Renal Replacement Therapy

REVIEW Open Access

Prevalence of inherited changes of uric acid levels in kidney dysfunction including stage 5 D and T: a systematic review

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Abstract

Background/aims: Familial juvenile hereditary nephropathy (FJHN) is characterized by hyperuricemia due to severely impaired urinary excretion of urate. Hereditary renal hypouricemia is an inborn error of membrane transport. Because studies of inherited tubulopathy is rare, prevalence and diagnosis of these inherited tubulopathy increase with genetic testing.The aim of this study is to investigate prevalence of clinical features, biochemical profiles, and genetic analysis of patients with changes in serum uric acid levels in inherited tubulopathy.

Main body: The paper has written based on searching PubMed and Google Scholar to identify potentially relevant articles or abstracts. In this retrospective study, a total 65 patients with changes of serum uric acid levels and kidney dysfunction were investigated. Clinical features, laboratory data at initial presentation, management, and outcomes were collected. Forty studies (65 participants) included in this review. The mean ± SD of age of study patients in inherited tubulointerstitial kidney disease was 25.29 ± 14.69 years. Mean ± SD age of patients at time of diagnosis in inherited renal hypouricemia was 18.83 ± 10.59 years. Correlation between exon region in mutated UMOD, SLC22A12, and SLC2A9 genes and serum uric acid levels were assessed and revealed significant statistical correlation between exon region of SLC2A9 mutation and serum uric acid levels. Prevalence of progression to end-stage kidney disease in patients with inherited tubulointerstitial kidney disease and inherited renal hypouricemia were assessed 20% and 2.5%, respectively. There was nephrolithiasis in two patients (2/25, 8%) with inherited renal hypouricemia.

Conclusions: This study shows that UMOD and SLC22A12 gene mutations were responsible for majority of autosomal-dominant tubulointerstitial kidney disease and inherited renal hypouricemia, respectively.

Keywords: Inherited tubulointerstitial kidney disease, Inherited renal hypouricemia, Uric acid, FEUA, Genetic analysis

Introduction

Description of states

Uric acid is the end product of purine metabolism in human, higher primates, and only a small number of other species. Uric acid behaves as a weak acid (pKa1 5.75) and occurs predominantly (98%) as urate anion at physiological pH, although more is in the uric acid form in urine at pH ~ 5–6 which affects its solubility and transport [1]. Recent studies disclosed the strong association between hyperuricemia and metabolic syndrome (MS), obesity, hypertension (HTN), type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, hypertriglyceridemia, acute kidney injury, chronic kidney disease (CKD), coronary heart disease, heart failure, and high mortality among cardiac and CKD patients. The association between uric acid and nephrolithiasis or pre-eclampsia is a non-debatable association [2]. There is a strong overlap across genes implicated in monogenic uricemic traits and gout in a range of genes in addition to those coding for uric acid transporters. While genome-wide association studies (GWAS) have been pivotal in the identification of loci associated with serum uric acid (sUA) levels and gout risk, such studies do not provide a direct link to causal genes. There are obvious and highly likely causal genes for some loci, while the causal gene is far from clear at other loci and so GWAS

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findings should be interpreted with this in mind. In addition, genetics is a likely contributor to the well-documented observation that certain ethnic groups have a higher risk than others for hyperuricemia and gout [3]. Consideration to this point that genotype precedes life events and is not affected by lifestyle, so role of genetic factors in changes of serum uric acid levels are needed.

Inherited tubulointerstitial kidney disease

Autosomal-dominant tubulointerstitial kidney disease (ADTKT) is a rare genetic kidney disease. ADTKD caused by mutations in the UMOD gene (ADTKD-UMOD) is the most common form of ADTKD. Other gene mutations causing ADTKD include mucin 1 (MUC1), hepatocyte nuclear factor 1 beta (HNF1b), renin (REN), and the alpha subunit of the endoplasmic reticular membrane transcolon (SEC61A1). Previously known as familial juvenile hyperuricemic nephropathy (FJHN) and uromodulin-associated kidney disease (UAKD), ADTKD-UMOD is characterized by early onset hyperuricemia and gout affecting both sexes, and the development of insidious renal failure with tubulointerstitial disease. These disorders characteristically do not have features of hematuria or proteinuria and some patients are found to have medullary renal cysts [4].

Idiopathic or inherited renal hypouricemia (iRHUC)

Hypouricemia is reported to occur in 0.8% of hospitalized patients and 0.2% of the general population. However, it is possible that the prevalence of hypouricemia is actually higher but undiagnosed. Hypouricemia can be associated with decreased fractional excretion of uric acid and increased xanthine excretion (e.g., hereditary xanthinuria caused by an autosomal recessive deficiency of xanthine dehydrogenase (XDH)). Extremely low hypouricemia can be due to XDH. More typically, hypouricemia is associated with high fractional excretion of uric acid due to genetic causes, including mutations in genes such as solute carrier protein 22 family, member 12 [SLC22A12 (URAT1)], and solute carrier family 2, member 9 [SLC2A9 (GLUT9)].

Dysuricemia

Normal serum uric acid levels

Normal serum urate concentrations are 3.5–7.2 mg/dl (210–430 μmol/l) in males and 2.6–6 mg/dl (155–360 μmol/l) in children and premenopausal females, respectively.

Hyperuricemia

FJHN is an autosomal-dominant condition characterized by a hypoexcretion of urate leading to hyperuricemia, gout, and renal disease. Type one (FJHN1) is associated with heterozygous mutations in the uromodulin (UMOD) gene on chromosome 16p12.3. Type two (FJHN2) is associated with mutations in the renin gene (REN) on chromosome 1q32 and type three (FJHN3) has been mapped to 2p22.1-21. An atypical variant of FJHN, associated with diabetes and renal cysts, has been linked to mutations in HNF-1β on chromosome 17q12. Hyperuricemia has been arbitrarily defined as > 7 mg/dl in men and > 6.5 mg/dl in women in normal renal function [5]. Other references, hyperuricemia [(UA >7 mg/dl) for men and (UA > 6 mg/dl) for women and children)] is considered as abnormal value [6]. Hyperuricemia in CKD as an elevation in the serum urate concentration out of proportion to the degree of renal insufficiency has been defined as follows: greater than 9 mg/dl if the plasma creatinine concentration ≤ 1.5 mg/dl, greater than 10 mg/dl if the plasma creatinine concentration is between 1.5 mg/dl and 2 mg/dl, and greater than 12 mg/dl with more advanced renal failure. Hyperuricosuria is defined as urinary excretion of urate excretion > 800 mg/day in men and > 750 mg/day in women [7]. Urate clearance is defined 8.7 ± 2.5 ml/min or fractional excretion of urate (FEUA) of 7.25 ± 2.98% in males. FEUA in healthy subjects is in the range of 6–8% while that in gouty patients is in range of 3–5%. In other references, normal range of FEUA in females and males are 7.3± 1.3% and 10.3± 4.2% in male, respectively.

Hypouricemia

Inherited renal hypouricemia (iRHUC) is a heterogenous inherited disorder characterized by impaired tubular uric acid transport, reabsorption insufficiency, and/or acceleration of secretion with severe complications, such as exercise-induced acute kidney injury (EI-AKI), and nephrolithiasis. EI-AKI presents with severe loin pain and patchy ischemia after anaerobic exercise (ALPE). More typically, hypouricemia is associated with high fractional excretion of uric acid due to genetic causes, including mutations in genes such as SLC22A12 (URAT1) and SLC2A9 (GLUT9) or factors such as uricosuric usage, renal tubulopathy, neoplasias, and other conditions. Loss-of-function mutation (compound heterozygous and/or homozygous) in the SLC22A12 gene has been named as iRHUC1, and patients with iRHUC, caused by heterozygous defects in the SLC2A9 gene coding GLUT9, have been described as iRHUC2. Renal hypouricemia is arbitrarily defined serum uric acid < 2 mg/dl (119 μmol/l).

Genetic testing

Although no specific therapies are yet available for the different types of ADTKD, genetic testing is currently the only way to definitively prove ADTKD and its respective subtypes and exclude the disease in affected family members. The mutation in the UMOD gene,

encoding the uromodulin protein, that is, Tamm-Horsfall protein, represents the pathogenetical background of FJHN. Uromodulin is expressed by epithelial cells of the thick ascending limb (TAL) of the loop of Henle and by distal convoluted tubules and the most abundant protein in urine. Uromodulin contains an N-terminal signal peptide (the cleavage site is most likely located between position 23 and 24), three calcium binding epidermal growth factor (cbEGF)-like domains between positions 31 and 148 and a fourth potential cbEGF-like domain at positions 281–336, and a zona pellucida (ZP) domain from aminoacid 336 to 585 and a glycosyl phosphatidyl inositol (GPI) anchor attachment site at position 614. Uromodulin is a very highly conserved protein showing approximately the same degree of sequence similarity (77–83% identities) with its rat, mouse, dog, and cow homologs. An important feature is the high content of cysteine residues (48 out of 640 amino acids), 7.5% that are prevalently distributed in the N-terminus. Uromodulin is synthetized as an 84-kDa precursor that is slowly converted to the mature glycosylated protein with an apparent molecular weight of 97 kDa. The maturation rate appears to be dependent on the retention time in the endoplasmic reticulum (ER) probably because the rate-limiting step is the formation of the correct set of disulfide bonds in that compartment. Mutations affecting the disulfide bond pattern cause domain misfolding with a damaging effect on the global protein structure. Since the mutant isoforms are predicted to impair the proper folding of uromodulin, it is hypothesized the delayed export to the plasma membrane to be due to a longer retention time in the ER, where the proper set of disulfide isomerases. Therefore, mutant uromodulin transient through the ER is delayed and the protein eventually accumulates in the ER or within the cytoplasm, possibly in compartments of ER origin. Uromodulin aggregates could occur by either intermolecular disulfide bonds or abnormal polymerization of the misfolded protein. Hyperuricemia in MCKD/FJHN and glomerulocystic kidney disease patients is secondary to volume contraction. This may result from a reduced NaCl reabsorption in the TAL due to loss of water impermeability as a consequence of intracellular accumulation of mutant uromodulin. The decreased sodium uptake in the TAL would be compensated by enhanced Na^+ reabsorption in the proximal tubule thus increasing the activity of the urate transporter URAT1. The vast majority of uromodulin mutations reported to so far are likely to affect the protein folding. Uromodulin mutations affect the protein intracellular trafficking delaying its transit through the ER with chronic effect that discloses a functional/molecular/clinical correlation. This eventually results in intracellular accumulation of uromodulin aggregates in tubular epithelial cells and significant reduction of secreted protein in patient urine. Several transporters playing a role in reabsorption and secretion have been identified in idiopathic renal hypouricemia. Urate reabsorption transporters include URAT1 (SLC22A12) [Fig.1], glucose transporter 9 [GLUT9 (SLC2A9)], organic anion transporter 4 [OAT4 (SLC22A11)], and organic anion transporter 10 [OAT10 (SLC22A13)]. Furthermore, urate excretion transporters contain ABCG2/BCRP (ABCG2), NPT1 (SLC17A1) and NPT4 (SLC17A3), OAT1 (SLC22A6), and OAT3 (SLC22A8). Low-frequency variants of SLC22A12 transporter associated with renal hypouricemia type 1. Solute carrier family 2, member 9 (SLC2A9) encodes a urate transporter known as GLUT9 (glucose transporter 9, a member of the GLUT family of hexose transporters) which is a class II glucose/fructose transporter. Two GLUT9 isoforms differ in membrane targeting, with human GLUT9a trafficking to the basolateral membrane and GLUT9b to the apical membrane of MDCK cells [8]. In other studies, two isoforms of GLUT9 have been described that differ only by the first 29 residues of the N-terminal domains. The short isoform (GLUT9a) appears to be expressed at both apical and basolateral membranes in proximal tubule epithelium cells (and indeed may contribute to the import of urate from the peritubular interstitium and thus facilitate renal urate secretion). The long isoform (GLUT9b) is predominantly expressed on the basolateral membrane and is the only known basolateral efflux transporter for urate. As previously mentioned, SLC2A9 gene exists in two variants: GLUT 9a and GLUT 9b. Low-frequency variants of SLC2A9 transporter associated with renal hypouricemia 2 [3]. Furthermore, this point should be considered that SLC2A9 is the most reported gene associated with serum UA levels along with ABCG2 in gout and hyperuricemia. Multiplex panels for next-generation sequencing could be advantageous. Possible rationale for genetic testing in ADTKD has been described in Table 1.

