Association between Serum Uric Acid Levels and

Type 2 Diabetes Mellitus in Hospital Universiti Sains Malaysia

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ABSTRACT: Uric acid (UA) is the end product of purine metabolism in humans. Previous studies showed that serum UA levels were associated with diabetes mellitus (DM). However, there are limited studies done on the association between UA and diabetic control in type 2 diabetes mellitus (T2DM). Therefore, the aim of this study was to know the relationship between these two parameters in our population. A retrospective record review was conducted involving adult patients who were diagnosed to have T2DM from 1st January 2012 to 31st June 2014. Good controlled of T2DM was defined as HbA1c level less than 6.5% whereas HbA1c level more than 6.5% was considered as poor control. Descriptive statistics and Independent t-test were utilized and the level of significance was set at $p<0.05$. Seventy seven patients had good glycemic control and another 77 patients had poor glycemic control. The mean of serum UA in good control patients was 348.8 µmol/L (98.56) and 300.7 µmol/L (89.99) in poor control patients ($p = 0.002$, 95% CI 18.06, 78.17). This study suggests a positive association between the plasma concentration of UA and good controlled DM. Our study also found out that age, gender, duration of T2DM, waist circumference and serum triglyceride were significant associated factors with serum UA level in T2DM patients in Hospital USM. As UA has a role in oxidative stress which may further contribute to development of diabetic complications, the findings could help in proposing UA to become a risk marker for diabetic complication in the future.

Keywords: Uric acid, type 2 diabetes mellitus, triglyceride, waist circumference

Introduction

Uric acid (UA) is the end product of purine metabolism in humans due to the loss of uricase activity (Álvarez-Lario and Macarrón-Vicente, 2010). Depending on its chemical microenvironment, UA may also be pro-oxidant (So and Thorens, 2010). Previous epidemiological studies showed elevation of UA was associated with an increased risk of hypertension (Shankar *et al.*, 2006), cardiovascular disease (Gagliardi *et al.*, 2009), chronic kidney disease (Chonchol *et al.*, 2007) and increase mortality and morbidity (Katsiki *et al.*, 2013). Elevated level of UA is also a component of the metabolic syndrome (Yoo *et al.*, 2005).

It is also known that serum UA is positively associated with serum glucose in healthy subjects (Modan *et al.*, 1987) and has the potential relations with diabetic complications (Katsiki *et al.*, 2013).Pro-oxidant action of UA is involved in accelerated atherosclerosis which is one of the complication of T2DM (Hayden and Tyagi, 2004). However, its association with diabetes mellitus (DM) is still unclear. Some studies showed that subjects with higher levels of serum UA are more at risk of developing type 2 diabetes (Dehghan *et al.*, 2008) and positively associated with DM (Chien *et al.*, 2008). While other studies showed that higher serum UA levels were inversely associated with DM (Bandaru and Shankar, 2011; Nan *et al.*, 2007). Furthermore, hyperuricaemia is also associated with possible confounding factors including age, race, gender, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), insulin treatment, duration of DM, smoking, elevated serum triglyceride and cholesterol concentrations (Tseng, 2005; Yamada *et al.*, 2011). There are also studies looking into the association between serum UA and diabetic control but the findings are limited. They revealed that patients with glycated haemoglobin (HbA1c) ≥9% had lower uric acid (Ioachimescu *et al.*, 2007). Therefore, our study focused on the association between serum UA level and the status of diabetic control among T2DM patients.

Material and Methods

A retrospective record review was conducted involving adult patients who were diagnosed to have T2DM and underwent follow ups in Family Health and Physician Clinics of Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan from 1st January 2012 to 31st June 2014. The exclusion criteria were patients with cardiovascular and kidney disease, on treatment for hyperuricemia and incomplete data. Good controlled of T2DM was defined as obtaining a

single measurement of HbA1c level of less than 6.5% or an average of less than 7% if there were repeated measurements. Study subjects were selected using simple random sampling method. The study form was created to include variables such as socio-demography factors, use of insulin treatment, duration of DM, serum uric acid levels and HbA1c levels. All the data were collected from the record office of Hospital USM.

Serum UA levels were measured via uricase method using Architect C8000. Data were entered and analysed using IBM SPSS Statistics 20. Descriptive statistics and Independent t-test were utilized. Level of significance were set at $p<0.05$. The association between serum UA levels and the socio-demographic characteristics, clinical characteristics and biochemical status were determined by simple linear regression and general linear regression. Simple linear regression analysis was used to explore the data to screen for possible variables that may be associated with serum UA levels. The variables with p value of < 0.05 and clinically important based on the literature review were selected for general linear regression (GLR) which were age, gender, waist circumference (WC), diabetic status and serum triglyceride (TG) levels. Thisresearch has obtained the approval from Human Research Ethics Committee of USM (FWA Reg. No: 00007718; IRB Reg. No: 00004494).

