function to Worse in Diabetes

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Abstract

Background: It’s unclear the exact level of serum urate acid (SUA) which can prevent renal function worse although all internists has been known the target of blood glucose, blood pressure and lipid in diabetes. It’s time to aim for a reasonable SUA target to prevent renal failure in diabetes.

Methods: Using the physical examination results of 3427 diabetic patients in Jiangchuan Community, Shanghai, China, the relationship between SUA and estimated glomerular filtration rate (eGFR) decline was analyzed, and the appropriate cut-off point for SUA to predict eGFR decline was determined. Meanwhile, the population attributable risk proportion (PARP) of eGFR decline in diabetic patients
above this SUA cut-off point was calculated.

**Results:** eGFR decreased accompany with the increased SUA level and was negatively associated with the level of SUA significantly. After adjusting for potential confounders, SUA also was an independent risk factor of eGFR decline. The best appropriate SUA point, predicting eGFR decline obtained by ROC curve, was 326.5μmol/L which may prevent from eGFR decline in 33% male patients and 355.5μmol/L which may prevent from eGFR decline in 18% female patients. Compared with SUA>326.5μmol/L male and SUA>355.5μmol/L female group respectively, the relative risk of eGFR decline in SUA≤326.5μmol/L male and SUA≤355.5μmol/L female group is decreased significantly.

**Conclusions:** SUA is an important risk factor for eGFR decline in diabetes. 326.5μmol/L in male and 355.5μmol/L in female may be used as the reasonable SUA target to retard renal function to worse in Chinese diabetes.

**Keywords:** Diabetes; Renal function; Serum urate acid; Target

**Background**

Impaired renal function, often deteriorating continuously and resulting to end-stage renal disease, is the common chronic complication in diabetes. Diabetic kidney disease (DKD) has become the main cause in patients requiring renal replacement therapy [1, 2]. It’s important to look for controllable risk factors to take appropriate measures to inhibit diabetic renal function to worse.
Previous study has shown that serum urate acid (SUA) is an independent risk factor for renal function damage in new-onset kidney disease [3,4]. However, it is still unknown the SUA concentration target for initiating or continuing treatment to retard renal function to worse and prevent end-stage renal disease in diabetes while all internists know the target of blood sugar, glycosylated hemoglobin A1c (HbA1c) and blood lipid in diabetes[5,6,7].

Therefore, an appropriate target concentration for SUA to prevent renal function worse, assessed by estimated glomerular filtration rate (eGFR), was investigated on the base of the relationship between SUA and eGFR, estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, in diabetic patients via the physical examination data of 3427 diabetic patients in Jiangchuan Community, Shanghai, China, from October 2011 to September 2014. It will help initiate or continue to lower SUA concentration therapy to retard the renal function decline in Chinese diabetes.

**Methods**

**Study population**

The physical examination is free provided by government in diabetic patient residing in Jiangchuan Community, Minhang District, Shanghai City. From October 2011 to September 2014, 3427 diabetic patients, including 1475 males and 1952 females, with complete information and signed informed consent were included in our study.
Research methods

Questionnaire, physical examination and laboratory measurements were completed by professionals. Name, age, gender and history of hypertension were included in the questionnaire. Meanwhile, height, weight, waist circumference, hip circumference and blood pressure of the patients were measured as physical examination. Blood routine, fasting blood sugar (FBG), glycosylated hemoglobin A1c (HbA1c), blood lipids, serum creatinine and urate acid were detected using blood of diabetic patients fasted for 8 hours while urine albumin-to-creatinine ratio (UACR) was detected using urine in the morning.

