**MEDICAL SCIENCE MONITOR**

# Association between Serum Fructosamine and Kidney Function in Nondiabetic Individuals without Chronic Kidney Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background:  Serum fructosamine (SF) has been considered to be an indicator that estimates glycemic control in patients with diabetes mellitus (DM). There is increasing evidence that SF concentration and oxidative stress are significantly elevated in patients with chronic kidney disease (CKD). However, the data about SF and its association with kidney function are lacking in nondiabetic individuals without CKD. We included 1891 nondiabetic individuals who had not been diagnosed with CKD to determine the association between SF and kidney function.

Material/Methods:  We conducted a retrospective analysis on the basis of the biochemistry database in nondiabetic individuals without CKD.

Results:  When eligible participants were stratified in accordance with SF quartiles, from the bottom to the top quartile of SF, a significant decrease of estimated glomerular filtration rate (GFR) was observed in baseline data. SF concentration was negatively associated with estimated GFR (r=−0.066, P=0.004) in the Pearson correlation analysis. Estimated GFR was associated with SF levels independently of glucose (GLU), total cholesterol (TC), triglyceride (TG), and total protein (TP) in multivariable logistic regression analysis (OR=0.984; CI 95% 0.977–0.991; P<0.001).

Conclusions:  We suggest that mild elevation of SF concentration is associated with estimated GFR in nondiabetic individuals without CKD. These findings indicate that SF may underlie CKD in nondiabetic individuals.

MeSH Keywords:  **Fructosamine • Glomerular Filtration Rate • Renal Insufficiency, Chronic**

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## Background

Chronic kidney disease (CKD) is associated with atherosclerosis in patients with diabetes mellitus (DM) and in nondiabetic individuals [1]. Very recently, a strong association of early CKD and body adiposity index (BAI) has been reported in 67 non-diabetic, obese, out-clinic patients, and suggested that BAI was a valuable predictor of early stages of CKD in patients with obesity [2]. It is generally known that several indicators are associated with CKD in the clinical laboratory such as microalbumin, urine protein, and serum creatinine. Naro Ohashi et al. [3] reported a significant correlation between plasma glucagon-like peptide-1 levels and hemoglobin A1C (HbA1c), and found that plasma glucose levels might be improved by alogliptin in patients with steroid-induced hyperglycemia.

Serum fructosamine (SF) is a marker that estimates glycemic control formed via nonenzymatic processes [4], and that it is similar with glycosylated albumin and reflects glycemic control about 2–3 weeks in patients with DM [5,6]. In clinical practice, SF has been widely used to monitoring glycemic control in patients with DM. Some earlier investigations suggested that SF was a useful indicator for estimating the plasma glucose status in patients with CKD [7], Selvaraj N et al. [8] indicated that SF and oxidative stress were significantly elevated in patients with CKD compared with healthy individuals. However, in the available literature, the data about SF and its association with kidney function lacks data from nondiabetic individuals without CKD. Thus, we included 1891 nondiabetic individuals who had not been diagnosed with CKD to assess the association between SF and kidney function.

## Material and Methods

In this cross-sectional study we included 1891 nondiabetic individuals without CKD. Samples were collected in the morning and all subjects had fasted. Individuals with following diseases and/or situations were excluded: DM, serious cardiovascular disease, hypertension, presence of chronic dialysis, presence of kidney or liver dysfunction, malnutrition, hematologic disease, infectious disease, malignant tumor, mental disorders, and vegetarians. We conducted a retrospective analysis on the basis of the biochemistry database in nondiabetic individuals without CKD. Our study used the Modification of Diet in Renal Disease (MDRD) formula adjusted coefficient of the Chinese people to evaluate glomerular filtration rate (GFR) [7]. The abbreviated MDRD formula is defined as: GFR=186×(serum creatinine$^{-1.154}$) × age$^{-0.203}$×1.233×0.702 (if female). Estimated GFR<60 mL/min/1.73 m$^2$ is considered as outcomes of CKD in this study. The biochemistry tests were performed by the Roche 8000 automatic biochemical analyzer, consecutively, the reference range of serum creatinine is 53–115 umol/L in our laboratory.

