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PHYSICIAN CONNECT

Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Physician Connect" which contains latest and interesting news.

This issue contains:

1. Relationship between skin sodium content and blood pressure response with renal denervation
2. Comparison of four histological grading methods for autoimmune hepatitis to enhance diagnostic sensitivity
3. Evaluation of the kidney function trajectory, related variables, and outcomes in individuals with type 2 diabetes
4. Case report on recurrent exercise-induced acute kidney injury linked to hypouricemia

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Looking forward to your valuable feedback.

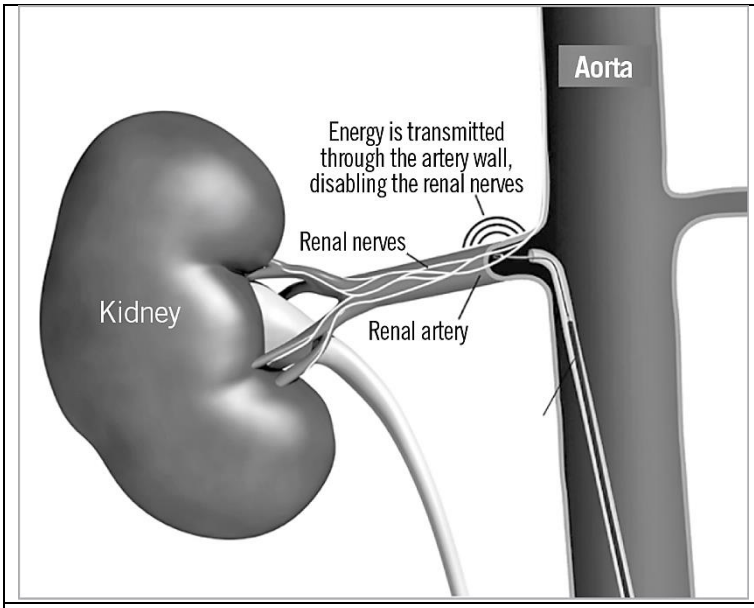
Best Regards,

Medical Team, Micro Labs Limited.s

Relationship between skin sodium content and blood pressure response with renal denervation

Introduction:

Hypertension is a controllable risk factor for cardiovascular disease, contributing significantly to mortality and morbidity globally. The Global Burden of Disease Study 2017 conducted a systematic study which revealed that the primary risk factor for both death and disability-adjusted life-years was high systolic blood pressure (SBP). Although the definition of hypertension varies per guideline, the indications for antihypertensive medication are generally consistent.[1] In individuals with HTN, the prevalence of treatment-resistant hypertension (TRH) was almost 10%. The pathophysiology of TRH has been discovered to be significantly influenced by increased sodium (Na) retention and increased sympathetic nervous system (SNS) activity. In addition to medication and lifestyle modifications, the ESH 2021 and ESC 2023 consensus statements suggested renal denervation (RDN) as an additional therapeutic option to help individuals with uncontrolled TRH achieve blood pressure management. Patients with TRH have high sodium (Na) levels in their muscles and skin.[2] The purpose of this study was to determine if tissue Na concentration in individuals with TRH predicts their blood pressure (BP) response to RDN.



Renal denervation therapy for hypertension

Methods:

In this single-centre, post-hoc investigation, RDN and Na-MRI were performed on 58 individuals with uncontrolled TRH. Office and 24-hour ambulatory blood pressure were recorded at baseline and 6 months later. Prior to RDN, tissue Na content was assessed by Na-MRI at baseline. In this study, study participants were divided into responders and non-responders based on the median systolic 24-hour ambulatory blood pressure (ABP) drop after 6 months. The relationship between BP response to RDN and tissue Na content in skin and muscle was also investigated.