Relevant Definition

(1) Definition of diabetes is fasting venous blood glucose $\geq 7.0\text{mml/L}$ and/or 2h postprandial blood glucose $\geq 11.1\text{ mmol/L}$ and/or previous diagnosis of diabetes. (2) Evaluation of GFR (eGFR) was calculated by CKD-EPI formula. $\text{eGFR}=141\times(\text{Scr/K})^{a}\times(0.993)^{\text{age}}\times1.018$ (female). The K value is female=62 and male= 80 in the formula. The value is as follows: female Scr$>62$ then $a=-1.209$ and Scr$\leq 62$ the $a=-0.329$; male Scr$>80$ then $a=-1.209$ and Scr$\leq 80$ then $a=-0.411$. The unit of age is years, serum creatinine is mg/dl and eGFR is ml•min$^{-1}$•(1.73 m$^{2}$)$^{-1}$. (3) eGFR$<90$ ml•min$^{-1}$•(1.73 m$^{2}$)$^{-1}$ is defined as eGFR decrease. (4) Body Mass Index (BMI) = body weight (kg) / square of height (m$^{2}$). (5) Waist-to-Hip Ratio (WHR) = Waist (cm) / hipline (cm).
**Statistical analysis**

All data were analysed by SPSS version 22. The categorical variables were expressed as composition ratio (%). The difference between groups was performed by Chi-square test. The Linear correlation was performed by Pearson correlation analysis. The risk factor analysis was performed by unconditional binary logistic regression. The receiver operating characteristic curve (ROC) analysis was used to determine the appropriate cut-off point of SUA as a reference indicator for indicating eGFR decline. Population Attributable Risk Percentage (PARP%) = \(100 \times \frac{P \times (OR-1)}{P \times (OR-1) + 1}\) (P = percentage of the population above the cut-off point in the all study population).

**Results**

**General Data**

3427 diabetic patients from Jiangchuan Community were enrolled in the study, including 1475 males aged 35-92 years with 68.85 ± 8.66 averaged years old, and 1952 females aged 37-92 years with 67.76 ± 8.71 averaged years old. The prevalence of eGFR decline in all patients was 38.97% (1353/3472). In addition, the prevalence of eGFR decline in males (46.51%, 686/1475) was significantly higher than that in females (34.17%, 667/1952) (Table 1A).
Table 1A  Prevalence of eGFR decline in patients

| Parameter | Total (3427) | Male (1475) | Female (1952) |
|-----------|--------------|-------------|---------------|
|           | ≥90 <90      | ≥90 <90     | ≥90 <90       |
| N         | 2074 1353    | 789 686     | 1285 667      |
| Proportion| 59.73% 38.97%| 53.49% 46.51%| 65.83% 34.17%|

Subsequently, the subjects were grouped according to the SUA quartile. Accompany with the increase of SUA, age and triglyceride (TG) gradually increased while eGFR, fasting blood glucose (FBG), high density lipoprotein-cholesterol (HDL-C) and glycosylated hemoglobin A1c (HbA1c) gradually decreased significantly in males (Table 1B). Similarly, in females, accompany with the increase of SUA, age, systolic blood pressure (SBP), total cholesterol (TC), TG, low density lipoprotein-cholesterol (LDL-C), leukocyte and urinary albumin creatinine ratio (UACR) gradually increased while eGFR, FBG, HDL-C, HbA1c and hemoglobin (Hb) decreased markedly (Table 1C).

Table 1B  General clinical data of male diabetic patients

| Parameter | SUA≤293 | 345≥SUA>293 | 403≥SUA>345 | SUA >403 | P value |
|-----------|---------|-------------|-------------|----------|---------|
| N         | 374     | 367         | 368         | 366      |         |
| Age(years)| 67.99±8.69 | 68.71±8.51 | 68.66±8.58  | 70.07±8.76*,# | 0.011   |
| SBP(mmHg) | 132.82±15.86 | 136.29±60.76 | 133.49±15.58 | 135.41±16.23 | 0.453   |
| DBP(mmHg) | 80.14±8.51  | 80.83±8.24  | 81.92±35.48 | 83.22±38.92 | 0.429   |
Compared with SUA$\leq 293$, *$p<0.05$; compared with 345$\geq$SUA$>293$, $\Delta p<0.05$; compared with 403$\geq$SUA$>345$, $\# p<0.05$.