Objectives as questions

As established diagnosis of ADTKD should ideally be based on demonstration of the underlying genetic defect, due to lack of distinctive clinical features in ADTKD, clinical suspicion should be around by a compatible family history alone and should lead to genetic testing. Because studies of inherited tubulointerstitial disease are rare and there may be missed diagnosis of ADTKD in CKD, this research must answer to two questions:

What does this research do?

Although ADTKD is at present considered a very rare disease, it is tempting to speculate that its uncharacteristic presentation, together with a confusing terminology, has resulted in significant underdiagnosis. ADTKD-

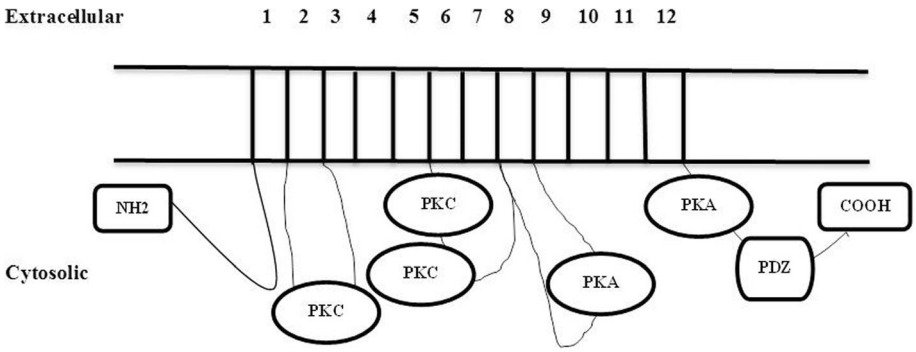

Fig. 1 Schematic presentation of URAT1 (SLC22A12). URAT1 belongs to the organic ion transporter family (SLC22). URAT1 consists of 555 amino acid residues and 12 predicted putative transmembrane domains (TMs) with large hydrophilic loops between the first and second as well as six and seventh TMs and intracellular NH2 and COOH terminals with a PDZ binding motif at its end. There are several PKC and PKA phosphorylation sites in transporter

UMOD is the most common genetic kidney disease after autosomal-dominant polycystic kidney disease but it is an underrecognized diagnosis in CKD and end-stage kidney disease (ESKD) patients. Therefore, prevalence and diagnosis of ADTKD increase with genetic testing.

How does this research work?

Genetic factors are also likely involved in dysuricemia in CKD. FJHN results from a mutation in uromodulin and is associated with progressive renal disease with the prominent development of glomerulosclerosis and tubulointerstitial fibrosis (TIF). GWAS have successfully identified genomic loci containing susceptibility variants associated with the risk of complex traits and markers of renal function. In particular, common variants in the UMOD gene have been associated with the risk of CKD, eGFR, and other complex traits, such as kidney stones and hypertension. GWAS have also found association between polymorphisms in urate transport and the risk for gout [9, 10]. GWAS aim to identify disease/phenotype-associated susceptibility genes, and multiple GWAS have correspondingly confirmed a strong correlation of both SLC2A9 and SLC22A12 with sUA concentration providing further the evidence of their causative role in iRHUC. This research finds out diagnostic methods and correlation between genetic tests and serum uric acid changes in kidney dysfunction. Moreover, this study investigates clarification of cause-and-effect relationships using Mendelian randomization.

Materials and methods

Criteria for considering studies for review (eligibility criteria)

Type of studies

All case studies (case reports) investigated genetic tests in relation to changes of serum uric acid levels in patients with kidney dysfunction.

Type of participants

All patients with changes of serum uric acid levels with familial origin and kidney dysfunction in all ages since neonate to old age in both male and female sex levels were considered in this study. They were assessed for primary and secondary outcomes dependent on available data.

Type of outcome measures

Primary outcomes End-stage kidney disease, kidney transplantation, and tubulointerstitial fibrosis were primary endpoints in this study.

Table 1 Possible reasons for genetic testing of ADTKD

I	Adults with CKD suspected to have ADTKD who wish to confirm the diagnosis
II	Members of affected families with normal kidney function who wish to donate a kidney
III	Healthy adult individuals at risk who are interested in establishing a genetic diagnosis
IV	Adults interested in undergoing preimplantation genetic diagnosis to avoid their child's inheritance of a disease-causing mutant allele
V	Children suspected of having a REN mutation

ADTKD autosomal-dominant tubulointerstitial kidney disease, *CKD* chronic kidney disease
Adapted from Eckardt et al, KI 2015

Secondary outcomes Cardiovascular events, metabolic syndrome, nephrolithiasis, and proteinuria were secondary points in this study.

Information sources

The paper has written based on advanced searching via PubMed and Google Scholar databases to identify articles published since 1913 (inception) to October 2019.

Search methods for identification of studies

Electronic search The mentioned search used the following search terms of ADTKD, hereditary renal hypouricemia, and advanced search with terms of kidney and uric acid.

Searching other resources The authors reviewed references of all included articles and performed handsearching of related journals to identify the additional relevant studies.

Study selection

The search strategy was used to obtain titles and abstracts of studies that might be relevant to the review. The titles and abstracts were screened by author, who discarded studies that were not applicable; however, studies and reviews that might include relevant data or information on studies were retained initially. The authors independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

Data collection and analysis

Data extraction and management Data extraction was carried out by authors and studies that reported in non-English language journals were to be translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was included.

Data items

All patients with changes of serum uric acid levels, elevated serum creatinine levels, or decreased estimated glomerular filtration rate (eGFR) that gene analysis performed in those, were considered for this research. Clinical features such as age, sex, different symptoms, and physical signs were extracted from this study. Furthermore, biochemical variables of serum uric acid, serum creatinine (SCr), eGFR, serum total creatin phosphokinase (CPK), serum total cholesterol, serum triglyceride, hemoglobin (Hb), FEUA, uric acid clearance (UACl), creatinine clearance (CrCl), urine protein, hematuria, urine crystals, genetic testing at initial presentation, imaging, management, and outcomes were collected.

Assessment of risk of bias and quality in included and across articles

Case reports were analyzed using criteria developed by the Joanna Briggs Institute Critical Appraisal tool for case reports that has different assessment tools for each study design in question. This evaluation tool has eight items for case reports.

Statistical analysis

Data were entered in Microsoft Excel 2010 software. Categorical variables are recorded as frequency (N) and percentage (%). The continuous variables were determined as to whether they were normally distributed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution are reported as mean ± standard deviation (SD), and nonparametric variables are expressed as median. Comparison between two continuous variables was assessed with two-tailed Student t test. Correlation between continuous variables with normal distributed data was analyzed using product moment correlation (Pearson's correlation coefficient test) [r]. Significance was assessed with p value of < 0.05.

Summary of findings' tables

GRADE (Gradings of Recommendations Assessment, Development and Evaluation) approach was used to rate the quality of evidence and grading strength of recommendations and define the GRADE system, GRADE process of developing recommendations, and endpoint of the GRADE evidence summary [evidence profile (EP) and the summary of findings table (SoFs)]. EP includes the quality of evidence assessment that randomized control trial (RCT) start with high rating and observational study start with low rating and final rating of quality for each outcome graded high, moderate, low, or very low. The present study analyzes the prevalence of data not the effect size, rate ratio, relative risk, risk difference, and rate difference; for this reason, this approach cannot used.

Results

Description of studies

Results of the search and study selection

After searching electronic databases, authors identified 1391 records. After duplicated articles were removed and titles and abstracts screened, authors retrieved 94 full-text articles for further assessment. Of these, 40 published articles (65 case reports) were included and 64 studies due to non case reports and not subjected-related articles were excluded (Fig. 2).

Included studies (criteria) Forty published articles (65 case reports or participants) were eligible for inclusion in this review.

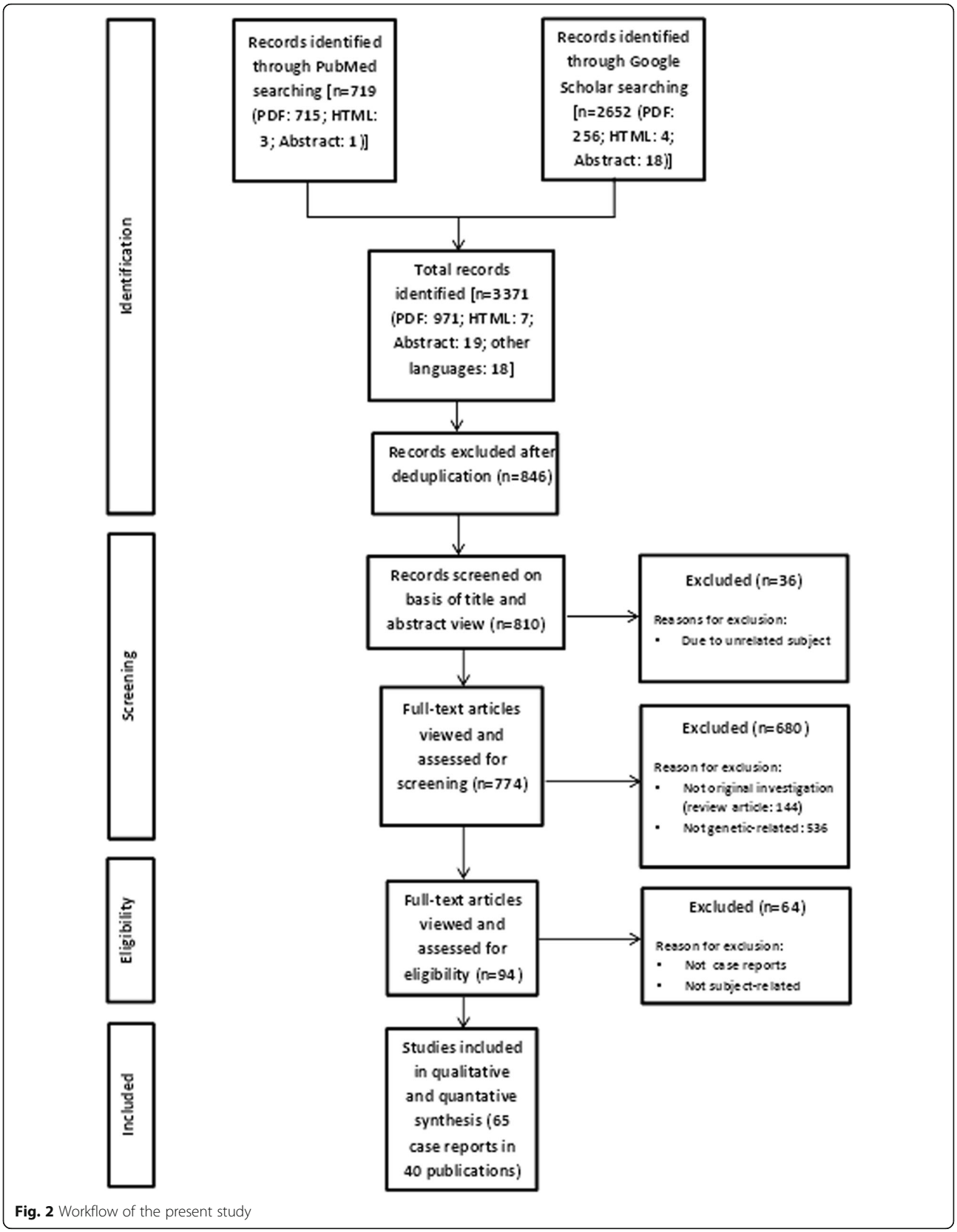

Fig. 2 Workflow of the present study

Study characteristics

Study design Randomized data were planned with systematic review design in this retrospective study, and those articles were collected as non-randomized method.