## Statistical analysis

The data were described using means ±SD. SF concentration was stratified by quartiles in the study. The $\chi^2$ test and one-way ANOVA were used to test the differences of variables, a correlation analysis between SF and GFR was performed using the Pearson correlation. Multivariable logistic regression analysis was also used to assess the potential factors that were potential relevant to SF concentration (1$^{st}$ versus 4$^{th}$ quartile). The data used SPSS16.0 (SPSS Inc., Chicago, IL, USA) statistical software for statistical analysis. $P<0.05$ was determined as significant.

## Results

In the entire group of participants, there were 1489 males and 402 females, whose mean age was 57 years (range, 18–98 years). Mean values of SF, serum creatinine (Cr), glucose (GLU), total protein (TP), globulin (GLB), albumin (ALB), and estimated GFR were 2.07±0.33 mmol/L, 78.1±15.54 umol/L, 5.47±1.15 mmol/L, 72.1±4.73 g/L, 29.3±4.68 g/L, 42.8±3.21 g/L, and 97.4±22.24 mL/min/1.73 m$^2$, respectively. The main biochemical characteristics of all participants, stratified by SF quartiles, are presented in Table 1. In the baseline, age, triglyceride (TG), total cholesterol (TC), ALB, GLB, GLU, Cr, and GFR significantly changed across SF categories. From the bottom to the top quartile of SF, we observed that estimated GFR in the top quartiles of SF concentration was lower compared with estimated GFR in the lower SF concentration quartiles (99.5±22.21 mL/min/1.73 m$^2$ *vs.* 91.5±21.44 mL/min/1.73 m$^2$).

When we used the Pearson correlation to identify the association between SF concentration and estimated GFR, our results showed that SF concentration was inversely correlated with estimated GFR in all participants (r=–0.066, P=0.004), as shown in Figure 1. In multivariable logistic regression after adjustment for sex, age, values of high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TC, TG, TP, ALB, GLB, GLU, Cr, and GFR, estimated GFR was still associated with SF concentration and it was independent of GLU, TC, TG, and TP (Table 2).

## Discussion

The main finding of this study is that SF concentration is associated with estimated GFR independently of GLU, TC, TG, and TP in nondiabetic individuals without CKD. Decreased kidney function causes a higher incidence and hospital admission rate in heart failure patients [9]. Accumulated data suggest that CKD is a substantial risk factor for patients with endstage renal failure and cardiovascular diseases [10,11]. Coca et al. [12]

**Table 1.** Baseline characteristics of the entire participants by SF quartiles (n=1891).

| SF quartiles (mmol/L) | I ≤1.84 | II 1.84–2.00 | III 2.00–2.26 | IV >2.26 | P-values |
| --- | --- | --- | --- | --- | --- |
| | n=496 | n=469 | n=464 | n=462 | |
| Gender (male/female) | 387/109 | 365/104 | 371/93 | 366/96 | 0.835 |
| Age(y) | 55.2±13.70 | 56.6±14.02 | 57.6±13.27 | 58.7±13.58 | 0.001 |
| High density lipoprotein cholesterol (mmol/L) | 1.3±0.31 | 1.4±0.34 | 1.3±0.33 | 1.3±0.37 | 0.134 |
| Low density lipoprotein cholesterol (mmol/L) | 2.9±0.74 | 3.00±0.77 | 3.1±0.78 | 3.0±0.84 | 0.008 |
| Triglycerides (mmol/L) | 1.6±0.80 | 1.7±1.01 | 1.9±1.13 | 2.4±2.55 | <0.001 |
| Total cholesterol (mmol/L) | 4.6±0.93 | 4.8±1.00 | 4.9±1.03 | 5.0±1.11 | <0.001 |
| Total protein (g/L) | 71.4±4.46 | 71.8±4.91 | 72.4±4.83 | 72.8±4.61 | <0.001 |
| Albumin (g/L) | 43.0±3.16 | 42.7±3.06 | 42.6±3.13 | 42.9±3.47 | 0.169 |
| Globulin (g/L) | 28.4±4.53 | 29.2±4.87 | 29.8±4.51 | 29.9±4.65 | <0.001 |
| Glucose (mmol/L) | 5.2±0.82 | 5.3±0.89 | 5.5±1.14 | 5.8±0.51 | <0.001 |
| Creatinine (umol/L) | 77.1±15.81 | 77.0±16.70 | 78.9±14.92 | 79.4±14.51 | 0.027 |
| Glomerular filtration rate (mL/min/1.73 m$^2$) | 99.5±22.21 | 99.8±25.09 | 95.7±19.39 | 91.5±21.44 | <0.001 |
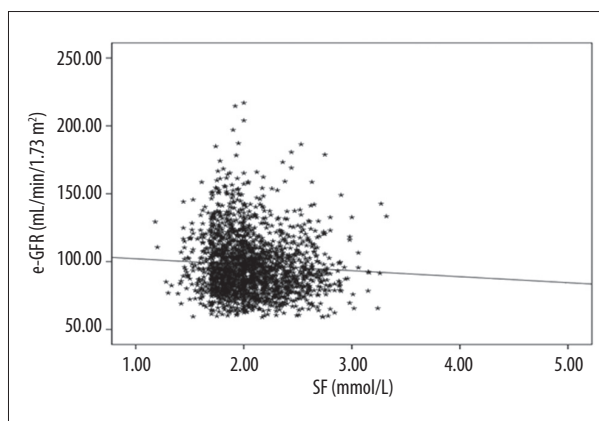