Results:

This study involved 58 patients, with an average age of 62 years. The majority of patients were male and overweight. Approximately 50% of the individuals had type 2 diabetes (T2D). After six months of RDN, 24-hour ABP fell by -8.6/-4.7 mmHg. Low tissue salt concentration in the skin ($p = 0.040$), female gender ($p = 0.027$), aldosterone antagonist consumption ($p = 0.032$), high baseline 24-hour night-time heart rate ($p = 0.045$), and high LDL cholesterol ($p < 0.001$) were the characteristics of BP-Responders. This study found that six months following RDN, there was a link between baseline 24-hour systolic ABP and BP response ($r = -0.394$, $p = 0.003$). Furthermore, the BP response and skin sodium concentration were correlated ($r = 0.339$, $p = 0.013$) (Figure 1). Skin and muscle Na contents were 20.9 ± 4.3 AU and 20.6 ± 4.4 AU, respectively, at baseline. The skin and muscle Na content did not alter six months after RDN (20.9 ± 4.3 AU compared baseline 21.1 ± 4.9 AU; $p = 0.915$ and 20.6 ± 4.4 AU versus baseline 20.9 ± 4.0 AU; $p = 0.683$).

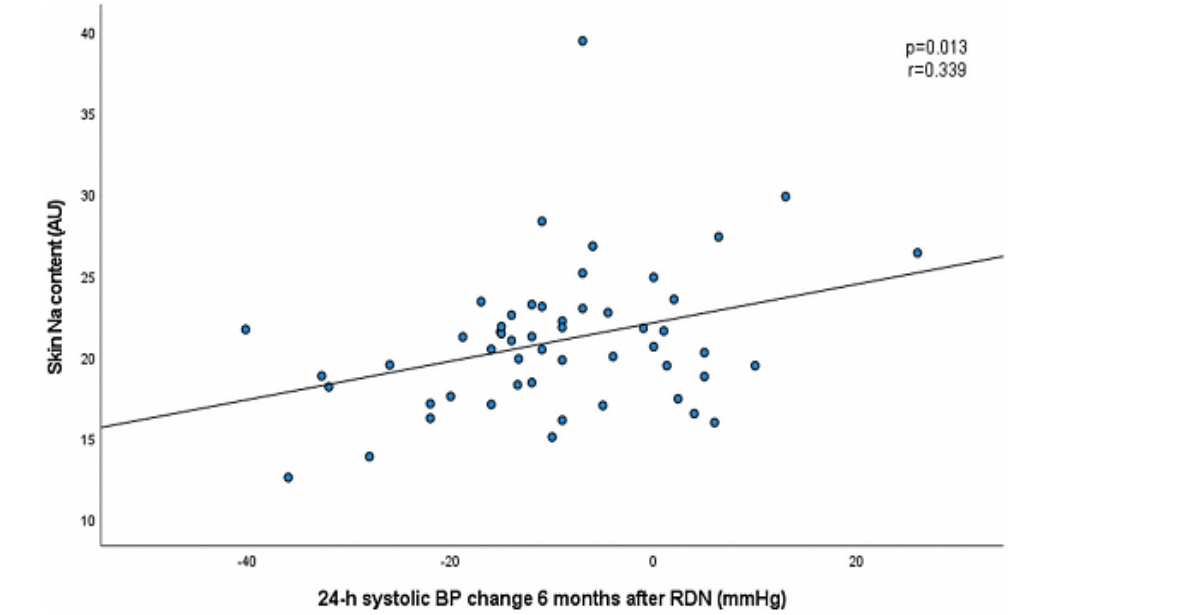


Fig 1: Correlation between the baseline skin sodium content and the 24-hour systolic ambulatory blood pressure change at 6 months post renal denervation

Discussion:

The current study found that six months after RDN, office BP decreased by -12.9/-7.7 mmHg and 24-hour ABP decreased by -8.6/-4.7 mmHg. In this study, there was no change in the Na content of the skin or muscles six months after RDN.[2] Similarly, Ott et al. conducted Na-MRI on 41 individuals who received RDN and found no change in tissue Na concentration after 6 months.[3]

Conclusion:

This study concluded that baseline 24-hour ABP Na-MRI, in addition to clinical criteria, may help identify individuals with uncontrolled TRH for RDN therapy.