Systolic blood pressure (SBP); diastolic blood pressure (DBP); body mass index (BMI); waist-to-hip ratio (WHR); estimated glomerular filtration rate (eGFR); serum urate acid (SUA); fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG); high Density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), glycosylated hemoglobin A1c (HbA1c); hemoglobin (Hb) and urinary albumin creatinine ratio (UACR).

| Parameter | Female | P value |
|-----------|--------|---------|
|           | SUA$\leq$259.5 | 303$\geq$SUA$>259.5$ | 350$\geq$SUA$>303$ | SUA$>350$ |
| N         | 488    | 490     | 497     | 477     |
Compared with SUA ≤ 259.5, *p<0.05; compared with 303 ≥ SUA > 259.5, ▲ p<0.05; compared with 350 ≥ SUA > 303, # p<0.05.

### Analysis of the linear correlation between SUA and eGFR

The results from Pearson correlation analysis show that SUA was positively correlated with age, TG and Leukocyte, but negatively correlated with eGFR, FBG,
HDL-C and HbA1c (Table 2). Furthermore, SUA was most closely associated with eGFR (male r=-0.377; female r=-0.419). The results suggested a linear negative correlation between SUA and eGFR significantly.

| Variables   | Total (n=3427) | Male (n=1475) | Female (n=1952) |
|-------------|----------------|---------------|-----------------|
|             | r value        | P value       | r value         | P value        | r value       | P value       |
| Age         | 0.128          | <0.001        | 0.078           | 0.003          | 0.147         | <0.001        |
| SBP         | 0.049          | 0.004         | 0.019           | 0.470          | 0.095         | <0.001        |
| DBP         | 0.004          | 0.800         | 0.075           | 0.004          | <0.001        | 0.987         |
| BMI         | 0.034          | 0.049         | 0.033           | 0.207          | 0.050         | 0.026         |
| WHR         | 0.043          | 0.012         | 0.046           | 0.077          | 0.011         | 0.619         |
| eGFR        | -0.414         | <0.001        | -0.377          | <0.001         | -0.419        | <0.001        |
| FBG         | -0.155         | <0.001        | -0.194          | <0.001         | -0.150        | <0.001        |
| TC          | -0.019         | 0.277         | 0.054           | 0.037          | 0.053         | 0.019         |
| TG          | 0.149          | <0.001        | 0.203           | <0.001         | 0.158         | <0.001        |
| HDL-C       | -0.250         | <0.001        | -0.177          | <0.001         | -0.210        | <0.001        |
| LDL-C       | -0.003         | 0.849         | 0.010           | 0.688          | 0.058         | 0.011         |
| HbA1c       | -0.152         | <0.001        | -0.187          | <0.001         | -0.154        | <0.001        |
| Leukocyte   | 0.161          | <0.001        | 0.076           | 0.004          | 0.214         | <0.001        |
| Hb          | 0.055          | 0.001         | -0.030          | 0.257          | -0.068        | 0.003         |
| ACR         | 0.073          | <0.001        | 0.057           | 0.027          | 0.096         | <0.001        |
Effects of SUA on eGFR

The risk for eGFR decline increased significantly with OR of 0.21 (95% CI, 0.15 to 0.28), 0.41 (95% CI, 0.30 to 0.55), 0.60 (95% CI, 0.44 to 0.80) and 1 for quantiles 1 through 4 in male and OR of 0.21 (95% CI, 0.16 to 0.28), 0.37 (95% CI, 0.29 to 0.48), 0.43 (95% CI, 0.33 to 0.55) and 1 for quantiles 1 through 4 in female, respectively. After adjustment for baseline age, SBP, DBP, BMI, WHR, FBG, TC, TG, HDL, LDL, HbA1c, Leukocyte, Hb and UACR, SUA was still found an independent risk factor for eGFR decline, with adjusted OR of 0.16 (95% CI, 0.12 to 0.26), 0.39 (95% CI, 0.26 to 0.56), 0.59 (95% CI, 0.41 to 0.86) and 1 for quantiles 1 through 4 in male and adjusted OR of 0.15 (95% CI, 0.10 to 0.23), 0.39 (95% CI, 0.27 to 0.57), 0.49 (95% CI, 0.34 to 0.71) and 1 for quantiles 1 through 4 in female, respectively (Table 3). The results suggested that SUA is an independent risk factor for eGFR decline in both male and female patients.