Sample sizes Sample sizes ranged from 65 to 72 patients in this study that seven patients excluded from this study.

Setting Most patients in this study were referred to single centers but several reports indicated multi-center follow-up.

Participants All patients included in this study had changes of serum uric acid levels, elevated serum creatinine levels, or decreased eGFR. Gene analysis was performed in these patients, and chromosomal analysis was done in one patient in an old published article (1986).

Excluded studies (criteria)

Patients were excluded from the study if they had characteristics of inherited renal hypouricemia or inherited tubulointerstitial kidney disease without genetic testing in initial presentation.

Risk of bias and quality in the included studies

Assessment of risk of bias and quality of included articles was performed using Joanna Briggs Institute critical appraisal tools for case reports. Based on this assessment, 14 case reports presented with five scores (14/40, 35%), ten case reports with four scores (10/40, 25%), six case reports with seven scores (6/40, 15%), and eight case reports with six scores (8/40, 20%) in ITIKD patients (Additional file 1: Table S1a). Moreover, nine case reports presented with seven scores (9/25, 36%), six case reports with four scores (4/25, 16%), three case reports with eight and six scores (3/25, 12%), and one case report with three and five scores (1/25, 4%) in iRHUC patients (Additional file 1: Table S1b).

Results of case studies

Patients' characteristics

Among 94 full-text articles obtained in this research paper, 40 published articles were included in this study. These 40 articles included 65 case reports that were examined 65 patients with hereditary changes of serum uric acid levels and renal dysfunction for qualitative and quantitative synthesis [10–49]. Mean ± standard deviation (± SD) age of patients at time of diagnosis in inherited tubulointerstitial kidney disease was 25.29 ± 14.69 years (ranging from 9 months to 62 years). Of these, 19 patients (19/40, 47.5 %) were male and 21 patients (21/40, 52.5 %) were female. Mean ± SD age of patients in male and female levels at time of diagnosis in inherited tubulointerstitial kidney disease were 21 ± 10.21 years (ranging from 3 years to 42 years) and 29.17 ± 16.87 years (ranging from 9 months to 62 years), respectively. There was no statistical significance for age between two sex levels in ITIKD (p value 0.07). Mean ± SD age of patients at time of diagnosis in inherited renal hypouricemia was 18.83 ± 10.59 years (ranging from 10 months to 42 years). Of these, 19 patients (19/25, 76 %) were male and six patients (6/25, 24 %) were female. Mean ± SD age of patients in male and female levels at time of diagnosis in inherited renal hypouricemia were 18.46 ± 10.36 years (ranging from 10 months to 40 years) and 20.01 ± 11.22 years (ranging from 11 years to 42 years), respectively. There was no statistical significance for age between two sex levels in iRHUC (p value 0.78). Distribution of age groups in two sex levels in ITIKD and iRHUC has been described in Table 2 (Additional file 2: Table S2).

Patients' complaints

Patient's history and physical examination are of paramount importance, especially in the setting of inherited changes of serum uric acid levels and kidney dysfunction. The symptoms in most of patients were unmentioned 20/40 (50%) and 8/40 of patients (20%) presented with gouty attacks at initial time in ITIKD patients. Six of forty (15%) patients at initial time of presentation were asymptomatic. The signs of patients with ITKID were unmentioned in fifteen cases (15/40, 37.5%), and there were normal physical examination in 11 patients of ITIKD (11/40, 27.5%). There were tophi with whitish discharge in left ear lobe and right little finger in two patients (2/40, 5 %) with ITIKD. In patients with iRHUC, severe exercise had essential role for causing symptoms in these patients (10/25, 40%) as nine patients (9/25, 36%) suffered loin pain with bilateral nature in 6/25 (24%), abdominal pain in 8/25 (32%), and vomiting in 7/25 (28%) of patients at initial time of presentation. Five patients (5/25, 20%) were asymptomatic and some of patients complained decreased urine volume and nausea (3/25, 12%) in this study. There were stone passage and family history of nephrolithiasis in two patients (2/25, 8 %) in iRHUC. Three patients with iRHUC (3/25, 12%) had unmentioned and normal physical examinations. Moreover, there were costovertebral angle tenderness in four patients of iRHUC (4/25, 16 %) that three of those were bilateral. Two patients of iRHUC presented with oliguria in this study (2/25, 8 %) (Additional file 3: Table S3 a, b).

Laboratory data

Prevalence of inherited tubulointerstitial kidney disease and inherited renal hypouricemia in this study resulted in 40 patients (40/65, 61.5%) and in 25 patients (25/65,

Table 2 Prevalence of agegroup variable in both male and female sex in inherited renal hypouricemia and inherited tubulointerstitial kidney disease

Age	iRHUC			ITIKD		
Disease						
Age group	Male (19/25)	Female (6/25)	Total (25)	Male (19/40)	Female (21/40)	Total (40)
1 mo-9 y/o	4/19 (21%)	0/6	4/25 (16%)	2/19 (10%)	2/21 (9.5%)	4/40 (10%)
10-19 y/o	7/19 (36.8%)	4/6 (66.6%)	11/25 (44%)	9/19 (47.3%)	6/21 (28.5%)	15/40 (37.5%)
20-29 y/o	5/19 (26.3%)	1/6 (16.6%)	6/25 (24%)	5/19 (26.3%)	4/21 (19%)	9/40 (22.5%)
30-39 y/o	2/19 (10.5%)	0/4	2/25 (8%)	1/19 (5.2%)	3/21 (14.2%)	4/40 (10%)
40-49 y/o	1/19 (5.2%)	1/6 (16.6%)	2/25 (8%)	2/19 (10.5%)	2/21 (9.5%)	4/40 (10%)
50-59 y/o	0/19	0/6	0/25	0	3/21 (14.2%)	3/40 (7.5%)
≥ 60 y/o	0/19	0/6	0/25	0	1/21(4.76%)	1/40 (2.5%)

iRHUC inherited renal hypouricemia, *ITIKD* inherited tubulointerstitial kidney disease

38.4%), respectively. Metabolic syndrome definition according to National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) is diagnosed co-occurrence of greater or equal than of three of five metabolic abnormalities: abdominal obesity (BMI ≥ 25 kg/m^2 or waist circumference > 40 inches in male and > 35 inches in female), hyperglycemia, hypertension (HTN), and dyslipidemia in combination. None of these patients had metabolic syndrome or syndrome X or insulin-resistant syndrome in the present study. Prevalence of any risk factors of metabolic syndrome has been described in the present study (Additional file 4: Table S4 a, b). The obtained laboratory data of patients in this study are classified as follows:

ITIKD

Serum uric acid levels have been evaluated in all patients with inherited tubulopathy in this study but quantitative values were not mentioned in three patients. There were hyperuricemia in 31 patients (31/40, 77.5%) in accordance with elevated serum uric acid levels in two sex groups (> 6 mg/dl in female and > 7 mg/dl in male) at initial presentation (Table 3a). Mean ± SD of elevated serum uric acid levels were assessed 9.55 ± 2.55 mg/dl. Furthermore, there were hyperuricemia in 34 of patients (34/40, 85%) in accordance with elevated serum uric acid levels of ≥ 5.5 mg/dl in this study. Mean ± SD values of elevated sUA levels were assessed, 9.24 ± 2.6 mg/dl indicative of risks for hyperuricemic effects on organ disorders in lower values of sUA. Perhaps, for this risk, we must think to treat lower rang of sUA values. Kidney dysfunction was assessed in accordance to reduced SCr levels or eGFR in these patients in this study. Serum creatinine levels were measured in 58 patients (58/65, 89.2%), and there were insufficient data in 7 patients (7/65, 10.7%). Elevated baseline SCr levels were observed in 31 patients (31/40, 77.5%) of inherited tubulopathy with mean ± SD of 2.14 ± 1.77 mg/dl in accordance with elevated SCr levels in two sex groups (> 1 mg/dl in female and > 1.3 mg/dl in male). eGFR has been measured in nine patients with ITIKD, three patients were in CKD stage II (3/40, 7.5%), three patients in CKD stage IIIa (3/40, 7.5%), one patient in CKD stage IIIb (1/40, 2.5%), and two patients in CKD stage IV (2/40, 5%). Prevalence of anemia in 6/40 (15%) patients of ITIKD was assessed with mean ± SD of decreased hemoglobin levels of 9.75 ± 1.45 g/dl. There was no significant statistical analysis between anemia and sUA in this study (p value 0.72) (Fig. 3). FEUA were measured in 12 patients (12/40, 30%) with inherited tubulopathy, but decreased FEUA were seen in ten patients (10/40, 25%) with mean ± SD of 4.25 ± 1.47 %. Serum Bun levels were measured in 13 patients (13/40, 32.5%), and serum Bun levels were raised in 11 patients (11/40, 27.5%) with mean ± SD values of 81.41 ± 47 in this study. There was no correlation between SCr and sUA levels in ITIKD (p value 0.26). Furthermore, no correlation was seen between SCr levels and FEUA (p value 0.139) (Fig. 4). No correlation between eGFR and sUA levels was seen with p value of 0.175 in the present study (Fig. 5). Twenty-four-hour protein excretion was measured in six patients with ITIKD in the present study while there was overt proteinuria (> 150

Table 3 a, b Prevalence of changes of sUA levels in both sex levels in inherited renal hypouricemia and inherited tubulointerstitial kidney disease

Frequency of decreased sUA levels in both male and female sex (a)

sUA < 2 mg/dl	No. (total=17)	Male (No.=12)	Female (No.=5)
< 0.5	3/17(17.6%)	1/12 (8.3%)	2/5 (40%)
0.5-1	7/17 (41.1%)	5/12 (41.6%)	2/5 (40%)
1.1-1.9	7/17 (41.1%)	6/12 (50%)	1/5 (20%)

Frequency of elevated sUA levels in both male and female sex (b)

sUA > 6 mg/dl	No.(total=31)	Male (No.= 16)	Female (No.=15)
6 - 8	12/31 (38.7%)	5/16 (31.2 %)	7/15 (46.6%)
8.1-10	8/31 (25.8%)	4/16 (25%)	4/15(26.6%)
10.1-12	6/31 (19.3%)	3/16 (18.7%)	3/15 (20%)
> 12	4/31 (12.9%)	3/16 (18.7%)	1/15 (6.6%)

sUA Serum uric acid, *No.* Number

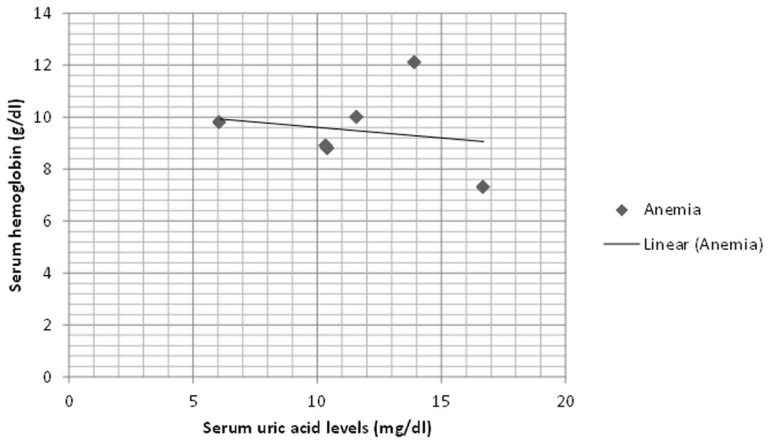

Fig. 3 Correlation between serum uric acid levels and serum hemoglobin in patients with inherited autosomal tubulointerstitial kidney disease

mg/day) in three patients (3/40, 7.5%) with mean ± SD values of 810.33 ± 356.8 mg/day. There was insufficient data for albuminuria, FEUA, uric acid excretion (UAE), and UACl in patients with ITIKD in the present study.

