Association Between Serum Lipid Levels and Estimated Glomerular Filtration Rate in Type 2 Diabetic Patients

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Introduction. Dyslipidemia is a common metabolic abnormality in Type 2 diabetic Mellitus (T2DM) patients with kidney dysfunction. Therefore, the current study was conducted to assess the association between serum lipid levels and estimated glomerular filtration rate (eGFR) in T2DM patients.

Methods. This cross-sectional study was performed on 802 participants, aged 40 years or more who had referred to the Abu Reyhan Clinic of Shahid Mohammadi Hospital in Bandar Abbas, Hormozgan province, Iran. Biochemical variables including FBS, triglycerides, total cholesterol, LDL-C, and HDL-C levels were measured using the enzymatic method. The association between serum lipid profile and eGFR was assessed using the Spearman correlation coefficient test and linear regression model.

Results. Mean ± SD age of the subjects (72.3% females) was 53.55 ± 5.56 years old. Mean ± SD of eGFR-EPI and eGFR-MDRD was 86.30 ± 17.48 and 86.80 ± 23.29, respectively for all the subjects. In the current study, a negative association was observed between eGFR-EPI and FBS (r = -0.123, β = -0.172) and TGs (r = -0.080, β = -0.096) (P < .01). Also, there was an inverse association between the eGFR-MDRD and FBS (r = -0.123, β = -0.172) and TGs levels (r = -0.074, β = -0.086) (P < .05). However, the concentration of other lipid profiles was not associated with the eGFR level (estimated by EPI and MDRD methods).

Conclusion. Our findings suggested that the patients with reduced eGFR level are more likely to have greater TG serum level. Therefore, high TG levels can be considered as a potential biomarker for predicting renal complications in the patients with T2DM.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), as an important global health threat plays a key role in increasing the comorbidities and mortality worldwide.1 The global prevalence of diabetes has rapidly increased over the recent decades (accounting for 8.8% of adult population) and it is estimated that about 642 million people will have the T2DM by 2040.1,2 Diabetes has been recognized as the common cause of nephropathy and end-stage renal disease characterized by albuminuria or reduced kidney function.3 Kidney failure, as a serious global health concern imposes high burden of cardiovascular events and death in the diabetic patients with chronic kidney disease (CKD).4,5 accordingly a study reported that individuals with kidney dysfunction and microalbuminuria are four times more prone to be affected with the cardiovascular.
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diseases (CVD) than those with normal kidney function. Poor glycemic control, lipid abnormalities, hypertension, smoking habits, dietary factors, and genetic background play major parts in progression of diabetic nephropathy. Diabetic dyslipidemia, as a common disorder in T2DM is a main risk factor for CVD causing death in the patients with CKD. Also, abnormal lipid profile of the patients can be a risk factor for progression of diabetic nephropathy. Recently, some reports with inconsistent results mostly conducted on the nondiabetic individuals have reported that dyslipidemia may be a common and persistent complication in the patients with CKD. Furthermore, the association of serum lipid levels with estimated glomerular filtration rate (eGFR) has been assessed in different age groups of people worldwide; based on results of most studies, the lower concentration of high-density lipoprotein cholesterol (HDL-C), higher levels of triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) are related to the decline in the eGFR level and increased risk of CKD development. However, in a study, relationship between some lipid components including total cholesterol (TC), LDL-C, and HDL-C with the eGFR has not been convincing and meaningful.

Most previous studies on the association between lipid profile components and CKD have focused on the dyslipidemia and renal diseases in non-diabetic individuals. Therefore, epidemiological studies on the association of lipid profile levels with eGFR in the general population without CKD or in T2DM patients are limited, and the results are also inconsistent. Also, it is unclear to confirm convincingly that lipid abnormalities play a primary role in the development of diabetic nephropathy or dyslipidemia occurs as a secondary complication following the progression of kidney dysfunction.

Considering the limited and contradictory evidence regarding the association between dyslipidemia and outcomes in the earlier stages of CKD before reaching kidney failure (decline in eGFR), and also the unclear role of dyslipidemia as a predictor (or mediator) of declining kidney function among the patients with T2DM, the current study was conducted to evaluate the association between lipid profile levels and eGFR among Iranian patients with T2DM.