Table 3  The effect of SUA on eGFR via binary logistic regression analysis [OR (95% CI)]

| Variables | Male | Female |
|-----------|------|--------|
|           | Q1   | Q2     | Q3    | Q4    | P value | Q1   | Q2     | Q3    | Q4    | P value |
| Unadjusted| 0.21 | 0.41   | 0.60  | 1     | 0.001   | 0.21 | 0.37   | 0.43  | 1     | <0.001 |
|           | (0.15-0.28) | (0.30-0.55) | (0.44-0.80) |     |          | (0.16-0.28) | (0.29-0.48) | (0.33-0.55) |     |          |
| Model 1   | 0.15 | 0.34   | 0.59  | 1     | 0.005   | 0.14 | 0.34   | 0.45  | 1     | <0.001 |
|           | (0.10-0.22) | (0.23-0.49) | (0.41-0.85) |     |          | (0.09-0.21) | (0.30-0.49) | (0.32-0.65) |     |          |
| Model 2   | 0.14 | 0.34   | 0.60  | 1     | 0.004   | 0.14 | 0.35   | 0.46  | 1     | <0.001 |

Model 1, adjustment for baseline age; Model 2, adjustment for baseline SBP, DBP, BMI and WHR on the basis of model 1; Model 3, adjustment for baseline other components on the basis of Model 2.

The best cut-off point of SUA for predicting eGFR decline

The cut-off point of SUA obtained by ROC curve was used as the appropriate point for the prognosis of eGFR decline. It was 326.5μmol/L in male and 355.5μmol/L in female respectively. At the points, the sensitivity was 0.727, the specificity was 0.530, and the area under the curve was 0.669 (95% CI, 0.64 to 0.696) (Figure 1), population attribution eGFR decline population risk (PARP) was 33.799% in male patients while the sensitivity was 0.369, the specificity was 0.855, the area under the curve was 0.659 (95% CI, 0.633 to 0.684) (Figure 1), and PARP was 18.943% in female patients (Table 4A, 4B).

![ROC curve for SUA cut-off point to predict eGFR decline in patients](image-url)
Table 4A  The appropriate cut-off points of SUA in patients

|       | Cut-point | PPV(%) | NPV(%) | Sensitivity | 1-specificity | Youden’s index |
|-------|-----------|--------|--------|-------------|---------------|----------------|
| Male  | 326.5     | 57.354 | 69.068 | 0.727       | 0.470         | 0.257          |
| Female| 355.5     | 56.925 | 72.294 | 0.369       | 0.145         | 0.224          |

Positive predictive value (PPV); Positive predictive value (NPV)

Table 4B. PARP in eGFR decline (SUA 326.5μmol/L in male and 355.5 in female, respectively)

| Variables | OR (95%CI)       | PARP (%) |
|-----------|------------------|----------|
| Male      | 3.591(2.692-4.789) | 33.799   |
| Female    | 3.251(2.359-4.482) | 18.943   |

**Analysis on the relative risk of eGFR decline at different SUA levels**

Patients were divided into two groups according to SUA 326.5μmol/L in male while SUA 355.5μmol/L as cut-off point in female. Subsequently, binary logistic regression analysis was used to find the significant risk of eGFR decline at different SUA levels.

