A Cross-Sectional Study on the Microalbuminuria, glycated hemoglobin, and Vitamin C Intake of Patients with Type 2 Diabetes Mellitus

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Abstract: Diabetic nephropathy (DN) is a major complication occurring in type 2 diabetic (T2DM) patients and characterized by persistent albuminuria and decreased renal function. Microalbuminuria (MAU) is a well-known early marker of DN in T2DM patients. This study aimed to analyse the possible associations among glycated hemoglobin (HbA1c), daily vitamin C (ascorbic acid) intake, and urinary microalbumin, as predictors of DN in T2DM patients. The cross-sectional study was utilized to analyze the secondary data from the National Health and Nutrition Examination Survey. The study population comprised 510 patients who were not diagnosed with hypertension prior to T2DM. Statistical analysis was done by using R 3.5.1 version and this study analyzed by simple linear and stepwise multiple regression. Among patients with T2DM, 19.0% had MAU, 75.7% had normoalbuminuria, and 5.3% had macroalbuminuria. The value of HbA1c was significantly higher in patients with MAU and macroalbuminuria than in normoalbuminuria. As a result of the study, microalbuminuria was predicted by HbA1c and there was an interaction between daily vitamin C intake and HbA1c. This means that microalbuminuria is a risk marker for DN and is associated with HbA1c and vitamin C. Therefore, in type 2 diabetic patients, periodic screening of blood glucose and high-dose vitamin C intake are required for preventing MAU and DN.

Keywords: Albuminuria, Ascorbic Acid (vitamin C), Diabetes Mellitus, Glycated Hemoglobin (HbA1c), Type 2 Diabetes Mellitus

1. Introduction

As of 2019, the worldwide prevalence of diabetes (DM) is estimated to be about 422 million, with a prevalence of about 8.5%[1]. According to a report by the International Diabetes Federation, the prevalence of DM is expected to rise to 700 million by 2045[2][3]. In Korea, 1 out of 6 adults over the age of 30 and 3 out of 10 adults over the age of 65 suffered from DM according to the Korean Diabetes Association[4].

T2DM accounts for more than 90% of DM patients[3], and diabetes nephropathy (DN) is one of the risk factors for chronic or end-stage renal disease[5]. In the absence of other kidney diseases, DN is caused by kidney damage result from DM and is diagnosed by confirming an increase in proteinuria[6].

Microalbuminuria (MAU) is the most important marker for the diagnosis of diabetic renal complications. It serves as a predictor of early stages and progression of renal function[7]. Further, MAU
is reversible, as it can resolve with aggressive treatment, and is a helpful marker for the risk of cardiovascular disease. Therefore, it has been reported to be an early predictive factor of mortality related to cardiovascular, renal, and other diseases in T2DM, than blood glucose and blood pressure[8]. According to a study of patients with T2DM, the average blood pressure of diabetic patients with MAU was 120-139/80-89mmHg, the pre-hypertension level, and the blood pressure continued to increase in proportion to the progress of proteinuria, reported that the hypertension is closely related to the occurrence of MAU[9]. The American Diabetes Association (ADA) guides measuring the changes in MAU and glomerular filtration rate annually to assess the renal functions in patients with T2DM[10].

Further, appropriately managing renal and cardiovascular complications by assessing MAU is crucial to preventing complications in both hypertension and T2DM[11].

Hyperglycemia greatly affects the occurrence and deterioration of DN. Therefore, strict glycemic control from the early stages is important to prevent and treat MAU[12]. Triglycerides (TG), high low-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels due to hyperglycemia were predictors of vascular complications and associated with MAU[11][13].