Prior to Renal denervation (RDN), Na-MRI can help identify patients with treatment resistant hypertension (TRH) who have a BP decrease above the median, making them ideal candidates for the procedure.

Reference:

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Comparison of four histological grading methods for autoimmune hepatitis to enhance diagnostic sensitivity

Introduction:

Autoimmune hepatitis (AIH) is an inflammatory liver disease that can affect individuals of various ages, genders, and ethnicities. AIH is defined by the presence of autoantibodies, hypergammaglobulinemia with specific IgG rise, and interface hepatitis on liver histology. Early diagnosis is challenging due to the diverse clinical picture and lack of standardized tests.[1] AIH is diagnosed based on clinical symptoms, test results (e.g., elevated liver enzymes, serum immunoglobulin G [IgG], and autoantibodies), histological findings, and elimination of alternative causes. The International Autoimmune Hepatitis Group (IAIHG) introduced diagnostic scoring systems in 1993, which were refined in 1999 and simplified in 2008 to identify a homogenous sample of AIH patients for study. AIH diagnosis requires a liver biopsy, as represented in the histology components of the 1999 and 2008 IAIHG systems. The IAIHG's 1999 and 2008 scoring systems have limitations for identifying autoimmune hepatitis (AIH) based on histological criteria.[2] This study assessed the histology components of four scoring systems in AIH patients: the revised original scoring system ("1999 IAIHG"), the simplified scoring system ("2008 IAIHG"), the modified histologic criteria ("2017 UCSF"), and the new histologic criteria proposed by the International AIH Pathology Group ("2022 IAHPG").

Methods:

This retrospective analysis examined the liver biopsies and medical records of 68 individuals from two separate medical facilities who were diagnosed with AIH between 2006 and 2016 using the 1999 IAIHG method. The four histological scoring systems were compared, and the histology characteristics were thoroughly examined. The histology scores of the 2008 IAIHG system (maximum of 2 points) and the 1999 IAIHG system (maximum of 5 points) were computed for each case. This study assessed the modified histology ratings for the 2017 UCSF and 2022 IAHPG proposals. This study applied the 2022 IAHPG system's categories of "likely AIH" (2 points), "possible AIH" (1 point), and "unlikely AIH" (0 point) to the 2008 IAIHG system.

Results:

Of the 68 patients whose clinical characteristics were examined, 55 (80.9%) were female. When the patients were diagnosed, the mean age was 58 years old (range:20–87), and 16 patients (23.5%) had a BMI greater than 25 kg/m^2. 32 individuals (47.1%) had an acute presentation or worsening of their condition. At the time of diagnosis, thirty-six (52.9%) patients had symptoms, such as nausea, stomach pain, and jaundice, and one (1.5%) patient

had hepatic decompensation. Out of 68 patients, 56 (82.4%) satisfied the "probable" or "definite" AIH criteria of the 2008 IAIHG classification. Additionally, 40/68 (58.8%) had histologic score 2 (maximum). The number of histology score 2 patients increased to 60/68 (88.2%) and the number of "probable" or "definite" AIH cases increased to 61/68 (89.7%) by using the 2017 UCSF criteria. Using the 2022 IAHPG histology score, the majority of patients (64/68; 94.1%) had histologic score 2 and were diagnosed as "probable" or "definite" AIH (62/68; 91. 2%).The pre-treatment criteria were used for the 1999 IAIHG (updated original score system). By the 1999 IAIHG method, all patients satisfied the definite or probable criteria (60.3% deemed "definite," 39.7% deemed "probable"). The histologic score component had a mean value of 4.43 and ranged from 0 to 5, which was the maximum histology score. The maximum histologic score of five was assigned to 50 (73.5%) instances using this approach (Table 1).