The results show that the OR in SUA≤326.5μmol/L male group is 0.331, with adjusted OR of 1.0 for SUA>326.5μmol/L male group, and the OR in SUA≤355.5μmol/L female group is only 0.290, with adjusted OR of 1.0 for SUA>355.5μmol/L female group (Table 5).
Table 5  OR from the relative risk of eGFR decline at different SUA levels in diabetic patients (95% CI)

|        | Male                  | Female                |
|--------|-----------------------|-----------------------|
| SUA≤326.5 | SUA>326.5 | P value | SUA≤355.5 | SUA>355.5 | P value |
| 0.331 | 1 | <0.001 | 0.290 | 1 | <0.001 |
| (0.266-0.412) | | | (0.232-0.361) | |

Discussion

Diabetes, a chronic systemic metabolic disease characterized by long-term hyperglycemia, leads to glomerular filtration rate (GFR) decline via continuous impairment of renal function and has been the main cause in end stage renal disease (ERSD) [8]. The GFR decline still hasn’t been inhibited though the treatment has been actively used in controlling risk factors such as blood sugar, blood pressure, blood lipid and the renin-angiotensin system [9-12].

Previous studies have shown that hyperuricemia is an independent risk factor for renal dysfunction [13]. But it’s still unknown the SUA target concentration to prevent renal function worse although all internists has been known the target of blood glucose, blood pressure and lipid in diabetes. It’s time to aim for a reasonable serum urate target to retard renal function to worse in diabetes.

Therefore, the physical examination data from diabetic patients in Jiangchuan community, Shanghai City, China, were used to find out the SUA reasonable target on
the base of the relationship between SUA and eGFR in this study. It is the first time to elaborate the appropriate SUA target for treatment to retard eGFR decline in Chinese diabetic patients.

The results from this study showed that the overall prevalence of eGFR decline in the patients with diabetes was 38.97%, including 46.51% for men and 34.17% for women. eGFR levels gradually decreased accompany with the SUA increase in both male and female patients. At the same time, age and TG were gradually increased while FBG, HDL-C, and HbA1c were decreased gradually in male. Similarly, age, SBP, TC, TG, LDL-C, Leukocyte and UACR were increased while FBG, HDL, HbA1c and Hb were decreased gradually in female.

Subsequently, Pearson correlation analysis was used to find out the eGFR related linear factors. The results showed that SUA was positively correlated with age, TG, and Leukocyte but negatively correlated with eGFR, FBG, HDL, and HbA1c in both male and female diabetic patients. Among them, SUA has the closest relationship with eGFR (male, r=-0.377; female, r=-0.419). Our results are similar to other findings [14-16] in which SUA, age, TG, Leukocyte and HDL-C are significant correlated with eGFR levels. Glomerular hyperfiltration induced by hyperglycemia [17] could increase the urate acid excretion. It may the reason that the level of SUA negatively correlated with FBG and HbA1c.
Furthermore, binary logistic regression was used to analyze the effect of SUA on eGFR to further determine the relationship between SUA and eGFR. After adjustment for age, SBP, DBP, BMI, WHR, FBG, TC, TG, HDL, LDL, HbA1c, Leukocyte, Hb and UACR, SUA still was an independent risk factor for eGFR decline in both male and female with diabetes, with adjusted OR of 0.18 (95% CI, 0.12 to 0.26), 0.38 (95% CI, 0.26 to 0.56), 0.59 (95% CI, 0.41 to 0.86) and 1 for quantiles 1 through 4 in male and adjusted OR of 0.15 (95% CI, 0.10 to 0.23), 0.39 (95% CI, 0.27 to 0.57), 0.49 (95% CI, 0.34 to 0.71) and 1 for quantiles 1 through 4 in female, respectively. The risk of eGFR decline in Q1 group (SUAn ≤ 293 μmol/L, OR=0.18 [95% CI, 0.12 to 0.26]) was only 0.18 times of Q4 group in male while the risk of eGFR decline in Q1 group (SUAn ≤ 259.5 μmol/L, OR=0.14 [95% CI, 0.10 to 0.23]) was 0.15 times that of the Q4 group.