The UK Prospective Diabetes Study reported a decreased risk for progression to MAU and macroalbuminuria, and the deterioration rate of renal function was reduced in the group with T2DM that underwent strict blood glucose regulation (average HbA1c : 7.0%) compared with the control group (average HbA1c: 7.9%)[14]. In the Action to Control Cardiovascular Risk in Diabetes[15] and Action in Diabetes and Vascular Disease[16] trials, where the HbA1c targets were further lowered to 6.4% and 6.5%, respectively. strict blood glucose control had positive effects, such as preventing the incidence of MAU. Referring to previous literature, the ADA proposes the target HbA1c to be below 7% (<6.5% in Korea)[17]. From the above results, it was confirmed that hypertension, hyperglycemia or higher, and dyslipidemia were associated with MAU.

At the center of recent discussions regarding hyperglycemia control is vitamin C (ascorbic acid), an crucial nutrient and antioxidant. vitamin C facilitates insulin uptake by cells and glucose circulation in the body. Therefore, vitamin C deficiency can induce T2DM by affecting insulin release, glucose circulation, and metabolism[18]. Further, vitamin C protects the body from oxidative stress, which induces apoptosis in important organs[19].

Several researches have reported that vitamin C affects reducing the risk of renal disease and T2DM[20]. A study reported that 55.1% of patients with T2DM had vitamin C deficiency[21]. Vitamin C deficiency has also been associated with high total cholesterol and fasting blood glucose (FBS) levels[22]. In two studies on renal function, low blood vitamin C concentrations were associated with macroalbuminuria and renal dysfunction[20][22]. In addition to periodic MAU tests, blood glucose and blood pressure management, vitamin C supplementation, or vitamin therapy may help prevent diabetic complications in T2DM.

Previous studies have primarily analysed the relevance between HbA1c and MAU[9], vitamin C concentration and chronic kidney disease[20], or vitamin C concentration and HbA1c in patients with T2DM[22]. However, research on the association between HbA1c, daily vitamin C intake, and MAU in T2DM is limited. In line with this, the study aimed at the relationships among HbA1c, daily vitamin C intake, and MAU in patients with T2DM, and recommend strategies for T2DM management to help prevent DN.

2. Research Methodology

In this section, methods for data collection, physical measurement and biochemical blood collection, and vitamin C assessment were presented.
2.1 Research Design

This study is a cross-sectional study that secondarily analyzes data from the Korean National Health and Nutrition Examination Survey (KNHANES) conducted for two years from 2019 to 2020 to investigate the relationship between microalbuminuria, glycated hemoglobin, and daily vitamin C intake in T2DM.

2.2 Respondents of the Study and Data Collection

This study used data from the KNHANES (2019-2020) published by the Korea Disease Control and Prevention Agency (KCDC) of the Ministry of Health and Welfare. Since its launch in 1998, the KNHANES has been carried out periodically by the KCDC to estimate the health and nutritional status of community-dwelling residents. It is a cross-sectional study that presents nationally representative data by using a multi-stage stratification and probability sampling approach based on age, sex, and geographical locations, and includes physical examinations as well as surveys of nutrition and health. A total of 15,469 individuals participated. Of adults aged 30 years and over, the final study sample comprised 539 patients without hypertension prior to the diagnosis of T2DM. Since the hypertension of 140/90 mmHg has been reported to be associated with the MAU incidence[9], Patients diagnosed with hypertension prior to being diagnosed with T2DM were excluded. This is because the study has reported that hypertension occurs before MAU or simultaneously with the appearance of MAU[9]. After excluding 29 participants with missing data from the nutrition survey, 510 participants with data on daily vitamin C intake and suffering from T2DM were included [Fig. 1].

2.3 Data Gathering Procedure

2.3.1 Physical Measurements

Physical measurements, including body mass index (BMI), weight, height and waist circumference were obtained from the KNHANES database. Weight (kg) and height (m) were measured while shoes and socks were taken off, and BMI was calculated based on height and weight (kg/m²). The measurement of Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were conducted 3 times at five-
minute intervals and the last values were the average of the 2nd and 3rd values. A mercury sphygmomanometer was used in the sitting position. Waist circumference was categorized as follows: waist circumference <90cm and waist circumference ≥90cm for male participants and waist circumference <80cm and waist circumference ≥80cm for female participant. The definition of obesity was a case in which the BMI was 25kg/m² or more. Hypertension was defined as the SBP above of 140mmHg or DBP above of 90mmHg and was classified as cases prescribed antihypertensive drugs and cases previously diagnosed with hypertension by a doctor.