MATERIALS AND METHODS

Study Population

This cross-sectional study was conducted on 802 patients with diabetes who had referred to the Abu Reyhan Clinic of Shahid Mohammadi Hospital in Bandar Abbas, Hormozgan province, Iran, from May 2016 to May 2018. The patients were selected based on the inclusion and exclusion criteria and their medical records were assessed. Also, the clinical characteristics of the participants and study variables were measured and recorded. Patients who had been definitely diagnosed with T2DM by an endocrinologist based on the American Diabetes Association (ADA) diagnostic criteria, aged between 40-60 years old were enrolled in this study.

Cases with a history of other known renal diseases (except for those related to diabetes) and acute renal failure and eGFR level between < 30 or ≥ 180 mL/min/1.73 m² were excluded. Individuals were also excluded if they met the following exclusion criteria; patients with a history of transfusion or hemolytic anemia in the last three months, patients who had developed anemia after acute blood loss in the last three months, patients with a history of hypertriglyceridemia (TGs > 1750 mg/dL), those with a history of taking ribavirin and interferon-alpha in the last three months, those with a history of severe hyperbilirubinemia (> 20 mg/dL), pregnant women, and those with Hb < 7 mg/dL.

The protocol of this study was approved by the Institutional Ethics Committee of the Shahid Mohammadi Clinical Research Center, Hormozgan University of Medical Sciences, Bandar-Abbas, Iran (Ethics code of IR.HUMS.REC.1398.365). Written informed consent was obtained from all the participants.

Measurements and Definitions

Participants weight was measured in light clothing, without shoes or socks using a digital scale (Seca 803, German) with an accuracy of 100 g. Height was also recorded to the nearest 0.1 cm in standing position without shoes, using a stadiometer. Body mass index (BMI) of participants was calculated as their weight (kg) divided by the square of their height (m²). Blood samples were taken from patients in a sitting position after 12 to 14 h of overnight fasting based on the standard protocol. We analyzed blood samples at the laboratory of Abu Reyhan Clinic of Shahid
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Mohammadi Hospital. Fasting blood sugar (FBS), TG, TC, and HDL-C were measured using the enzymatic colorimetric method and commercial kits (Pars Azmoon, Tehran, Iran). LDL-C was also calculated by the serum profile and TC, TG, and HDL-C concentrations using the Friedewald formula. The standard colorimetric Jaffe_Kinetic reaction method was used to determine the serum creatinine. The eGFR was calculated based on the mean creatinine level using two methods including Modification of Diet in Renal Disease (MDRD) and the Epidemiology Collaboration Equation (EPI).

MDRD [eGFR = 175 (or 186) x Serum creatinine - 1,154 x Age - 0.203 x (0.742 if female) x (1.212 if black)]

EPI [eGFR = 141 * min (Scr/κ, 1)α * max(Scr/κ, 1)-1.209 * 0.993 Age * 1.018 [if female] * 1.159 [if black]]

Diabetes was diagnosed based on the ADA diagnostic criteria as FPG ≥ 126 mg/dL or 2-h post 75 gram glucose load ≥ 200 mg/dL, or glycated hemoglobin (HbA1C) ≥ 6.5%, or the current therapy for a definite diagnosis of diabetes. Statistical Analysis

The SPSS software (version 23) was used to analyze data. P < .05 were considered as statistically significant. The normal distribution of the variables was checked by the Kolmogorov–Smirnov test and histogram chart. The characteristics of the participants were reported as mean ± SD for quantitative variables. We used independent two samples T-test for comparison of quantitative variables among the participants. Also, the correlation coefficient of eGFR with lipid profile levels was assessed using the Spearman correlation coefficient test. The β value was estimated for the levels of lipid profile components according to the eGFR by the linear regression model. The potential confounding variables in our study analysis included age, sex, hypertension, and BMI.

RESULTS

Total of 802 patients with T2DM (27.7% men) were included in the current study. The mean ± SD age was 53.55 ± 5.56 years. The mean ± SD with eGFR-EPI and eGFR-MDRD was 86.30 ± 17.48 and 86.70 ± 23.29, respectively.

Characteristics of the participants are presented based on the gender classification (Table 1). Male and female patients had different characteristics, with significant differences in age, BMI, HbA1c, FBS, Triglyceride, Cholesterol, and HDL-C.
patients had lower levels of HDL-C and BMI, and higher levels of hemoglobin and creatinine compared with female. However, no significant differences were observed in the concentrations of TG, LDL-C, FBS, TC, eGFR-EPI, eGFR-MDRD, and HbA1c between male and female subjects.