These results show that the SUA was an independent risk factor for eGFR decline and negative linear correlated with eGFR in diabetic patients. Higher urate acid is associated with lower eGFR in Chinese diabetes. It supports that we should find out the reasonable SUA target for treatment to protect the renal function in diabetes.

Initial threshold of treatment for reducing urate acid remains controversial in asymptomatic CKD patients with hyperuricemia [18, 19]. Moreover, the appropriate target level of SUA to prevent renal function worse in diabetic patients is still unknown. Therefore, we further explored the appropriate cut-off point of SUA on the
base of the relationship between SUA and eGFR via ROC curve according to male and female patients respectively. The eGFR decline was predicted by different SUA cut-off points. SUA cut-off point 326.5μmol/L in male and 355.5μmol/L in female were corresponded to the shortest distance of the ROC curves respectively. It indicated that the cut-off points of SUA had the greatest significance for predicting eGFR decline in male and female patients respectively. Therefore, SUA 326.5μmol/L in male and 355.5μmol/L in female may be used as the SUA target.

In addition, a large proportion of menopausal female patients over 65 years in which lower estrogen levels reduced SUA excretion [20] may be the reason why the SUA target level in female is higher than that in male.

Furthermore, the percentage of the population attributable risk proportion (PARP) at SUA 326.5μmol/L in male and 355.5μmol/L in female was calculated. The results show that 33.799% of eGFR decline could be inhibited after the level of SUA was under 326.5μmol/L in male while 18.943% of eGFR decline could be prevented after SUA below 355.5μmol/L in female. Subsequently, using 326.5μmol/L in male and 355.5μmol/L in female as SUA target, the relative risk of eGFR decline in SUA≤326.5μmol/L in male and SUA≤355.5μmol/L in female group was decreased significantly. It supported to use SUA≤326.5μmol/L in male and SUA≤355.5μmol/L in female as the SUA target which could protect renal function significantly in diabetes. Intervention treatment should to be considered for inhibiting renal function
decline if the level of SUA is higher than 326.5 μmol/L in male and 355.5 μmol/L in female diabetic patient.

Conclusions

Our study show that there is a significant negative linear correlation between the levels of SUA and eGFR, and SUA is an independent risk factor for eGFR decline in Chinese diabetic patient. The level of SUA below 326.5 μmol/L in male and 355.5 μmol/L in female as the target may effectively prevent 33.799% and 18.943% of eGFR decline, respectively. It was the first time to show the SUA target for treatment to inhibit GFR decline and protect renal function in Chinese diabetic patients.

Abbreviations

eGFR: Estimated glomerular filtration rate; SUA: Serum urate acid; PARP: Population attributable risk proportion; DKD: Diabetic kidney disease; HbA1c: Glycosylated hemoglobin A1c; FBG: Fasting blood sugar; UACR: Urine albumin-to-creatinine ratio; BMI: Body mass index; WHR: Waist-to-Hip ratio; TG: Triglyceride; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; Hb: Hemoglobin; ERSD: End stage renal disease.

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Authors’ Contributions

Heyuan Ding analyzed the data and prepared the manuscript. Yong Gu and Jianying Niu contributed to the conception of the study. Yingjun Qian, Qing Wu, and Weifeng Fan participated in collect of the data. Qiaojing Qin designed, analyzed, and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used and analysed during the current study are available from the corresponding author on reasonable request.
Ethical approval

The study was approved by the Ethics Committee of the Fifth People's Hospital of Shanghai in accordance with the principles of the Helsinki Declaration of 1964 and its further amendments or comparable ethical standards. Informed consent was obtained from all individual patients included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References
1. Chen H, Hao L, Yang C, Yan B, Sun Q, Sun L, et al. Understanding the rapid increase in life expectancy in Shanghai, China: a population-based retrospective analysis. BMC Public Health. 2018;18:256.

2. Tang SCW, Yu X, Chen HC, Kashihara N, Park HC, Liew A, et al. Dialysis Care and Dialysis Funding in Asia. Am J Kidney Dis. 2020;75:772-81.

3. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated urate acid increases the risk for kidney disease. J Am Soc Nephrol. 2008;19:2407-13.

4. Fukase H, Okui D, Sasaki T, M Fushimi, T Ohashi, T Hosoya. Effects of Mild and Moderate Renal Dysfunction on Pharmacokinetics, Pharmacodynamics, and Safety of Dotinurad: A Novel Selective Urate Reabsorption Inhibitor. Clin Exp Nephrol. 2020,24:17-24.

5. Jansen TL, Janssen M. Physicians and the 2017 guideline for the management of acute and recurrent gout: treat to avoiding symptoms versus treat to target. Clin Rheumatol. 2017;36:2399-402.

6. American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 ;43 (Suppl 1):S66-76.

7. Sakamoto M, Matsutani D, Minato S, Tsujimoto Y, Kayama Y, Takeda N, et al. Seasonal Variations in the Achievement of Guideline Targets for HbA1c, Blood Pressure, and Cholesterol Among Patients With Type 2 Diabetes: A Nationwide Population-Based Study (ABC Study: JDDM49). Diabetes Care. 2019;42:816-23.
8. Denhez B, Rousseau M, Dancosst DA, Lizotte F, Guay A, Auger-Messier M, et al. Diabetes-Induced DUSP4 Reduction Promotes Podocyte Dysfunction and Progression of Diabetic Nephropathy. Diabetes. 2019; 68:1026-39.

9. Oellgaard J, Gæde P, Rossing P. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney Int. 2017; 91:982-88.

10. Saranburut K, Vathesatogkit P, Thongmung N, Chittamma A, Vanavananan S, Tangstheanphan T, et al. Risk scores to predict decreased glomerular filtration rate at 10 years in an Asian general population. BMC Nephrol. 2017; 18:240.

11. Bjornstad P, Pyle L, Kinney GL, Rewers M, Johnson RJ, Maahs DM, et al. Adiponectin is associated with early diabetic kidney disease in adults with type 1 diabetes: A Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. J Diabetes Complications. 2017; 31:369-74.

12. Mauer M, Doria A. Urate acid and Diabetic Nephropathy Risk. Contrib Nephrol. 2018; 192:103-9.

13. Lytvyn Y, Bjornstad P, Lovshin JA, Singh SK, Boulet G, Farooqi MA, et al. Association between urate acid, renal haemodynamics and arterial stiffness over the natural history of type 1 diabetes. Diabetes Obes Metab. 2019; 21:1388-98.

14. Razi F, Nasli-Esfahani E, Bandarian F. Association of serum urate acid with nephropathy in Iranian type 2 diabetic patients. J Diabetes Metab Disord. 2018; 17:71-75.
15. Kansui Y, Matsumura K, Morinaga Y, Inoue M, Kiyohara K, Ohta Y, et al. Impact of serum urate acid on incident hypertension in a worksite population of Japanese men. J Hypertens. 2018; 36:1499-505.

16. Kawamoto R, Ninomiya D, Kikuchi A, T Akase, Y Kasai, T Kusunoki, et al. Association of neutrophil-to-lymphocyte ratio with early renal dysfunction and albuminuria among diabetic patients. Int Urol Nephrol. 2019; 51: 483-90.

17. Zhang J, Wei J, Jiang S, Xu L, Wang L, Cheng F, et al. Macula Densa SGLT1-NOS1-Tubuloglomerular Feedback Pathway, a New Mechanism for Glomerular Hyperfiltration during Hyperglycemia. J Am Soc Nephrol. 2019; 30:578-93.

18. Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford). 2017; 56: 1056-59.

19. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, et al. Management of Gout: A Systematic Review in Support of an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017; 166: 37-51.

20. Sciacqua A, Perticone M, Tassone EJ, Cimellaro A, Miceli S, Maio R, et al. Urate acid is an independent predictor of cardiovascular events in post-menopausal women. Int J Cardiol. 2015; 197:271-275.