Idiopathic renal hypouricemia

Serum uric acid levels were measured in all patients with inherited renal hypouricemia in this study but decreased sUA levels were seen in 17 patients (17/25, 68%) in accordance with sUA levels < 2 mg/dl with mean ± SD of 0.91 ± 0.5 mg/dl. FEUA was measured in 24 patients (24/25, 96%) with IRH but there was insufficient data in one patient (1/25, 4%) in this study (Table 3b). Mean ± SD of elevated FEUA was assessed with values of 87.22 ± 73.2% in the presented study. Baseline SCr levels were measured in 22 patients (22/25, 88%), and there was insufficient data in three patients (3/25, 12%) with iRHUC. Elevated baseline SCr levels were assessed in fifteen patients (15/25, 60%) with mean ± SD of 3.58 ± 2.52 mg/dl in iRHUC in accordance with elevated SCr levels in two sex groups (> 1 mg/dl in

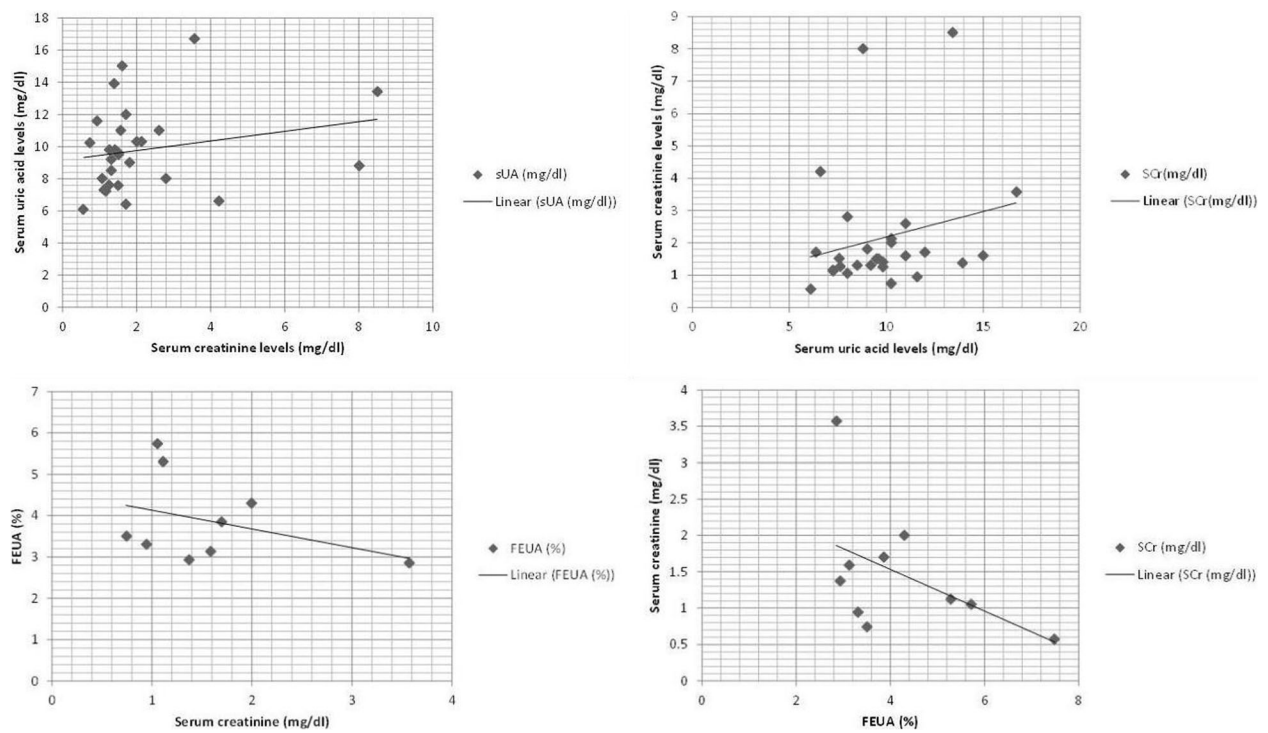

Fig. 4 Correlation between serum uric acid levels and serum creatinine vs. serum creatinine and serum uric acid levels, between fractional excretion of uric acid (FEUA) and serum creatinine vs. serum creatinine and FEUA in patients with inherited tubulointerstitial kidney disease

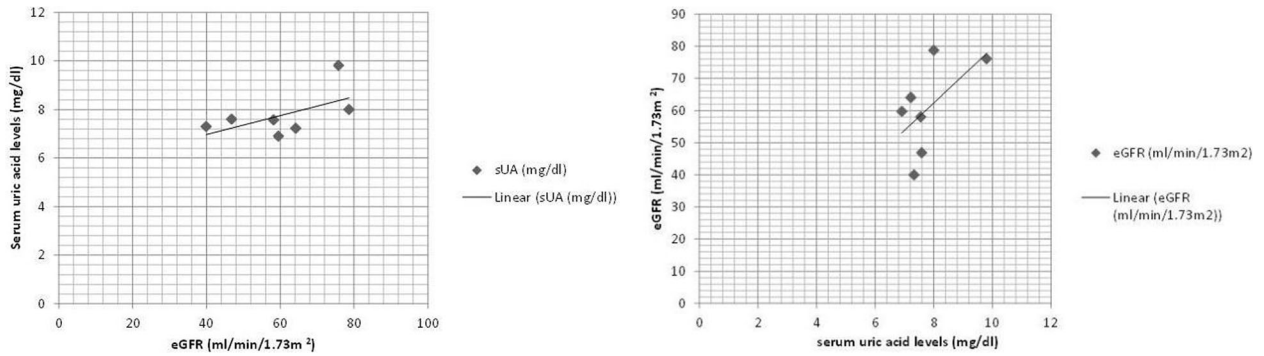

Fig. 5 Correlation between serum uric acid levels and estimated glomerular filtration rate (eGFR) vs. eGFR and serum uric acid in inherited tubulointerstitial kidney disease

female and > .3 mg/dl in male). Estimated GFR in iRHUC has measured in six patients based on creatinine with Cockcroft–Gault equation and in two patients with Cystatin C. Reduced eGFR in iRHUC was in CKD stages II and IV in one patient (1/25, 4%). Prevalence of anemia in patients with iRHUC was 3/25 (12%) with mean ± SD of 12.5 ± 0.29 g/dl in hemoglobin values. Serum Bun levels were measured in ten patients (10/25, 40%), and elevated serum Bun levels were seen in eight patients (8/25, 32%) with mean ± SD values of 79.7 ± 50.08 mg/dl in this study. There was no correlation between SCr and sUA levels in iRHUC (p value 0.07). Furthermore, there were no correlation between SCr levels and FEUA (p value 0.27) (Fig. 6). Twenty-four-hour protein excretion was measured in six patients with iRHUC in the present study while there was abnormal proteinuria in four patients (4/25, 16%). Quantitative proteinuria was measured in two patients (2/25, 8%) with mean ± SD values of 702.15 ± 97.85 mg/day. There was insufficient data for albuminuria, FEUA, UAE, and UACl simultaneously in patients with iRHUC in the present study.

Genetic testing

Genetic analyses of two inherited tubular diseases are as follows:

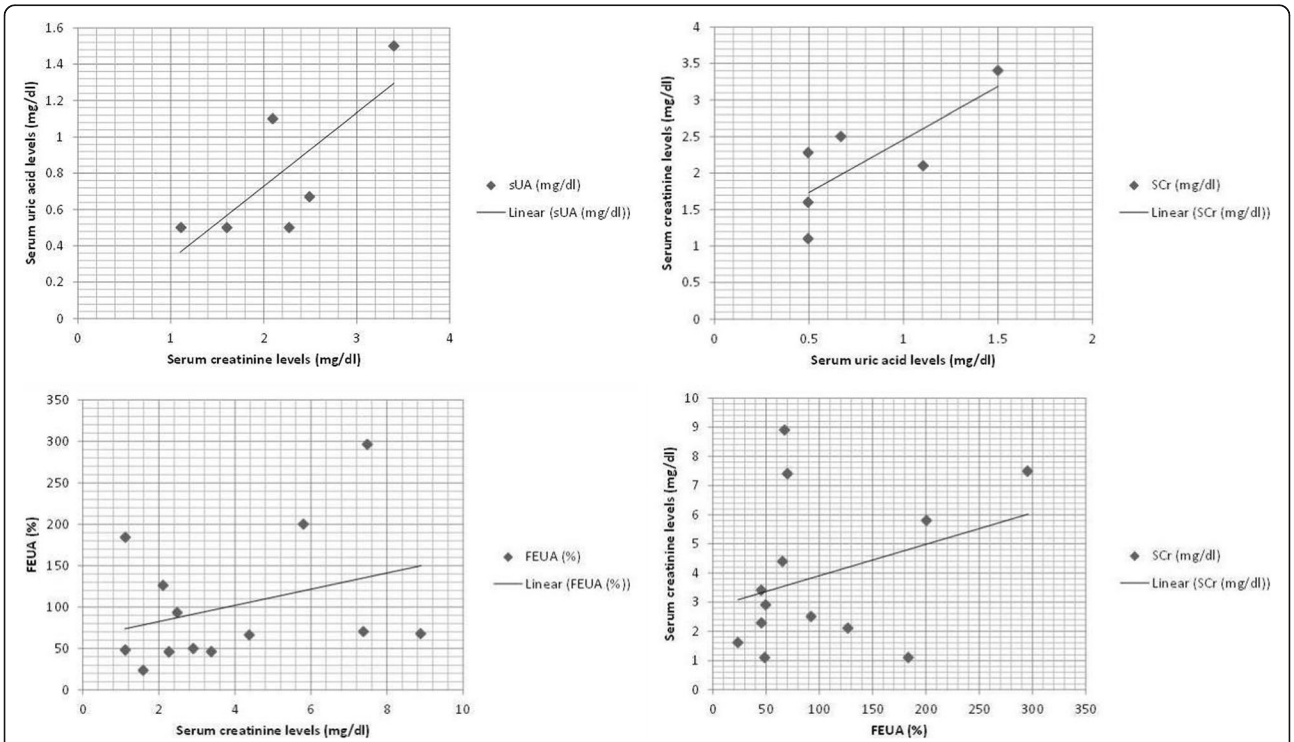

Fig. 6 Correlation between serum uric acid levels and serum creatinine vs. serum creatinine and serum uric acid levels, between fractional excretion of uric acid (FEUA) and serum creatinine vs. serum creatinine and FEUA in patients with inherited renal hypouricemia