	1999 IAIHG			2008 IAIHG			2008 IAIHG+2017 UCSF			2008 IAIHG+2022 IAHPG		
Histology score	1	4	5	0	1	2	0	1	2	0	1	2
	7 (10.3)	11 (16.2)	50 (73.5)	0 (0)	28 (41.2)	40 (58.8)	1 (1.5)	7 (10.3)	60 (88.2)	0 (0)	4 (5.9)	64 (94.1)
Total score	Probable (≥10)		Definite (≥16)	Probable (≥6)		Definite (≥7)	Probable (≥6)		Definite (≥7)	Probable (≥6)		Definite (≥7)
	68 (100)		41 (60.3)	56 (82.4)		42 (61.8)	61 (89.7)		44 (64.7)	62 (91.2)		45 (66.2)

Values are presented as number (%).
IAIHG, International Autoimmune Hepatitis Group; IAHPG, International Autoimmune Hepatitis Pathology Group.

Table 1: Validation of the overall patients (n = 68) autoimmune hepatitis scoring systems

Discussion:

While the 1999 IAIHG scoring system was considered the gold standard for diagnosing AIH, it was designed primarily for research and was too complex to be used in routine clinical practice. In order to offer a diagnostic criterion that was simpler to apply, the Simplified criteria were presented in 2008.[2] Previous study by Lohse AW et al. suggested that the 2008 IAIHG system's histology component may underestimate probable AIH cases. Proposals have been made to improve the system's diagnostic sensitivity.[3] In this retrospective investigation, histological score component of four AIH scoring systems in 68 patients who were diagnosed with AIH were analysed using the 1999 IAIHG system. It was to be expected that among the four scoring systems, the 2008 IAIHG method had the lowest sensitivity (82.4% for "Probable or definite AIH").[2]

Conclusion:

The histology score of AIH was raised by the recently suggested UCSF/IAHPG histological standards.The sensitivity for diagnosing AIH (≥"Probable AIH") increased from 82.4% to 91. 2% when the histology component of the 2008 IAIHG system was replaced with the 2022 IA HPG criteria.

The sensitivity for diagnosing Autoimmune hepatitis AIH (≥"Probable AIH") increased from 82.4% to 91.2% when the histology component of the 2008 IAIHG system was replaced with the 2022 IAHPG criteria.

Reference:

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Evaluation of the kidney function trajectory, related variables, and outcomes in individuals with type 2 diabetes

Introduction:

Diabetes, one of the most prevalent chronic illnesses in the world, raises the risk of renal and cardiovascular problems. Elevations in glycated haemoglobin (HbA1c) significantly increase the risk of micro and macrovascular problems.[1] The prevalence of diabetes mellitus (DM) has significantly increased over the past few decades and was expected to rise by roughly 17% (237 million) between 2019 and 2045. This will significantly increase the incidence of end stage kidney disease (ESKD) and diabetic kidney disease (DKD). Patients with diabetes have been shown to have significant differences in the patterns or trajectories of their estimated glomerular filtration rate (eGFR). Diabetes patients' kidney function varies, highlighting the importance of risk assessment, early prevention, and constant monitoring to prevent rapid loss of function. Just a few number of studies on the long term renal function trajectories of Asians with diabetes have been done.[2] The purpose of this study was to investigate the trajectory of estimated glomerular filtration rate (eGFR), related risk variables, and eGFR's link to end-stage kidney disease (ESKD) in a patient population of type 2 diabetics from various ethnic backgrounds.

Methods:

In this follow-up study, 62,080 type 2 diabetics who were at least 18 years old were included in a multi-institutional SingHealth Diabetes Registry. Latent class linear mixed models were utilized for the analysis of eGFR trajectories. Multinomial logistic regression was used to assess factors related to eGFR trajectories. The relationship between eGFR trajectories and ESKD was evaluated through the use of competing risk models. The chronic eGFR trajectories assessed by quarterly average eGFR served as the primary research outcome. The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate GFR based on factors such as age, gender, race, and serum creatinine measurement levels. ESKD was the secondary outcome.