2.3.2 Blood Biochemical Data

The diagnostic criteria for T2DM over the age of 30 were used as follows: FBS ≥126mg/dL, diagnosis by a doctor, or HbA1C≥6.5% with the use of hypoglycemic medication. All blood samples were obtained after fast for at least 8 hours from midnight, and FBS, total cholesterol, TG, HDL-C and creatinine levels were measured. MAU was assessed only once in morning spot urine samples and defined as 30–300mg/g creatinine, less than 30mg/g creatinine was considered normoalbuminuria, macroalbuminuria as UACR>300mg/g creatinine[9].

2.3.3 Vitamin C Intake Assessment

The survey on daily intake of vitamin C was performed using the 24-hour recall method. The average intake was computed by noting the ingredients and amount of food cooked and consumed one day before the survey. An experienced clinical nutritionist conducted a one-to-one interview and helped participants accurately remember the amount of food they consumed by presenting a prepared food model. The data from the dietary intake survey were entered into CAN-Pro 5.0 (The Korean Nutrition Society, Seoul, Korea) of the Korean Nutrition Society to calculate the nutrient intake. Since the calculated daily vitamin C intake was presented in the KNHANES data, those data were utilized. The currently used vitamin C criteria were based on the correlation between plasma concentration and white blood cell saturation, and determined by the gastrointestinal absorption of vitamin C, vitamin C metabolic rate according to the oxidative stress in the body, and renal excretion[23]. At 50–100mg/day of vitamin C intake, the plasma concentration increased proportionally to about 60μmol/L. When the intake was more than 100 mg/day, it reached a plateau at about 70–80μmol/L and excreted in urine beyond the threshold[24]. People who consume less than 100mg/day of vitamin C in food have an increased incidence of metabolic diseases compared to those who consume more, so the daily intake of vitamin C is set in plasma[25].

2.4 Data Analysis

The KNHANES data were collected using a complex sample design that included first-extraction unit, multi-stage stratification sampling, and weighted values to minimize selection bias. Statistical analysis was done by using R 3.5.1 version. According to general characteristics, MAU, HbA1c, and daily vitamin C intake were tested using chi-square test. The statistical significance of mean±standard deviation of continuous variables according to albuminuria group was tested using t-test, ANOVA test and Scheffe's test. The statistical significance of the percentage and standard error of categorical variables was verified by chi-square test. The effects of HbA1c and daily vitamin C intake on MAU were analyzed using simple linear regression and stepwise multiple regression.

2.5 Ethical Considerations

This study was a secondary data analysis using the 2019–2020 KNHANES data. As we received the
The findings of this study showed that MAU was affected by HbA1c as well as an interaction between HbA1c concentration and daily vitamin C intake in T2DM patients. MAU is a predictor of early stages of kidney complications and deterioration of kidney function [7][8]. In our study, MAU significantly differed according to HbA1c (p<.001), FBS (p<.001), TG (p<.05), serum creatinine (p<.001), SBP (p<.001), and waist circumference (p<.001)[Table 2]. Also, the prevalence of hypertension in T2DM was 25.7%, and the prevalence of MAU with hypertension was 7.1%. These results were similar to Raile et al[26]. In another study, a large proportion of the patients with T2DM and high blood pressure experienced both MAU and renal dysfunction, and hypertension resulted in an increase of the prevalence of MAU in T2DM patients[9]. The prevalence of MAU was higher for patients with longer durations of T2DM and comorbidities, such as high blood pressure, dyslipidemia, and renal dysfunction, than those with T2DM alone[26][27]. In conclusion, MAU was confirmed to be closely associated with hyperglycemia, high blood pressure, and dyslipidemia in patients with T2DM.