ITIKD

Importantly, failure to identify a mutation does not exclude the diagnosis of ADTKD, as not all pathogenic genes have yet been identified. Conversely, genetic findings, in the presence or absence of clinical manifestations need to be supported by functional studies to establish the causative role of genetic variants [50]. In the present study, 39 patients (39/40, 97.5%) had autosomal-dominant inheritance in UMOD gene the while main inheritance in one patient (1/40, 2.5%) had autosomal recessive pattern. Moreover, 30 patients (30/40, 75%) had heterozygous mutations and two patients were found to have homozygous mutations (2/40, 5%). In eight patients (8/40, 20%) heterozygous or homozygous mutation were not mentioned. The missense mutations found in 24 patients (24/40, 60%) with inherited tubulointerstitial kidney disease and one patient (1/40, 2.5%) found to have nonsense mutation in UMOD gene. The majority of patients were of Italian ethnicity (11/40, 27.5%), four patients (4/40, 10%) were Hungarian, and three patients (3/40, 7.5%) were of Japanese, German, Turkish descent. The most abundance of mutations (14/40, 35%) were located in exon 4, and others included exon 5 (13/40, 32.5%), exon 3 (5/40, 12.5), exon 6 (3/40, 7.5%), and exon 8 (1/40, 2.5%) (Table 4). There was no statistical correlation between elevated sUA levels and exon region of UMOD region in inherited tubulointerstitial kidney disease at a significance level (p value 0.30) (Fig. 7), but this study showed that mutations in exon region of 5 was associated with higher sUA levels versus lower sUA levels in other exons. Electrophenograhy was depicted in fifteen published articles in probands of ITIKD for sequence analysis of nucleotides in the present study.

Idiopathic renal hypouricemia

Differentiating between inherited and transient hypouricemia is challenging because low level of UA reflects malnutrition status. Therefore, a genetic utility for diagnosis of iRHUC has been established. Since the genotyping of two single-nucleotide polymorphism (SNP) costs less than 5 dollars in USA and requires only half a day, it will be a huge-advantage for medical doctors to consider this genetic test as a routine procedure. Really, genetic testing is indicated for preventing not only urolithiasis but also oxidative stress-induced disease progression for hypouricemic patients in the primary care setting [51]. It is divided into inherited renal hypouricemia type 1 (iRHUC1), caused by defects in the SLC22A12 gene, and inherited renal hypouricemia type 2 (iRHUC2), caused by the defects in the SLC2A9 gene. Hereditary renal hypouricemia usually occurs with hypouricemia (< 119 μmol/L) and increased renal excretion of uric acid (FEUA > 10%). Mutational analysis could be a useful indicator for the clinical and prognostic evaluation of patients with renal hypouricemia [44]. In the present study, 16 patients presented with iRHUC1 (16/25, 64%), eight patients with iRHUC2 (8/25, 32%), and one patient (1/25, 4%) with chromosomal analysis. The majority of patients with hereditary renal hypouricemia were located in exons 3 and 7 (3/25, 12%); exons 1, 4, and 5 (2/25, 8%); exon 8, 9, and 11 (1/25, 4%); and unmentioned exon (12/25, 48%). There was significant correlation between sUA levels and exon region of genes in iRHUC, statistically (p value 0. 037). Eight of 16 patients with iRHUC1 had homozygous mutations (8/16, 50%), and four patients found to have heterozygous and compound heterozygous mutations (4/16, 25%). Three probands of SLC22A12 gene had missense and deletion mutations (3/16, 18.7%), and two patients found to have nonsense mutations (2/16, 12.5%). Thirteen of these SLC22A12 mutations (13/16, 81.2%) were identified in male patients, and three probands were female (3/16, 18.7%). The majority of SLC22A12 mutations were located in exons 1, 4, 7, and 8 (in 2/16, 12.5% of patients) in iRHUC1. There was no significant correlation between exon regions of SLC22A12 gene in iRHUC1, statistically (p value 0.378). Four of 16 patients with SLC22A12 gene (4/16, 25%) were from Czech descent, and three patients were Korean and Japanese (3/16, 18.7%). Four patients with SLC22A12 gene mutations had decreased sUA levels of less than 1 mg/dl (4/16, 25%). Furthermore, seven of patients with SLC22A12 gene mutations had exercise-induced AKI (7/16, 43.7%) and two patients with this mutation revealed nephrolithiasis in ultrasonography (2/16, 12.5%). Eight patients with iRHUC (8/25, 32%) were included SLC2A9 mutations. Six of patients with SLC2A9 gene had homozygous mutations (6/8, 75%), and one patient found to have heterozygous and compound heterozygous mutations (1/8, 12.5%). Three patients with SLC2A9 gene had missense mutations (3/8, 37.5%), and one patient had nonsense mutation (1/8, 12.5%). The majority of SLC2A9 mutations were clustered in exons of 3 (3/8, 37.5%) and 5 (2/8, 25%) and SLC2A9 mutation of one patient located in exons 7 and11 (1/8, 12.5%). There was statistical correlation between sUA levels and exon region of SLC2A9 gene in iRHUC2 at significance level (p value 0.0339) (Fig. 7). Four of eight patients with SLC2A9 gene were from the Czech race (4/8, 50%), and one patient from Chinese, Pakistani, and Caucasian ethnicity (1/8, 12.5%) (Table 5). Five of patients with SLC2A9 mutations (5/8, 62.5%) were identified in male patients, and three probands were female (3/8, 37.5%). Furthermore, three of patients with SLC2A9 gene mutations had exercise-induced AKI (3/8, 37.5%), and none of patients with this mutation had nephrolithiasis. Three patients with homozygous SLC2A9 gene mutations had

Table 4 Genetic characteristics of probands with inherited renal hypouricemia in the present study

Case	RHUC	Status	Pathogenic factor (s) for clinical relevance	Mutation gene	Nucleotide change	Effect on coding sequence (a.a change)	Region (exon)	Type of inheritance	Race/ ethnicity	Ref
Proband 1	Type 1	Homozygous nonsense	Substitution of guanine to adenine means stop codon in URAT1 gene	URAT1encoding SLC22A12	c.G774A, p.TrP (TGG)	p.Trp-258Stop	4	AR	Korea	[13]
Proband 2	Type 2	Compound HTZ missense	Mutation in the fifth transmembrane domain and replacement of a highly conserved glycine residue with a basic charged aminoacid	SLC2A9	p.Gly216Arg and p.Arg380Trp, p.Gly216Arg in homozygocity, compound heterzygosity, p.Arg380Trp	p.Arg380Trp	7,11	AR	Pakistan	[14]
Proband 3	Type 1	Homozygous	?	SLC22A12	c.774 G>A	W258X p.[Trp258Ter]	4	AR	Korea	[15]
Proband 4		Without translocation	–	–	–	–	–	AR	Japan	[16]
Proband 5	Type 2	Homozygous nonsense mutation	Prematurely truncated GLUT9 protein	GLUT9 encoding SLC2A9	g.68G>A	p.Trp23Stop	3	AR	China	[17]
Proband 6	Type 1	HTZ missense	–	SLC22A12	c.1400C>T	p.T467M, rs20010413	–	AR	Sri Lanka	[18]
Proband 7	Type 1	Compound HTZ	–	URAT1 Encoding SLC22A12	G269A:R90H	R90H/W258X	–	AR	Korea	[22]
Proband 8	Type 1	Homozygous	–	SLC22A12	R90H/R90H	–	–	AR	Japan	[23]
Proband 9	Type 1	Compound HTZ	–	URAT1 encoding SLC22A12	R90H/W258X	–	–	AR	Japan	[23]
Proband 10	Type 2	HTZ missense	Segregation analysis not performed	SLC2A9	p.G216R	p.N333S	5,7	AR	Prague in Czech	[30]
Proband 11	Type 2	Homozygous mutation	No functional analysis performed	SLC2A9	p.G216R	p.C297W	5	AR	Prague in Czech	[30]
Proband 12	Type 2	Homozygous	Mutation in truncated protein	SLC2A9	g.43412_43413insC	p. Ile118HisfsX27	3	AR	Czech	[31]
Proband 13	Type 2	Homozygous	Mutation in truncated protein	SLC2A9	g.27073insC	p. Ile118HisfsX27	3	AR	Czech	[31]
Proband 14	Type 1	HTZ del	Colocalization studies: accumulation of URAT1 protein in the ER leading to misfolded protein partly	URAT1 encoding SLC22A12	c.1245_1253del	p.G366R	7, 9	AR	Czech	[34]
Proband 15	Type 1	HTZ	Colocalization studies: accumulation of URAT1 protein in the ER leading to misfolded protein partly	SLC22A12	c.1096G>C	p.L415_G417del	7, 9	AR	Roma ethnic group in Czech	[34]
Proband 16	Type 1	Homozy gous deletion	Colocalization studies: accumulation of URAT1 protein in the ER leading to misfolded protein partly	SLC22A12	c.1245_1253del	p.T467M	7	AR	Czech	[34]

Table 4 Genetic characteristics of probands with inherited renal hypouricemia in the present study *(Continued)*

Case	RHUC	Status	Pathogenic factor (s) for clinical relevance	Mutation gene	Nucleotide change	Effect on coding sequence (a.a change)	Region (exon)	Type of inheritance	Race/ ethnicity	Ref
Proband 17	Type 1	Compound HTZ	Mutation-induced structural instability or malfunction	SLC22A12	c.269G>A/c.1289_12	c.269G>A/p.R90H, c.1289_ 1290insGG/ p.M430fsX466	1, 8	AR	china	[35]
Proband 18	Type 2	Homozygous missense	1. Reduced UA transport activity 2. Mutation in the inner channel that expels UA from the cytoplasmic to extracellular regions	SLC2A9	c.512G>A	p. Arg 171 His	–	AR	caucasian	[36]
Proband 19	Type 1	Homozygous missense	–	URAT1 encoding SLC22A12	G269A:R90H	-	1	AR	Taiwan	[37]
Proband 20	Type 1	Homozygous nonsense	–	SLC22A12	G774A		–	AR	Japan	[39]
Proband 21	Type 1	Homozygous in SNP, ? partial deletion	–	SLC22A12	-	-	–	AR	Czech	[40]
Proband 22	Type 1	HTZ missense	–	SLC22A12	p.T467M	-	–	AR	Sri Lanka	[41]
Proband 23	Type 1	Compound HTZ	–	SLC22A12	p.T467M	p.L415-G417del	–	AR	Spain	[49]
Proband 24	Type 1	Homozygous	–	SLC22A12	p.T467M	p.T467M	–	AR	Spain	[49]
Proband 25	Type 2	Homozygous	–	SCLC2A9	p.T125M	p.T125M	–	AR	Spain	[49]