Results:

The trajectory of kidney function, as indicated by eGFR, was not linear. The trajectory pattern was first identified as steady, followed by progressive decline (21.9%), fast decrease (3.1%), and gradual decline (75%). Progressive or rapid decline was linked to younger age, female sex, Malay ethnicity, lower-class housing type, smoking at the time, higher glycated hemoglobin, lower low-density lipoprotein, higher triglyceride, uncontrolled blood pressure, albuminuria, cardiovascular disease, hypertension, and higher eGFR levels. Progressive eGFR reduction

raised the risk of ESKD by 6.14-fold (95% CI: 4.96-7.61), whereas rapidly drop increased the risk by 82.55-fold (95% CI: 55.90-121.89). The current study identified three trajectory classes using modified models: class 1, which was steady at first and subsequently declined gradually; class 2, which declined gradually; and class 3, which declined quickly. The majority of participants were in class 1 (n = 46,572, 75.0%), followed by class 2 (n = 13,586, 21.9%) and class 3 (n = 1922, 3. 1%). The standard linear mixed model found that persons in classes 1 to 3 experienced eGFR drop rates of -1.06 (-1.07, -1.05), -4.54 (-4.57, -4.52), and -9.93 (-9.99, 9.86) mL/min/1.73 m2 per year, adjusted for age (Table 1).

	% of sample	Mean (SD) baseline eGFR (mL/min/1.73 m^2)	Slope (95% CI) (mL/min/1.73 m^2/year)	*p* value
Class 1	76.0	82.4 (23.2)	−1.06 (−1.07, −1.05)	<.001
Class 2	20.6	81.5 (20.3)	−4.54 (−4.57, −4.52)	<.001
Class 3	3.4	87.7 (18.6)	−9.93 (−9.99, −9.86)	<.001

Abbreviations: eGFR, estimated glomerular filtration rate; 95% CI, 95% confidence interval.

Table 1: Annual eGFR change adjusted for age across various trajectories

Discussion:

Three different eGFR trajectories for individuals with type 2 diabetes were found in the current study: stable then gradual decline, progressive decline, and rapid decline.[2] In consistent with this result a previous study by Jiang G et al. found four non-linear eGFR trajectories: slow decline, curvilinear decline, progressive decline and accelerated decline.[3] In contrast, a study of 24,723 Chinese patients with prediabetes or diabetes found that around 86% had steady or rising eGFR trajectories.[4]

Conclusion:

Three nonlinear trajectory classifications of kidney function were discovered among multi-ethnic people with type 2 diabetes. One out of every four people experienced a gradual or quick drop in eGFR. The current study indicated that eGFR trajectories were linked to many social and modifiable risk variables, influencing the likelihood of ESKD.

In a current investigation, individuals with type 2 diabetes showed three unique eGFR trajectories: gradual decline, progressive decline, and rapid decline.

Reference:

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3. Jiang G, Luk AOY, Tam CHT, et al. Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with type 2 diabetes. Kidney Int. 2019;95:178-187.
4. Zuo Y, Wang A, Chen S, Tian X, Wu S, He Y. Distinct eGFR trajectories are associated with risk of myocardial infarction in people with diabetes or prediabetes. J Diabetes. 2021;13:124-133.

Case report on recurrent exercise-induced acute kidney injury linked to hypouricemia

Introduction:

Renal hypouricemia (RHUC) is caused by a hereditary deficiency in the uric acid reabsorption system, namely SLC22A12 (URAT1) and SLC2A9 (GLUT9). RHUC is defined by a reduction in serum uric acid concentration and an increase in its excreted portion. The biochemical indicators include hypouricemia and increased fractional excretion of uric acid (UA) (FE-UA). Clinically, urolithiasis, nephrolithiasis, and acute kidney injury—which frequently happens after physical exertion—present as symptoms of the condition in certain individuals. Although no medication was available, allopurinol has been used to prevent recurrent acute renal injury episodes.[1] The prevalence of renal hypouricemia ranges from 0.15 to 0.72%. Two kinds of RHUC have been identified. Mutations in the SLC22A12 gene (OMIN #220,150) and the SLC2A9 gene (OMIN #612,076) cause RHUC1 and RHUC2, respectively. RHUC2 demonstrated more clinical variability than RHUC1. Patients who were compound heterozygous or homozygous for RHUC2 had much lower blood UA levels (approaching zero) and greater renal excretion (exceeding 100%). In contrast, heterozygous RHUC2 family members have normal amounts of UA.[2] This was a unique instance of a patient with RHUC2 who had two heterozygous mutations in the SLC2A9 gene and manifested symptoms of recurrent EIAKI.

