | 0.039       | 0.603 |
| Citrate            | -0.022      | 0.766 |
| Sodium             | -0.044      | 0.553 |
| Magnesium          | 0.004       | 0.953 |
| Phosphate          | -0.113      | 0.127 |
| Phosphorus         | 0.024       | 0.747 |

63.6%, the negative predictive value (NPV) was 53.3%, the sensitivity was 42.9%, and the specificity was 72.7% (fig. 3).

### Discussion

By comparing density differences obtained by renal papillae attenuation measurements with commonly used CT in the diagnosis and follow-up of urinary system stone diseases, an idea which was suggested as Randall's plaques, that could be detected noninvasively, widespread, and more easily, was raised. This hypothesis, suggested for the first time by Eisner et al. [7] in 2008, was evaluated with a retrospectively regulated study which considered renal papillae measurements in 17 SF patients and 15 control participants (non-SF). According to this study, HU values in the SF group were found to be significantly higher. This result was verified with a limited number of studies and should be more generally supported.

Cakiroglu et al.'s [8] retrospective study, which was grouped and analyzed equivalent to our study, while a comparison between control and primary SF patients showed no significant difference, a statistically significant

**Fig. 3.** ROC curve of papillae HU to discriminate between primary and recurrent kidney stone formation.

difference was obtained between primary and recurrent SF patients. But in contrast to our study, when control participants were compared with all SF patients (primary and recurrent SF together), a statistically significant result was obtained.

In the study of Bhuskute et al. [11] published in 2009, ROC analysis was done in addition to papillae attenuation values. The cut-off value was 34 and AUC was 0.94 with levels of 90% for sensitivity, 90% for PPV, and 99% for NPV. When the ROC curve was used in another study with a wider series, the cut-off value was 40 and the AUC was 0.9 while PPV, NPV, sensitivity, and specificity values were 90, 93, 91, and 92%, respectively.

However, in the present study, no significant difference in terms of HU values between the control and primary SF patients was found. ROC analysis was done on primary and recurrent SF patients where the cut-off value was 30, the AUC was 0.596, and PPV, NPV, sensitivity, and specificity values were 63.6, 53.3, 42.9, and 72.7%, respectively. According to this, unlike the other studies it was found that the HU value was not determinative for primary stone formation risk. Instead it was found that it could be significant for the follow-up of stone recurrence in SF patients.

Another important difference, which was a subject of the majority of these previously published studies, was that HU values were significantly higher in all groups (control and SF patients) in contrast to ours [7, 9, 11, 13, 15, 16]. In terms of eliminating this differentiation between the stated attenuation values and presenting a common opinion, it is essential to provide standardization of inclusion criteria and HU measurement techniques and take into account other parameters such as family history, body mass index, and systemic medical history which are considered to be risks for stone formation. Also our study's purpose was to analyze the relationship between HU measurements and plasma and urine metabolites which are considered to have an effect on stone formation mechanisms. When urine calcium, oxalate, and citrate values were examined, 68 hypercalciuric, 14 hyperoxaluric, and 57 hypocitraturic patients' measured papillae HU values were found to be not significantly different from the other patients. As far as we know, there was only one previous study where the metabolic parameters were evaluated together.

In the prospective study organized by Shavit et al. [14], 111 control and recurrent SF patients were compared. HU values comparison among the groups showed a significant elevation in the recurrent SF group which was also the case in our study. As an important parameter, papillae attenuation data between hypercalciuric and normocalciuric patients were compared and it was determined that there was no significant difference. According to these findings, radiological density evaluation was reported to be more correlated than the metabolic

measurements in clinically significant stone formation. Although it had disadvantages of unknown stone composition, limited number of patients, and inclusion of only 1 group (recurrent SF) as a base, the findings of this study in general were supported by ours.

Another issue that attracted our attention when we compared the studies, was that the mean HU values of our control patients were higher, despite that the mean HU values of our recurrent SF patients were significantly lower. These differences were considered as addressing again the importance of patient and measurement standardization, mentioned before, in terms of the reliability of the data to be obtained. In addition to these, when the 2 SF groups of our study were compared, it was determined that in terms of stone formation risk, except for the elevation in the mean papillae HU value, urine volume in the recurrent SF group was statistically and significantly lower and the phosphorus amount was higher. This contributions to the importance and necessity of the hydration increase which is a part of the treatment and is suggested in order to avoid new stone formation, especially for primary SF patients.

Finally, our study had some limitations. Family history, systemic diseases such as diabetes mellitus, hypertension, or diseases that can lead to vascular calcification and thus can lead to differences in density measurements were not taken into account. Also, as a metabolic evaluation was not been done on the control patients, this may constitute some limitations in terms of the results obtained, when a comparison is done between the groups.

## Conclusion

This study implied that HU values could reflect the risk or severity of stone disease recurrence, but in contrast to earlier studies, it was not useful in the prediction of first time stone development. In order to designate the advantage of these measurements, included patient groups (primary SF and recurrent SF), profiles (stone composition, systemic medical history, metabolic values), and standardization of measurement techniques have to be more strictly taken into account in later studies.

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