HbA1c is a dual biochemical indicator for diabetes management and dyslipidemia and is used to screen for patients with a high risk of T2DM, as well as the prevention and management of complications[28]. In this study, 232 (45.5%) and 278 (54.5%) had HbA1c <7% and ≥7% [Table 1] and the MAU levels significantly differed in the comparison between the HbA1c<7% and HbA1c≥7% groups [Fig. 2][Table 2]. Our simple linear regression model showed that the HbA1c levels were associated with MAU in patients with T2DM (p<.001). Consequently, It was relevant that the increase of 1% in HbA1C and the 24% increase in UACR [Fig. 3].

Additionally, hyperglycemia results in an increased risk of the onset and progression of DN. Similar studies showed that, for T2DM, the strict blood sugar control group (HbA1c <7%) had a lower prevalence of MAU, compared with the poor blood sugar control group (HbA1c ≥7%)[7]. This result is similar to that reported in our study. In addition, hyperglycemia causes hyperlipidemia, and HbA1c was significantly different according to TG and HDL-C and was a predictor of vascular complications[13][23].

Patients with T2DM have been reported to have lower serum vitamin C concentrations than those without T2DM [18]. However, blood glucose did not show a significant relation to daily vitamin C intake in our results [Fig. 2][Table 2]. This was differed from the results of Mason et al[29] which showed vitamin C lowers the HbA1c, FBS, and postprandial glucose concentration. This result is because a large number of study participants were excluded in the process of selecting participants with MAU due to controlled T2DM (also, excluding participants who were diagnosed with hypertension before T2DM), and there were many missing nutritional surveys due to the COVID-19 pandemic.

[Table 1] Microalbuminuria Aaccording to General Characteristics of the Subjects.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UACR (mg/g creatinine)</th>
<th>HbA1c (%)</th>
<th>Vitamin C daily Intakes (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Macro (n=27)</td>
<td>MCU (n=97)</td>
<td>Normo (n=386)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.54 (.461)</td>
<td>112 (22.0%)</td>
<td>136 (26.7%)</td>
</tr>
<tr>
<td>Male</td>
<td>10 (2.0%)</td>
<td>43 (8.4%)</td>
<td>185 (36.3%)</td>
</tr>
</tbody>
</table>
### Table 2: Microalbuminuria Aaccording to Clinical and Laboratory Characteristics of the Subjects

(N=510)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UACR (mg/g Cr)</th>
<th>HbA1c (%)</th>
<th>Vitamin C daily Intakes (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Macro&lt;sup&gt;+&lt;/sup&gt; (n=27)</td>
<td>MCU&lt;sup&gt;+&lt;/sup&gt; (n=97)</td>
<td>Normo (n=386)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.41±10.42</td>
<td>67.07±10.52</td>
<td>64.04±10.71</td>
</tr>
<tr>
<td>Duration of T2DM</td>
<td>16.53±12.29</td>
<td>15.51±10.83</td>
<td>7.90±45.80</td>
</tr>
<tr>
<td>BMI (Km/m²)</td>
<td>25.83±2.67</td>
<td>25.04±3.04</td>
<td>24.40±3.20</td>
</tr>
<tr>
<td>UACR (mg/g Cr)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Daily vitamin C Intakes (mg/day)</td>
<td>107.58±167.10</td>
<td>64.32±37.39</td>
<td>62.25±87.22</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.26±1.64</td>
<td>7.84±1.36</td>
<td>7.22±1.23</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>143.88±41.06</td>
<td>157.95±60.73</td>
<td>134.59±38.36</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>217.47±217.11</td>
<td>147.91±89.19</td>
<td>139.18±97.95</td>
</tr>
</tbody>
</table>