Case presentation:

A 43-year-old man was hospitalized for 3 days of bilateral loin pain, nausea, and sleeplessness following strenuous activity. He did not have oliguria, hematuria, or myalgia. There was no history of nephrolithiasis and the family history was normal. He regularly used amlodipine, an antihypertensive medication. Upon admission, his blood pressure was 167/103 mmHg. The other physical check-up was unremarkable.

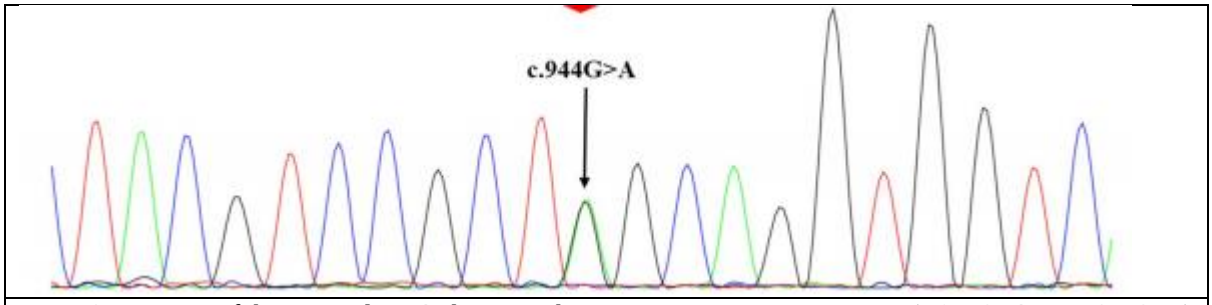

Fig 1. Sequencing of the mutated DNA showing a heterozygous nonsense mutation (c.944G>A, pTrp315Stop) in exon 7

The laboratory findings showed elevated levels of BUN (15 mmol/l) and Scr (450 μmol/l), whereas UA levels were exceedingly low at 32 μmol/l (0.54 mg/dl). His creatine kinase, lactate dehydrogenase, and complete blood count were normal. Urine protein level was 0.39 g (normal range <150 mg), protein/creatinine ratio was 417 mg/g (normal range <200 mg/g), albumin/creatinine ratio was 260 mg/g (normal range <30 mg/g), and urine β2 microglobulin

was 0.57 mg/l (normal range <0.2 mg/l). He had normal-sized kidneys with no signs of blockage, according to his renal ultrasonography. Within a week, his renal function improved spontaneously, and urine revealed no protein. A kidney biopsy was not conducted based on the data above. The patient experienced an acute kidney damage after playing soccer over 20 years ago. The patient's Scr reached 900 μmol/l and returned to normal within a month without dialysis. During his previous admission, his Scr was 65 μmol/l, BUN was 5 mmol/l, and UA was less than 30 μmol/l (0.50 mg/dL). Due to hypouricemia and elevated FE-UA, RHUC was suspected, prompting mutation screening of the SLC22A12 and SLC2A9 genes. DNA sequencing found no alterations in the SCL22A22 gene, but two heterozygous mutations in the SLC2A9 gene. In the next generation sequencing (NGS) data, copy number variation (CNV) analysis revealed that the SLC2A9 gene's exons 4 and 5 had been deleted. Using the qPCR-SYBR Green I technique, a 146 bp heterozygous deletion (chr4: 9,982,216–9,982,361) in exon 5 of the SLC2A9 gene was confirmed. Additionally, a heterozygous nonsense mutation (c.944G>A, pTrp315Stop) that was present in exon 7 of the SLC2A9 gene resulted in the introduction of an early "stop" codon (Figure 1). His renal function significantly improved two months after he was discharged from the hospital (Scr returned to 75 μmol/l), indicating that his kidneys had recovered from AKI (Figure 2).