AR autosomal recessive, *HTZ* heterozygous, *RHUC1*, *2* renal hypouricemia type 1 and 2, *SNP* single-nucleotide polymorphism

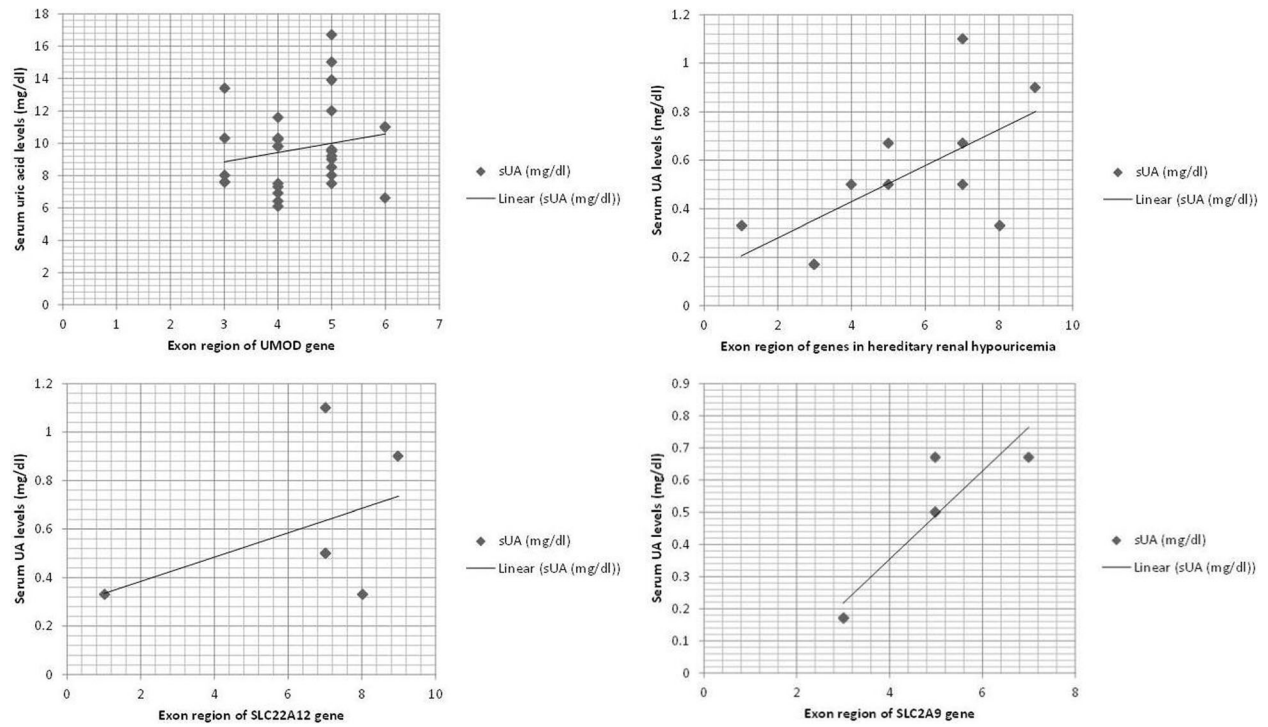

Fig. 7 Correlation between serum uric acid levels and exon region of UMOD gene in patients with inherited tubulointerstitial kidney disease and correlation between serum uric acid levels and exon region of mutated SLC22A12, SLC2A9 genes in patients with inherited renal hypouricemia

extreme hypouricemia (sUA ≤ 0.5 mg/dl), and two patients with homozygous and one patient with heterozygous SLC2A9 mutation were found to have severe hypouricemia (sUA < 1 mg/dl). Electrophenograhy were depicted in eight published articles in probands of idiopathic renal hypouricemia (Additional file 5: Table S5).

Imaging

ITIKD

In this study, chest x-ray showed normal results in one patient (1/40, 2.5%). Renal sonography was performed in 35 patients (35/40, 87.5%) that resulted abnormal findings in 28 patients (28/40, 70 %). Of these patients, 18 patients (18/40, 45%) showed small-sized kidneys (unilateral or bilateral) and 12 patients (12/40, 30%) were revealed renal cyst. Renal ultrasonography (US) scan performed in two patients (2/40, 5%) that one patient (1/40, 2.5%) revealed small echodense lesion in renal cortex and decreased paranchymal thickness (Additional file 6: Table S6).

iRHUC

Renal sonography performed in 12 patients (12/25, 48%) resulted to abnormal findings in four patients (4/25, 16%). Of these patients, eight patients (8/25, 32%) showed normal-sized kidneys, two patients (2/25, 8%) with hyperechogenic kidneys, and one patient (1/25, 4%) with enlarged kidneys were characterized. Delayed contrast-enhanced computed tomography (CECT) scan in one patient (1/25, 4%) showed patchy wedge shaped enhancement in kidney.

Pathology

ITIKD

Renal biopsy was performed in 14 of patients (14/40, 35%) with inherited tubulointerstitial kidney disease. Glomerular sclerosis were seen in two patients (2/40, 5%) and one patient (1/40, 2.5%) showed paranchymal damage. Twelve patients (12/40, 30%) showed interstitial fibrosis, and tubular atrophy were seen in ten patients (10/40, 25%).

iRHUC

Kidney biopsy was performed in five of 25 patients (5/25, 22.7%) with inherited renal hypouricemia. Two patients (2/25, 8%) revealed acute tubular injury, interstitial edema on kidney biopsy. One patient showed acute tubular necrosis (ATN) and tubulointerstitial lesion on kidney biopsy (1/25, 4%). Testicular biopsy in one patient (1/25, 4%) with familial renal hypouricemia revealed marked hyalinization of seminiferous tubules, interstitial fibrosis, and lack of spermatogenesis.

Table 5 Genetic characteristics of patients with inherited tubulointerstitial kidney disease in the present study

Case	Status	Pathogenic factor (s) for clinical relevance	Mutation gene	Nucleotide change	Effect on coding sequence (a.a change)	Region (exon)	Type of inheritance	Race/ ethnicity	Ref
Proband 1	HTZ missense	Proline residue, high mature: precursor ratio of uromodulin protein	UMOD	c.C518G	p.P173R	4	AD	Japan	[10]
Proband 2	HTZ missense	Altered evolutionary conserved residues in encoding UMOD gene	UMOD	c.187T>C	p.Cys63Arg	3	AD	Korea	[11]
Proband 3	HTZ missense	Co-segregation with disease, altered cysteine residue of uromodulin	UMOD	c.1382C>A	p.Ala461Glu	6	AD	Korea	[12]
Proband 4	HTZ missense	Co-segregation of disease phenotypes	UMOD	c0.667 TG	G, p.223, Cysteine	3	AD	China	[19]
Proband 5	missense	Ca-binding EGF-like domains of uromodulin protein	UMOD	c.189C > G	C63W	4	AD	Turkey	[20]
Proband 6	HTZ missense	Mutation in UMOD encoding uromodulin protein (THP)	UMOD	c.920A ⟶ C	p.K307 T	5	AD	Portugal	[21]
Proband 7	Sequence variant	Loss of a cysteine residue in the EGF domain of uromodulin protein	UMOD	c (0).2297> C	Cys77Arg	4	AD	Poland	[24]
Proband 8	HTZ substitution	Aminoacid substitution	UMOD	T403G	c.135G	4	AD	Japan	[25]
Proband 9	Homo nonsense	Aminoacid substitution	UMOD	c.589G>T	p.E197X	3	AD	Iran	[26]
Proband 10	HTZ missense	Altered evolutionary conserved residues in encoding UMOD gene	UMOD	c.688T>C	p. Trp 230Arg	4	AD	Japan	[27]
Proband 11	No gene mutation identified	No causal gene identified, new monogenic cause	UMOD, REN, HNF1β-negative	–	–	–	AD	UK	[28]
Proband 12	HTZ transversion mutation	Aminoacid substitution and significant conformational change	UMOD	c.891T>G	p.C297W	4	AD	Hungary	[29]
Proband 13	HTZ transversion mutation	Aminoacid substitution and significant conformational change	UMOD	c.891T>G	p.C297W	4	AD	Hungary	[29]
Proband 14	HTZ transversion mutation	Aminoacid substitution and significant conformational change	UMOD	c.891T>G	p.C297W	4	AD	Hungary	[29]
Proband 15	HTZ transversion mutation	Aminoacid substitution and significant conformational change	UMOD	c.891T>G	p.C297W	4	AD	Hungary	[29]
Proband 16	missense mutation	1. Conserved cysteine to glycine aminoacid substitution in uromodulin zona pollucida domain 2. Delay protein export to the PM due to insertion in ER 3. Uromodulin deficiency 4. Co-segregation	UMOD	c.1039T>G	p.C347G	6	AD	Berlin	[32]

Table 5 Genetic characteristics of patients with inherited tubulointerstitial kidney disease in the present study *(Continued)*

Case	Status	Pathogenic factor (s) for clinical relevance	Mutation gene	Nucleotide change	Effect on coding sequence (a.a change)	Region (exon)	Type of inheritance	Race/ ethnicity	Ref
Proband 17	Missense mutation	1. conserved cysteine to glycine aminoacid substitution in uromodulin zona pollucida domain 2. delay protein export to the PM due to insertion in ER 3. Uromodulin Deficiency 4. Co-segregation	UMOD	1039T>G	p.C347G	6	AD	Berlin	[32]
Proband 18	HTZ	1. Co-segregation	UMOD	C744G	Cys248Trp	6	AD	Italy	[33]
Proband 19	HTZ	1.Reduction of urinary excretion of UMOD 2. Co-segregation	UMOD	C744G	Cys248Trp	4	AD	Turkey	[33]
Proband 20	HTZ	Co-segregation	UMOD	C744G	Cys248Trp	4	AD	German	[33]
Proband 21	HTZ	Reduction of urinary excretion of UMOD	UMOD	C744G	Cys248Trp	4	AD	Switzerland	[33]
Proband 22	HTZ	1. Highly conserved of the cysteine residues in the UMOD protein throughout evolution 2. Co-segregation	UMOD	T229G	Cys77Gly	4	AD	USA	[33]
Proband 23	HTZ missense	1. Altered disulfide bond formation due to substitution, retention in ER leading to unfolded protein response and apoptosis 2. Highly conserved of the cysteine residues in the UMOD protein throughout evolution 3. Co-segregation	UMOD	c.949T>G	p.C317G	5	AD	India	[38]
Proband 24	HTZ missense	1. Altered disulfide bond formation due to substitution, retention in ER leading to unfolded protein response and apoptosis 2. Highly conserved of the cysteine residues in the UMOD protein throughout evolution 3. Co-segregation	UMOD	c.949T>G	p.C317G	5	AD	India	[38]
Proband 25	HTZ missense	Mutation in EGF1 domain, misfolding of the UMOD protein	UMOD	c.163G>A	p.Gly55Ser	4	AD	Brazil	[42]
Proband 26	–	–	UMOD	–	–	–	AD	USA	[43]
Proband 27	Homozyous missense	–	UMOD	c.263G>A	p.Gly88Asp	–	AR	Turkey	[44]
Proband 28	HTZ missense	ZP domain of uromodulin protein	UMOD	c.1648G>A	p.V550I	8	AD	China	[45]
Proband 29	–	–	UMOD	c.517G>A	p.proP173Ala	3	AD	Spain	[46]
Probands 30	HTZ	Protein deposits of misfolded uromodulin leading to misfolded protein accumulation in ER and ER stress, absence of uromodulin in apical membranes	UMOD	c.707C>G	p.pro236Arg	3	AD	Caucasian	[47]
Proband	HTZ missense	1. Accumulation of uromodulin into ER	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]