**Figure 1.** Scatter plot presents a negative correlation between SF and estimated GFR.

indicated that serum Cr levels were graded in association with short-term mortality in hospitalized patients, even mild changes in serum Cr concentration. Earlier investigations clearly showed

that oxidative stress and inflammatory factors were links between CKD and cardiovascular complications [13,14]. Very recently, some studies found that methoxy polyethylene glycol-epoetin beta may inhibit oxidative stress through enhancing the antioxidant defense system and reducing reactive oxygen species (ROS) in predialysis patients with CKD [15], Yimaz MI and Xu G et al. [16,17] reported that estimated GFR was negatively associated with malondialdehyde concentration and positively correlated with ROC activity, and that oxidative stress and inflammation alter GFR when CKD develops, which could indicate that oxidative stress and inflammation in the body cause decreased GFR.

In the present study, we found that estimated GFR is associated with increase of SF concentration in nondiabetic individuals without CKD. Importantly, glycation end-products such as SF were reported to be potent immunomodulatory actions, which is associated with the outcomes of ROS production and inflammation [18]. Several lines of evidence show that dietary

**Table 2.** Determinants of SF concentration (1st versus 4th quartile) in the participants analyzed by multiple logistic regression analysis.

| | OR (95% CI) | p-value |
| --- | --- | --- |
| Glucose (mmol/L) | 1.703 (1.474–1.967) | <0.001 |
| Total cholesterol (mmol/L) | 2.983 (2.096–4.254) | <0.001 |
| Triglycerides (mmol/L) | 1.245 (1.080–1.435) | 0.002 |
| Total protein (g/L) | 1.056 (1.022–1.090) | 0.001 |
| Glomerular filtration rate (mL/min/1.73 m$^2$) | 0.984 (0.977–0.991) | <0.001 |

antioxidants are able to reduce tissue glycation and that anti-oxidants play a vital role in preventing protein glycation [19,20], a finding from the study of Vlassopoulos et al. [21] indicating that various factors causing inflammation such as infection or smoking and oxidative stress can promote production of subsequent glycation. SF is a glycation end-product that is accumulated in the body, and may exert antigenic effects and contribute to tissue damage [22]. It is then noteworthy that up to 6% of hemoglobin and 12–16% of serum albumin is glycated through the process of glycation in nondiabetic individuals, and that tissue damage and function loss, through protein glycation, may occur in the pathogenesis of all kinds of chronic diseases, including CKD [23]. Obviously, the above results support that oxidative stress and inflammatory factors can help explain the association between increased SF concentration and reduced GFR in nondiabetic individuals without CKD. However, further research needs to clarify the mechanism between SF and reduced kidney function in nondiabetic individuals without CKD.

## Conclusions

Several shortcomings exist in this study. First, as a cross-sectional study, ability to establish temporal relation between elevated SF concentrations and GFR is limited. Additionally, our samples were measured from a single laboratory, SF values may be slightly different in the various populations and regions, and a multicenter study should be considered to determine whether the results are applicable to other races and regions. Finally, we only used estimated GFR to assess kidney function rather than more accurate measurements of kidney function. However, we still suggest that mild elevation of SF concentration is associated with estimated GFR in nondiabetic individuals without CKD. These findings indicate that SF may be useful as a CDK risk indicator in nondiabetic individuals.

### Statement

The authors have no financial conflicts of interest.

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