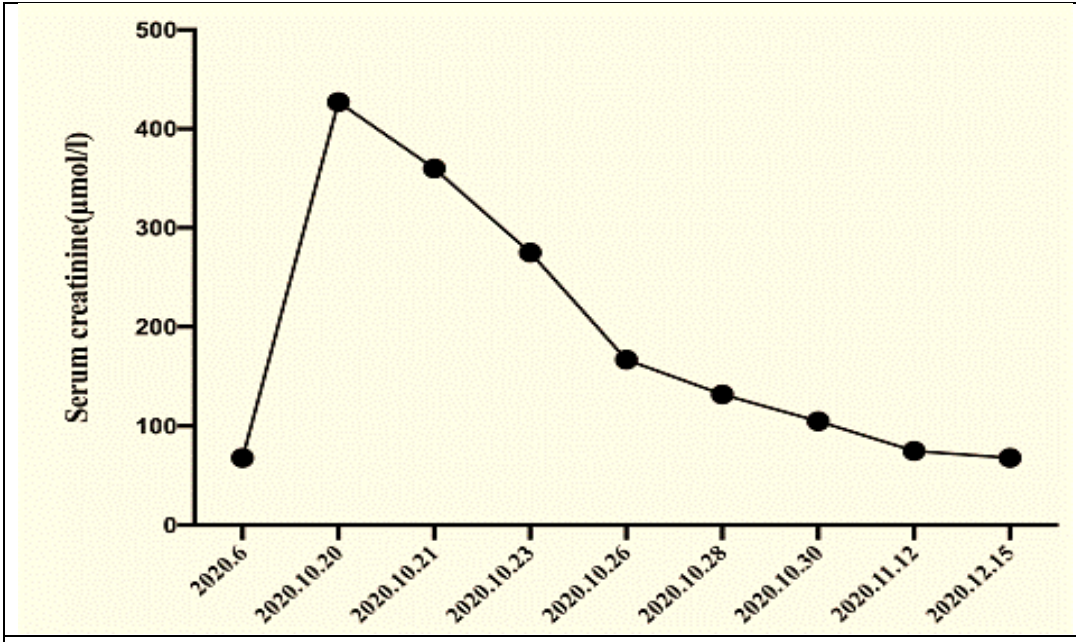

Fig 2. Serum creatinine evolution

Discussion:

There are two types of RHUCs. RHUC1 was caused by mutations in the SLC22A12 gene, which encodes a renal urate-anion exchanger called urate transporter1(URAT1). Mutations in the SLC2A9 gene, which codes for the high-capacity glucose and urate transporter known as glucose transporter 9 (GLUT9), result in RHUC2. There have been 18 recorded cases of EIAKI due to SLC2A9 mutations, with the majority having homozygous or compound heterozygous mutations. The exact mechanism of RHUC causing EIAKI is yet unclear. Exercise-induced oxidative stress from reactive oxygen species causes renal vasoconstriction, ischemia, and

oxidant damage, leading to decreased glomerular filtration rate and ATN.[2] In a previous study by Miyamoto D et al. found no significant differences in oxidative stress indicators between RHUC patients and healthy individuals before and after exercise.[3]

Conclusion:

This report of a patient who has RHUC2 as a result of the GLUT9-encoding SLC2A9 mutation. When patients exhibit reduced or normal blood concentrations of UA and symptoms of recurrent AKI, especially after vigorous exercise, the diagnosis of RHUC should be taken into consideration in clinical practice.

In clinical practice, the diagnosis of renal hypouricemia (RHUC) should be considered when patients have decreased or normal blood concentrations of uric acid (UA) together with symptoms of recurrent acute kidney injury (AKI), especially after severe physical activity.

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