Table 5 Genetic characteristics of patients with inherited tubulointerstitial kidney disease in the present study *(Continued)*

Case	Status	Pathogenic factor (s) for clinical relevance	Mutation gene	Nucleotide change	Effect on coding sequence (a.a change)	Region (exon)	Type of inheritance	Race/ ethnicity	Ref
31		2. Maturation impairement 3. Severe reduction of uromodulin excretion							
Proband 32	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]
Proband 33	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]
Proband 34	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]
Proband 35	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]
Proband 36	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]
Proband 37	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C317Y	950G>A	5	AD	Italy	[48]
Proband 38	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C315R	943T>C	5	AD	Italy	[48]
Proband 39	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C315R	943T>C	5	AD	Italy	[48]
Proband 40	HTZ missense	1. Accumulation of uromodulin into ER 2. Maturation impairement 3. Severe reduction of uromodulin excretion	UMOD	c.C315R	943T>C	5	AD	Italy	[48]

AD autosomal dominance, *ER* endoplasmic reticulum, *HTZ* heterozygous, *PM* plasma membrane, *UMOD* uromodulin

Treatment

Treatment modalities in two inherited tubular diseases are as follows:

ITIKD

Uric acid lowering therapy (UALT) is the best known therapy for hyperuricemia in ITIKD. In this study, prevalence of used drugs included UALT, e.g., allopurinol in 12 patients (12/40, 30%) and benzbromaron and colchicine in one patient (1/40, 2.5%). Other modalities of treatment contained renal replacement therapy [hemodialysis (HD) and peritoneal dialysis (PD)] in three patients (3/40, 7.5%) with ITIKD. Before and after treatment, mean ± SD values of sUA levels in ITIKD contained 6.19 ± 1.15 and 0.54 ± 0.23 mg/dl, respectively. Mean ± SD values of SCr levels before and after UALT resulted to 2.25 ± 0.48 and 1.93 ± 2.33 mg/dl, respectively.

iRHUC

There is no particular therapy for renal hypouricemia with limiting excessive exercise being recommended for preventing ALPE. Hydration with normal saline, diuretics, rest, and renal replacement therapy (RRT) are used for conservative therapy. Non-steroidal anti-inflammatory drugs (NSAID) must not be used in these patients because they may worsen to AKI via increased vasoconstriction. Avoidance of strenuous anaerobic exercise may prevent from repeated EIARF. Xanthine oxidase (XO) inhibitor use, e.g., allopurinol or febuxostat may be beneficial by lowering filtered UA. Allopurinol was used in one patient (1/25, 4%) with iRHUC. The rationale for use of allopurinol in this hypouricemic patient was to decrease the generation of UA, thus decreasing the filtered UA load and lowering the risk of precipitation of UA in the tubules. Other modalities of treatment contained RRT in five patients (5/25, 20%) of iRHUC (Additional file 7: Table S7).

Follow-up and outcome

Primary and secondary endpoints of two inherited tubulopathy are as follows (Additional file 8: Table S8):

ITIKD

In this study, serum UA levels has been assessed in five patients (5/40, 12.5.8%) after treatment with UALT but there was insufficient data in one patient (1/40, 2.5%) in ITIKD. Mean time of blood sampling for initial normal serum UA levels after drug treatment in these patients has been calculated, 24.66 ± 22.89 months with median time of 10 months. Outcome of hyperuricemia in renal disease include ESKD, kidney transplantation, TIF as primary endpoints and cardiovascular events, and metabolic syndrome and proteinuria as secondary endpoints. Eight patients of ITIKD (8/40, 20%) progressed to ESKD, and 12 patients (12/40, 30%) showed TIF in kidney biopsy. There was insufficient data about kidney transplantation in patients with ITIKD. There was proteinuria in one patient (1/40, 2.5%) with ITIKD in the present study. None of patients developed CVD and metabolic syndrome.

iRHUC

Mean time of blood sampling for initial normal serum UA levels after admission in these patients has been calculated, 15.25 ± 8.85 months with median of 13 months and IQR. Outcome of hypouricemia in renal disease include ESKD, kidney transplantation as primary endpoints and cardiovascular events, metabolic syndrome, nephrolithiasis, and proteinuria as secondary endpoints. One patient (1/25, 4%) progressed to ESKD, and one patient showed tubulointerstitial lesion on kidney biopsy in idiopathic renal hypouricemia. None of patients developed CVD, metabolic syndrome, or any of the components of metabolic syndrome. There was nephrolithiasis in two patients (2/25, 8%) with iRHUC.

Discussion

ITIKD

Familial juvenile hyperuricemic nephropathy is an autosomal-dominant condition characterized by defective urinary concentrating ability, gouty arthritis, interstitial nephritis, and chronic renal failure. It is a genetically heterogeneous condition, caused due to mutation in five genes: uromodulin (UMOD) (40%), renin (2.5%), hepatocyte nuclear factor-1 beta (2.5%), mucin 1 (MUC1), and SEC 61A1. Biochemical hallmarks of the disease are hyperuricemia out of proportion to the degree of renal failure and reduced fractional uric acid excretion. Finally, it is important to diagnose FJHN as a cause of CKD. The presence of asymptomatic renal insufficiency, normal urine sediment, evidence of tubulointerstitial nephropathy, and a positive family history in a patient should prompt testing for hyperuricemia and FEUA. In the present study, 19 patients (19/40, 47.5%) in ITIKD were male and 21 patients (21/40, 52.5%) were female. Hyperuricemia is a readily modifiable risk factor, rendering considerable clinical importance to a construct linking uric acid to CKD, and this entity complicated CVD. In fact, a study by Tangri et al supported the hypothesis that asymptomatic hyperuricemia is a CKD and CVD risk factor [52]. In our study, any advanced work up for CVD was performed and only work up for cardiac evaluation was electrocardiography. While uric acid was once the lonely dinner conversation for those suffering from gout or kidney stones, it is now being evaluated as a potential master conductor in the worldwide symphony of obesity, diabetes, and cardiorenal disease. Hyperuricemia

Table 6 Summary of inherited tubulopathy results in the present study

Study results	ITIKD	iRHUC
Prevalence	40/65 (61.5%)	25/65 (38.4%)
Age (years)		
Mean age ± SD	25.29 ± 14.69	18.83 ± 10.59
Male	21 ± 10.21	18.46 ± 10.36
Female	29.17 ± 16.87	20.01± 11.22
p-value:	0.07	0.78
Sex		
Male	47.5%	76%
Female	52.5%	24%
Symptoms		
Not mentioned	50%	
Gouty attacks	20%	
Asymptomatic	15%	
Loin pain		36%
EI-AKI		40%
Abdominal pain		32%
Vomiting		28%
Decreased urine volume		12%
Nausea		12%
Stone passage		8%
Signs		
Not mentioned	37.5%	12%
Normal physical examination	27.5%	12%
Oliguria		8%
Tophi with whitish discharge	5%	
Costovertebral angle tenderness		16%
Laboratory data		
sUA > 6 in male and > 7 mg/dl in female	77.5%	
Mean ± SD		
sUA ≥ 5.5 mg/dl	9.55 ± 2.55 mg/dl	
sUA< 2 mg/dl		0.91 ± 0.5 mg/dl
SCr (mg/dl)	2.14 ± 1.77 mg/dl	3.58 ± 2.52 mg/dl
eGFR		
Stage 0 & I		
Stage II	7.5%	4%
Stage IIIa	7.5%	
Stage IIIb	2.5%	
Stage IV	5%	4%
Hb (Mean±SD)	9.75 ± 1.45 g/dl	12.5 ± 0.29 g/dl
FEUA (Mean±SD)	4.25 ± 1.47 %	87.22 ± 73.2 %
Serum Bun (Mean±SD)	81.41 ± 47 mg/dl	79.7 ± 50.08 mg/dl
Proteinuria (Mean±SD)	810.33 ± 356.8 mg/day 62.96 ±	702.15 ± 97.85 mg/day
Genetic testing		
UMOD		
Heterozygous	75%	
Homozygous	5%	
Compound HTZ		
Not mentioned	20%	
Mutation		
Missense	60%	
Nonsense	2.5%	
Deletion		
Exon region		
Exon 4	35%	
Exon 5	32.5%	
Exon 3	12.5%	
Race		
Italian	27.5%	
Hungary	10%	
Japanese	7.5%	
German	7.5%	
URAT1 (SLC22A12)		
Prevalence		16/25 (64%)
Homozygous		8/16 (50%)
HTZ		4/16 (25%)
Compound HTZ		4/16 (25%)
Mutation		
Missense		3/16 (18.7%)
Deletion		3/16, (18.7%)
Nonsense		2/16 (12.5%)
?Partial deletion		6.25%
Male		13/16 (81.2%)
Female		3/16 (18.7%)
Exon region		
Exon 3, 7		12 %
cExon 1, 4, 5		8 %
Exon 8, 9, 11		4 %
sUA< 1 mg/dl		4/16 (25%)
EI-AKI		7/16 (43.7%)
Nephrolithiasis		12.5%
Race		

Table 6 Summary of inherited tubulopathy results in the present study *(Continued)*

Study results	ITIKD	iRHUC
Czech Republic		4/16 (25%)
Japanese		4/16 (25%)
Korean		3/16 (18.7%)
GLUT9 (SLC2A9)		
Prevalence		8/25 (32%)
Homozygous		6/8 (75%)
Heterozygous		1/8 (12.5%)
Compound heterozygous		1/8 (12.5%)
Mutation		-
Missense		3/8 (37.5%)
Nonsense		5/8 (25%)
Exon region		
Exon 3		3/8 (37.5%)
Exon 5		2/8 (25%)
Exon 7,11		1/8 (12.5%)
Race		
Czech		4/8 (50%)
Chinese		1/8 (12.5%)
Pakistani		1/8 (12.5%)
Caucasian		1/8 (12.5%)
Chromosomal analysis		
48 XXYY		1/25 (4%)
Gene analysis		NA
Imaging Renal US		
Small-sized	45%	
NI-sized kidney		32%
Renal cyst	30%	
Pathology		
ATN		4%
ATI		8%
Paranchymal damage	2.5%	
Interstitial edema		8%
Tubular atrophy	25%	
Interstitial fibrosis	30%	
Tubulointerstitial lesion (moderate)		4%
Treatment		
Allopurinol	30%	4%
Benzbroamaron and colchicine	2.5%	
RRT	7.5%	
sUA levels before & after treatment		
Mean±SD	6.19 ± 1.15 and 0.54 ± 0.23 mg/dl	
SCr levels before and after (mg/dl)		
Mean±SD	2.25 ± 0.48 and 1.93 ± 2.33 mg/dl	
Outcome		
ESKD	20%	4%
TIF	30%	
TIL	2.5%	4%
Proteinuria		
Nephrolithiasis		8.3%
Follow/UP		
Mean time of initial sUA after treatment	24.66 ± 22.89 months	15.25 ± 8.85 months
Median	10 months	13 months