UACR=urinary albumin/creatinine ratio; Macro=macroalbuminuria; MCU=microalbuminuria; Normo=normoalbuminuria; DM=diabetes mellitus; HbA1c= glycosylated hemoglobin.
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| HDL-C (mg/dL) | 43.53 ±12.23 | 44.62 ±10.95 | 47.64 ±10.67 | 3.36 (.042)* | 48.15 ±11.01 | 46.01 ±10.61 | 2.08 (.037)* | 46.75 ±10.71 | 48.20 ±11.46 | -0.98 (.33) |
| Serum creatinine (mg/dL) | 1.06 ±0.28 | 0.85 ±0.32 | 0.82 ±0.22 | 8.09 (p<.001)*** | 0.86 ±0.27 | 0.82 ±0.22 | 1.61 ±0.11 | 0.84 ±0.24 | 0.83 ±0.28 | 0.11 (.91) |
| SBP (mmHg) | 130.53 ±19.23 | 128.78 ±16.49 | 120.66 ±13.96 | 12.36 (p<.001)*** | 121.69 ±15.31 | 122.99 ±14.74 | -0.91 (.36) | 122.32 ±14.96 | 122.86 ±15.32 | -0.27 (.79) |
| DBP (mmHg) | 72.47 ±9.04 | 71.46 ±9.56 | 71.55 ±9.59 | 6.09 (p<.001)*** | 71.72 ±9.69 | 71.44 ±9.44 | 0.31 (.76) | 71.66 ±9.58 | 71.02 ±9.40 | 0.52 (.61) |
| Waist circumference (cm) | 94.00 ±7.75 | 90.20 ±8.18 | 87.81 ±8.72 | 6.09 (p<.001)*** | 88.00 ±9.39 | 88.82 ±8.09 | -0.97 (.33) | 88.59 ±8.67 | 87.66 ±8.84 | 0.81 (.42) |

Macro=macroalbuminuria; MCU=microalbuminuria; Normo=normoalbuminuria; DM=diabetes mellitus; BMI=body mass index; UACR=urinary albumin/creatinine ratio; HbA1C=glycosylated hemoglobin; FBS=fasting blood sugar; TG=triglyceride; HDL-C=high density lipoprotein-cholesterol; SBP=systolic blood pressure; DBP=diastolic blood pressure; Significance of Scheffe's test; p<.05.

[Table 3] Stepwise Multiple Regression Model According to Microalbuminuria (N= 510)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>5.86 5.39</td>
<td>1.09 1.09</td>
</tr>
<tr>
<td>Daily vitamin C intake</td>
<td>-0.99</td>
<td>1.56</td>
</tr>
<tr>
<td>Interaction of HbA1c and Daily vitamin C intake</td>
<td>0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>Adj R²</td>
<td>0.002</td>
<td>0.11</td>
</tr>
<tr>
<td>R² change</td>
<td>0.108</td>
<td></td>
</tr>
<tr>
<td>F(p)</td>
<td>1.179 (.281)</td>
<td>4.078 (.010)*</td>
</tr>
</tbody>
</table>

HbA1c=glycosylated hemoglobin; Adj R²=Adjusted R².
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Fig. 3 Scatter Plot of the Correlation between HbA1c Concentration and Microalbuminuria. ACR=albumin-to-creatinine ratio; HbA1C=glycosylated hemoglobin. Note: The p-values were obtained using simple linear regression; **p<0.01.