Table 2 represents the characteristics of the individuals based on the eGFR level categories (estimated by EPI and MDRD methods). In comparison with the subjects with eGFR-EPI > 60, T2DM patients with eGFR-EPI ≤ 60 were significantly older and had significantly higher levels of TG, HbA1c, and creatinine (P < .05). Also, T2DM patients with eGFR-MDRD of ≤ 60 were significantly older and had high levels of creatinine, HbA1c, FBS, and TG. However, there was no significant difference in other characteristics among the patients with T2DM based on the eGFR categories.

In the current study, the association between serum lipid components and FBS levels with eGFR (estimated by EPI and MDRD methods) was assessed in the patients with T2DM using the Spearman correlation coefficient test and linear regression model (Table 3). A negative association was observed between the levels of eGFR-MDRD, FBS (r = -0.123, β = -0.141), and TG (r = -0.074, β = -0.086), (P < .01). Also, the lower level of eGFR-EPI was significantly associated with higher levels of FBS (r = -0.123, β = -0.172) and TG (r = -0.080, β = -0.096) (P < .01). However, there was no significant association between the levels of TC, HDL-C, LDL-C, and eGFR (estimated by EPI and MDRD methods).

**DISCUSSION**

In the current study, the association between serum lipid component levels and eGFR was assessed in the patients with T2DM. The results showed a relationship between higher TG level and decreased eGFR. However, there was no significant association between HDL-C, LDL-C, and TC levels and eGFR in the patients with T2DM.

Findings of the current study are partially in

<table>
<thead>
<tr>
<th>Variable</th>
<th>eGFR-EPI Categories</th>
<th>eGFR-MDRD Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 60</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.90 ± 4.40</td>
<td>53.31 ± 5.61</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.44 ± 5.22</td>
<td>25.77 ± 4.68</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.84 ± 1.82</td>
<td>12.66 ± 1.59</td>
</tr>
<tr>
<td>HbA1c</td>
<td>9.92 ± 2.65</td>
<td>8.89 ± 2.07</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>224.37 ± 112.16</td>
<td>194.21 ± 78.84</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>200.24 ± 140.50</td>
<td>156.56 ± 86.96</td>
</tr>
<tr>
<td>LDLc, mg/dL</td>
<td>179.05 ± 47.52</td>
<td>171.28 ± 43.72</td>
</tr>
<tr>
<td>HDLc, mg/dL</td>
<td>96.30 ± 37.82</td>
<td>95.17 ± 36.01</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>41.25 ± 11.49</td>
<td>42.94 ± 11.71</td>
</tr>
</tbody>
</table>
| Data are presented as mean ± standard deviation.

**Table 3.** Finding of the Spearman correlation coefficient and linear regression models assessing association of lipid profiles and fasting blood glucose concentrations with eGFR (estimated by EPI and MDRD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>eGFR-MDRD</th>
<th>eGFR-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>-0.129</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>-0.123</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>-0.074</td>
<td>0.035</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>-0.019</td>
<td>0.584</td>
</tr>
<tr>
<td>Low density lipoprotein-cholesterol</td>
<td>0.002</td>
<td>0.959</td>
</tr>
<tr>
<td>High density lipoprotein-cholesterol</td>
<td>0.012</td>
<td>0.742</td>
</tr>
</tbody>
</table>

*P-value was determined using Spearman correlation coefficient test
†P-value was determined using linear regression model
Linear model was adjusted for age, sex, hypertension, and body mass index.
agreement with the results of previous studies on the association between serum lipid component levels including TG, HDL-C, LDL-C, and TC with eGFR in various age groups worldwide. \[12-16\] Results of a study on the Chinese patients with CKD have reported an association between the higher TG level and lower eGFR level however, the relationship of other lipid profiles (TC, LDL-C, and HDL-C) with eGFR has not been meaningful. \[12\] Another study conducted on the middle-aged and elderly Chinese patients has indicated that higher levels of TG and LDL-C and low level of HDL-C were closely related to the decreased eGFR level. \[13\] Moafi \textit{et al.} also revealed that lipid abnormalities can be associated with the decreased eGFR level among the children and adolescents. \[14\] Furthermore, two other studies have reported that low HDL-C and elevated LDL-C levels can be associated with the decreased eGFR and progression of CKD in a community-based population. \[15,16\]