ATI acute tubular injury, *ATN* acute tubular necrosis, *eGFR* estimated glomerular filtration rate, *EI-AKI* exercise-induced acute kidney injury, *ESKD* end-stage kidney disease, *FEUA* fractional excretion of uric acid, *IRH* idiopathic renal hypouricemia, *ITIKD* inherited tubulointerstitial kidney disease, *NA*, not available, *RRT* renal replacement therapy, *SCr* serum creatinine, *SD* standard deviation, *TIF* tubulointerstitial fibrosis, *TIL* tubulointerstitial lesion

and its association with obesity and various components of metabolic syndrome have been documented in previous studies. Elevated uric acid may turn out to be one of the more important remediable risk factors for metabolic and cardiovascular diseases [53]. Furthermore, in clinical practice, hyperuricemia is an indication for investigating MS criteria and the presence of MS is an indication for investigating the serum UA concentration [54]. There was insufficient data in our study, and none of patients had metabolic syndrome or any of components of its syndrome in the present study. Several studies have shown an association between hyperuricemia and AKI, and a study by Kaushik et al discussed about this association. Early identification and modification of these risk factors may help prevent or favorably influence the outcome of AKI [55, 56]. An accumulating body of evidence implicates gout and/or uric acid elevation as an independent predictor for hypertension, atrial fibrillation, and cardiovascular disease. It is well accepted that hyperuricemia is associated with crystal-related pathologies such as nephrolithiasis. In population-based studies, hyperuricemia was shown to be an independent risk factor for developing T2DM. Recent findings suggest that uric acid is an inflammatory factor may have a role in endothelial dysfunction and act as a mediator of diabetic nephropathy (DN). In a study by Behradmanesh et al., serum uric acid had a significant positive association with DN. It might be hypothesized that serum uric acid plays a role in DN in T2DM [57]. The relationship between uric acid and kidney function seems to be two-sided. On the one hand, a decline in eGFR (kidney function parameter) may

lead to elevation of uric acid; on the other hand, an increase in uric acid seems to alter glomerular function through renal vasoconstriction and increased rennin expression while our study was not revealed association between elevated sUA levels and SCr or eGFR [58]. The majority of mutations so far published are clustered in exon 4 between codons 52 and 282, and most of those are missense mutations affecting cysteine residues of UMOD gene. In the present study, the majority of mutations (14/40, 35%) were located in exon 4 and this finding was consistent with UMOD mutations reported in the literature review. Probands with exon 4 mutations had nephritis with gout or hyperuricemia, even in the absence of family history. Now, it is recommended that exon 5 should be included in the initial sequencing effort [20, 21]. As previously mentioned, this study resulted that mutations in exon 5 was associated with higher sUA levels versus lower sUA levels in other exons. Exon 4 contains 3 calcium binding epidermal growth factor (cbEGF)-like domains, between residues 31 and 148. A fourth potential cbEGF-like domain extends from aminoacids 281-336, throughout exon 5. They contain six conserved cysteine residues responsible for the proteins tertiary structure, as a result of intramolecular disulfide bonding. It has been hypothesized that protein misfolding, consequence of mutations in these cbEGF-like domains, may affect uromodulin intracellular trafficking and lead to cellular protein accumulation and apoptosis. The release of cells debris and uromodulin aggregates in the interstitium could stimulate an inflammatory response and, in addition, be responsible for tubular obstruction and medullary cyst formation. It has been proposed that hyperuricemia in these patients is secondary to a reduced TAL sodium reabsorption with volume contraction and a compensatory increase in proximal urate reabsorption. A study by Li et al evaluated 200 Chinese CKD patients for 24-h UAE, UACl, FEUA, and albuminuria. They suggested that urinary uric acid excretion is negatively associated with albuminuria and serum uric acid [59]. In our study, there was insufficient data for proteinuria and albuminuria for determining correlation between albuminuria and 24-h UAE, UACl, and FEUA.

iIRHUC

Idiopathic or inherited renal hypouricemia characterized by impaired renal tubular uric acid reabsorption was first reported in 1972. As previously said, loss-of-function mutations in URAT1 coded by SLC22A12 gene on chromosome 11q13 and mutation in GLUT9 encoded by SLC2A9 gene on chromosome 4p15.3-p16 cause renal hypouricemia type 1 and 2. GLUT9 mediates renal urate reabsorption on both sides of proximal tubular cells. URAT1 is expressed only on the apical side and is indirectly coupled with Na^+ -anion cotransporters, such as monocarboxylic acid transporter1/2 (MCT1/2) [60]. For this reason, the renal UA absorption defect is more severe in SLC2A9-associated hypouricemia than in hURAT1-associated disease, thus explaining why SLC22A12 mutations had less severity of nephrocalcinosis or uric acid stone versus SLC2A9 mutations. Unexpectedly "normal" serum UA in acute renal failure (ARF) is an important clue to renal hypouricemia. In order to elucidate the genetic defect in this disorder, other candidate genes need to be identified for iRHUC patients without SLC22A12 and SLC2A9 gene mutations. The SLC2A9 genetic variants are responsible for a portion of the variance in serum UA concentrations: 5–6% in females and 1–2% in males. Patients with iRHUC are usually asymptomatic and often incidentally discovered after an episode of EI-AKI without rhabdomyolysis. However, a long-term follow-up of patients with iRHUC showed decreased ability of urine concentration, uric acid nephrolithiasis, hematuria, and progressive renal interstitial fibrosis. The pathogenesis of EI-AKI in iRHUC remains unclear. Two mechanisms have been initially proposed. One mechanism is acute uric acid nephropathy due to increased uric acid production from adenosine triphosphate (ATP) degradation during exercise. The other is oxidative stress from free oxygen produced

Table 7 Correlation between biochemical tests together and biochemical tests and genetic testing in inherited tubulointerstitial kidney disease and inherited renal hypouricemia

Statistical analysis	ITIKD	iRHUC	Interpretation
Correlation between SCr and sUA	No correlation (*p* value 0.26)	No correlation (*p* value 0.07)	Effect of sUA changes on kidney dysfunction and effect of kidney dysfunction on sUA levels changes
Correlation between SCr and FEUA	No correlation (*p* value 0.139)	No correlation (*p* value 0.27)	Effect of FEUA changes on kidney dysfunction and effect of kidney dysfunction on FEUA changes
Correlation between eGFR and sUA	No correlation (*p* value 0.175)	–	Effect of decreased eGFR on sUA changes
Correlation between Hb and sUA levels	No correlation (*p* value 0.72)		
Correlation between sUA and exon region	No correlation (*p* value 0.30)	Presence of correlation (*p* value 0.037)	Effect of exon region of UMOD and SCL2A9 gene mutations on changes of sUA levels

eGFR estimated glomerular filtration rate, *FEUA* fractional excretion of uric acid, *Hb* hemoglobin, *iRHUC* inherited renal hypouricemia, *ITIKD* inherited tubulointerstitial kidney disease, *SCr* serum creatinine, *sUA* serum uric acid, *UMOD* uromodulin

during exercise. A third mechanism had been proposed subsequently for EI-AKI. That is, reduced clearance of urate-coupled anions by human urate transporter 1(hURAT1) due to loss-of-function mutations of either hURAT1 or GLUT9 may exert toxic effects on renal proximal tubules, leading to toxic acute tubular necrosis [61]. In the present study, EI-AKI was seen in ten patients (10/25, 40%) before disease symptoms in iRHUC and was high risk for this entity. Moreover, 16 of the patients (16/25, 64%) with iRHUC in this study were found to have SLC22A12 mutations (iRHUC1). Thirteen of these SLC22A12 mutations (13/16, 81.2%) were identified in male patients and three probands were female (3/16, 18.7%). Furthermore, seven of the patients with SLC22A12 gene mutations had exercise-induced AKI (7/16, 43.7%) and two patients with this mutation revealed nephrolithiasis in ultrasonography (2/16, 12.5%). These findings were in agreement with study by Ichida et al., and these findings indicate that SLC22A12 was responsible for the majority of renal hypouricemia genetically [62]. In the present study, eight of patients (8/25, 32%) with iRHUC were found to have SLC2A9 mutations (iRHUC2) and that three of those were preceded with EI-AKI (3/8, 37.5%). Moreover, this present study revealed significant correlation between sUA levels and exon region of SLC2A9 mutation. The other important point in patients with SLC2A9 gene mutation is homozygous or heterozygous status. Five patients (5/8, 62.5%) with homozygous SLC2A9 gene mutations had severe sUA levels, and one patient (1/8, 12.5%) with heterozygous SLC2A9 mutation was found to have moderately low sUA levels. This finding was in agreement with studies by Cha et al. and Dinour et al. that concluded homozygous or compound heterozygous mutation of SLC2A9 gene had a much significant effect on UA lowering, that is UA was near zero and heterozygous mutation has a significant effect on lowering UA level and [63, 64]. The endpoint in our study was the presence of insufficient data for proteinuria and albuminuria for determining correlation between albuminuria, 24-h UACl, UAE, and FEUA. Summary of results have been tabulated as frequency and mean ± SD in Tables 6 and 7. There were limitations in this study. There was insufficient data in electronic records. For the reliable genotype-phenotype relations, more patients were needed to be analyzed for predicting phenotype-genotype associations of genetic disorders.

Conclusions

Uric acid is a real risk factor for the development of metabolic, renal, and cardio vascular diseases. The cell membrane urate transporters are responsible for the intra-extracellular uric acid shift, and hence, they are important determinants of the offending role of uric acid. Low uric acid levels might carry high risk similar to the high levels. The present study revealed high prevalence of FJHN-UMOD and association between mutations in exon region of 5 with higher sUA levels. Furthermore, the majority of probands in iRHUC had SLC22A12 gene mutations rather than SLC2A9 mutations. Moreover, the other important result in the present study was the presence of significant correlation between exon region of mutated SLC2A9 gene and sUA levels in iRHUC. From this point of view that inherited tubulointerstitial kidney disease are underrecognized and underreported disease and hypouricemia is often regarded as an unrecognized or neglected disorder, urate concentration in serum and urine may provide an initial indication of tubular defect of uric acid before sequencing analysis is performed. Then, genetic testing can be decision-making based on serum and urine uric acid concentrations. It is obvious that early recognition of these rare genetic disorders by nephrologists helps in its diagnosis, treatment, and prevention in further probands.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s41100-020-0258-z.

Additional file 1: Table S1a, b. JBI critical appraisal tool for case reports in included articles of AD-TIKD and iRHUC.

Additional file 2: Table S2. Raw data of age and sex parameters in inherited tubulopathy.

Additional file 3: Table S3a. Data of symptoms in inherited tubulointerstitial kidney disease and inherited renal hypouricemia. **Table S3b.** Data of signs in patients with inherited tubulointerstitial kidney disease and inherited renal hypouricemia.

Additional file 4: Table S4a, b, c. Data of laboratory findings in inherited tubulointerstitial kidney disease and inherited renal hypouricemia.

Additional file 5: Table S5. Raw data of genetic analysis in clinical studies.

Additional file 6: Table S6. Raw data of imaging modalities in clinical studies.

Additional file 7: Table S7. Raw data of treatment modalities in clinical studies.

Additional file 8: Table S8. Raw data of follow-up in clinical studies.

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Authors' contributions

The authors contributed in the study concept, design, data collection, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review and being the guarantor. The authors read and approved the final manuscript.

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Author requested that the datasets be presented in additional supporting files.

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Authors of published articles stated that research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. They described that subjects (or their parents or guardians) were given their informed consent and study protocol was approved by the institute's committee on human research.

Consent for publication
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Competing interests
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