A stepwise multiple regression model implied that MAU was affected by the concentration of HbA1c ($\beta=18.31$, $p<.05$) and interaction between HbA1c and daily vitamin C intake ($\beta=0.15$, $p<.05$). This result indicates that 11% of MAU cases can be predicted by blood glucose control and interaction between blood glucose control and daily vitamin C intake, compared with daily vitamin C intake only [Table 3]. The status of vitamin C is controlled by renal secretion and reabsorption in the renal tubules, and patients with DN have reduced vitamin C levels due to increased vitamin C clearance. Thus, low serum blood vitamin C concentration has been shown to affect macroalbuminuria, renal dysfunction (serum creatinine, estimated glomerular filtration rate), and blood pressure[20]. However, in this study, daily vitamin C intake and MAU were not statistically significant. In the stepwise regression model predicting MAU, HbA1c alone was not significant in first step, but HbA1c and the interaction between HbA1C and daily vitamin C intake was significant in second step. These results suggest that adding vitamin C intake to strict blood glucose control (target HbA1c, 6.0–6.9%) increases their predictive value for MAU.

Based on the results of previous studies, vitamin C deficiency in T2DM is related to hyperglycemia, high blood pressure, and MAU. Hypertriglyceridemia due to hyperglycemia causes aggregation of fat infiltration and deposition in renal tubules, resulting in progressive tubular interstitial damage, which is associated with decreased renal function and progression of albuminuria in T2DM[19][21][23]. Therefore, a high-dose vitamin C diet may prevent the deposition of dyslipids in blood vessels and subsequently lead to MAU prevention by restoring renal function, estimated glomerular filtration rate and serum creatinine in T2DM patients.

In our study, the average age of T2DM patients was 64.7 years and 411(80.6%) and 99(19.4%) had vitamin C<100mg/day and ≥100mg/day [Table 1]. Also, their daily vitamin C intake was 64.32mg/day, which is less than the recommended daily vitamin C intake of 100 mg/day and the daily vitamin C intake significantly differed with age and TG ($p<.05$) [Table 2]. That is, the concentration of daily vitamin C in the blood decreased as the age of patients with T2DM increased. Moreover, the prevalence of vitamin C deficiency was 80.6%, which is consistent with the findings of Park[25]. That is, the serum vitamin C levels in older patients with T2DM were lower than those of younger patients with T2DM. Given that these can cause vascular changes along with exacerbation of T2DM, resulting
A vitamin C-rich diet or high-dose supplements should be considered for the prevention of hyperglycemia and diabetic complications, especially in older patients with T2DM. Hence, it is necessary to provide policy support for high-dose vitamin C supplements in consideration of the economic problems of older T2DM patients.

This study has a few limitations. UACR measurements were made using one spot urine sample. Considering the short collection period of urine, the sensitivity of proteinuria quantification is low[30]. In the future, experimental studies involving vitamin C intake are needed to analyze the relationship between HbA1c and MAU in T2DM patients.

5. Conclusion

The purpose of the study is to evaluate the possible relevance between glycated hemoglobin, daily vitamin C intake and urinary microalbumin as a predictor of DN in T2DM patients. As a result of this study, it was found that HbA1c and vitamin C affect the production of MAU.

Health education for MAU prevention in T2DM should include at lifestyle modifications such as dietary control to prevent hyperlipidemia regular aerobic exercise, and vitamin C-rich diet. ‘The community-based hypertension and diabetes control program’ initiated by the KCDC in 2007 requires not only the application of these educational programs, but also comprehensive monitoring and evaluation programs related to it. If UACR monitoring is done at the community level, it is expected to play a pivotal role in preventing and resolving the complications of T2DM.

In patients with T2DM, microalbuminuria is a helpful predictor of renal failure in people with T2DM, a common risk of poor blood sugar control and elevated blood pressure. In particular, it was found that elderly T2DM patients had a worsening of these diseases in the case of vitamin C deficiency. The results derived from this study also highlight the significance of blood sugar control and the early identification of MAU in patients with T2DM, and will serve as an opportunity for health education on antioxidant diets and non-drug therapies.

6. Acknowledgments

This research was supported by "Regional Innovation Strategy (RIS)" through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (MOE)(2022RIS-005)

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No.1, pp.19-62.


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DOI: https://doi.org/10.3390/antiox11020245

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DOI: https://doi.org/10.1186/s13613-020-0640-6

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