Overall, the available evidence shows that the lipid abnormalities especially hypertriglyceridemia can predict the increased risk of diabetic nephropathy as a main microvascular complication observed in the patients with T2DM. However, most of the previous studies have overwhelmingly focused on the patients with kidney dysfunction or ESRD. In current study, we have assessed the association between serum lipid profile levels and eGFR in the patients with T2DM who were in the earlier stages of CKD before reaching kidney failure. Results of the current study indicated that TG level was significantly associated with a decline in the eGFR, independent of the confounding factors including age, sex, BMI, and hypertension. The association between serum lipid components and eGFR was also evaluated in the patients with and without CKD (in the subjects with eGFR of < 60 and eGFR of ≥ 60), however, the number of CKD cases was not high enough to detect the association owing to reduced study power.

Based on current knowledge, the relationship between reduced eGFR level and lipid abnormalities is still far from fully understood. Also, it is unclear to definitely state that lipid abnormalities play a primary role in the development of diabetic nephropathy or dyslipidemia is a secondary complication following the progression of kidney dysfunction. However, some potential mechanisms have been previously suggested related to the reduced eGFR or renal dysfunction concomitant with dyslipidemia. Changes in the metabolism of lipoproteins in the subjects with kidney dysfunction have been reported as one of the mechanisms in the previous studies. \[19,20\] Reduction of catabolism and elimination of triglyceride-rich apo B-containing lipoproteins have been observed due to the impaired lipolysis in the patients with kidney diseases. Moreover, the decline in the amount of apo A-containing lipoproteins has been found as a result of a decrease in the amount of lipoprotein-A-1. \[12\] Furthermore, insulin resistance occurs in the T2DM patients with renal insufficiency or reduced eGFR, and these individuals have shown to have a decreased insulin secretory response. Previous reports suggested that insulin resistance is obviously associated with low HDL and increased TG levels. \[21,22\] Also, the patients with uncontrolled diabetes and renal dysfunction are at higher risk of macro-albuminuria or micro-albuminuria, which could be a mediator of structural changes in the lipoproteins and dyslipidemia. \[21,23\] Likewise, alteration in other Triglyceride-Rich Lipoprotein (TRL) metabolism and changes in the route of reverse cholesterol transport, structural change in the lipoproteins, increased amount of lipoprotein (a), and post-ribosomal modifications in the lipoproteins are other potential mechanisms underlying dyslipidemia in the patients with kidney dysfunction. \[21,24\]

Diabetic dyslipidemia, as a main risk factor of CVD is mostly complicated with diabetic nephropathy. \[25,26\] Indeed, impaired lipid metabolism including elevated levels of VLDL-C, LDL-C, and TG and a decline in the HDL-C level may be observed in T2DM patients with nephropathy. \[25\] Therefore, management and control of dyslipidemia in diabetic nephropathy is an extremely essential approach due to higher risk of CVD-related mortality in these patients. \[27-29\] The ADA recommends that serum lipid levels in the patients with T2DM should be checked at least annually. \[27\] According to the recommendations by the ADA and the American Heart Association (AHA), dyslipidemia must be considered as an important therapeutic goal in the management of diabetes, especially if it is concomitant with nephropathy. \[25\] Medications such as statins must be preferably prescribed for T2DM patients with nephropathy to decrease the CVD and kidney dysfunction. \[25,30,31\] Other lifestyle changes
including modification of diet, weight control or weight loss, increased physical activity, and lack of smoking can be beneficial in these patients to achieve optimal serum lipid levels.

There were some strengths in this study. For instance, it was the first study to assess the association between lipid profile and eGFR in T2DM patients in the Middle East and North Africa (MENA) region. Measurement of eGFR using both EPI and MDRD methods was another strength of the current study. This study had some limitations as well. It was difficult to derive causal relation between concentration of lipid profiles and eGFR level because of cross-sectional nature of this study. Also, despite controlling the effect of various confounders in our analysis, possibly there may be residual confounding factors, which we could not exclude due to unknown or unmeasured factors.

In conclusion, it was found that high TG level is closely related to a decreased eGFR level in the patients with T2DM. Results of this study provided the evidence that high TG level can be considered as an applicable biomarker for predicting the kidney dysfunction in the patients with T2DM. Indeed, hypertriglyceridemia not only increases the risk of CVD, but may also play an important role in the progression of diabetic nephropathy.

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CONFLICT OF INTERESTS
The authors declared no conflict of interests.

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