Results

There were significant associations between serum UA with age, gender and duration of T2DM among T2DM patients in Hospital USM as shown in Table 1. Table 2 shows the univariable analysis between clinical and biochemical factors with serum UA level among T2DM patients in hospital USM. WC, diabetic status and serum TG were found to be significantly associated with serum UA level at the univariable level. The other variables like SBP, DBP and serum TC were found to be not significantly associated.

Table 3 shows that the significant variables associated with serum UA level were age ($p=0.007$), gender ($p<0.001$), WC ($p=0.001$), diabetic status (0.003) and serum TG level ($p=0.003$) after controlling the confounder with general linear regression. All significant variables in simple logistic regression analysis were found to be significant in general linear regression ($p<0.05$) except for duration of T2DM which was found to be non-significant at multivariable level.

Table 1: General characteristic factors associated with serum UA level among T2DM patients in Hospital USM (n = 154)

Factors	Simple linear regression Crude b[a] (95%CI)	t-stat	*P*-value
Age (year)	-1.86 (-3.26, -0.47)	-2.64	**0.009**
Gender			
Female	0	4.77	**< 0.001**
Male	69.95 (40.99, 98.90)		
Race			
Malays	0	0.54	0.592
Others	13.11 (-35.13, 61.34)		
Smoking status			
Non-smoker	0	0.62	0.537
Smoker	23.30 (-51.09, 97.68)		
Duration of T2DM (year)	-4.89 (-8.29, -1.49)	-2.85	**0.005**
Insulin treatment			
No	0	-0.88	0.382
Yes	-14.59 (-47.47, 18.29)		

[a]Crude regression coefficient

Table 2: Clinical and biochemical factors associated with serum uric acid level (μmol/L) among T2DM patients in Hospital USM (n = 154)

Factors	Simple linear regression Crude b[a] (95%CI)	t-stat	*P*-value
WC (cm)	2.08 (0.76, 3.39)	3.12	**0.002**
SBP (mmHg)	-0.52 (-1.82, 0.77)	-0.80	0.426
DBP (mmHg)	0.43 (-1.65, 2.51)	0.41	0.684
Diabetic status		3.16	**0.002**
Poor control	0		
Good control	48.12 (18.07, 78.17)		
Serum TC levels (mmol/L)	-9.19 (-23.20, 4.82)	-1.30	0.197
Serum TG levels (mmol/L)	42.80 (19.99, 65.62)	3.71	**< 0.001**

[a] Crude regression coefficient

Table 3: Significant associated factors of serum uric acid level (μmol/L) among T2DM patients in Hospital USM (n = 154)

Factors	General linear regression Adj. b[a] (95%CI)	t-stat	*P*-value
Age (years)	-1.66 (-2.87, -0.45)	-2.71	**0.007**
Gender			
Female	0	4.04	**< 0.001**
Male	55.19 (28.21, 82.18)		
WC (cm)	2.04 (0.89, 3.20)	3.51	**0.001**
Diabetic status			
Poor control	0	2.97	**0.003**
Good control	40.40 (13.53, 67.27)		
Serum TG levels (mmol/L)	30.80 (10.34, 51.24)	2.98	**0.003**

[a] Adjusted regression coefficient

Forward linear regression method was applied in this study and the model assumptions are fulfilled. There were no interactions amongst independent variables. No multicollinearity was detected. Adjusted coefficient of determination (R^2) = 0.313

Results from general linear regression analysis (Table 3) have shown that there is a significant linear negative relationship between age and serum UA level. Those who are 1 year older have 1.66 unit lower in serum UA level (Adj.[a] : -1.66 ; 95% CI: -2.87, -0.45; $p = 0.007$). There is a significant linear positive relationship between gender and serum UA level. In comparing male and female, male have serum UA 55.19 unit more than female (Adj.[a] : 55.19 ; 95% CI: 28.21, 82.18; $p < 0.001$). For every increase of 1 cm in WC, there will be 2.04 unit increase of serum UA level (Adj.[a] : 2.04 ; 95% CI: 0.89, 3.20; $p = 0.001$).

There is a significant linear positive relationship between diabetic status and serum UA. Good controlled patients have serum UA level 40.40 unit higher than poorly controlled patients (Adj.[a]: 40.40; 95% CI: 13.53, 67.27; $p = 0.003$). There is a significant linear positive relationship between TG and serum UA. For every increase of 1 unit in serum TG level, there is a 30.80 unit increase of serum UA level (Adj.[a] : 30.80 ; 95% CI: 10.34, 51.24; $p = 0.001$). Twenty nine percent (29.0%) of the variation in serum UA level is explained by age, gender, WC, diabetic status and serum TG level according to the general linear regression model.

Discussion

There are not many studies to show that there is association between serum UA with hypertension, cardiovascular disease, and chronic kidney disease (Chen *et al.*, 2009; de Oliveira and Burini, 2012; Kanbay *et al.*, 2013; Kim *et al.*, 2010). The association between serum UA and DM had also been studied but the findings were inconsistent (Dehghan *et al.*, 2008; Taniguchi *et al.*, 2001). In our population, the study regarding UA are minimal. Therefore, we examined the association between serum UA levels and DM in patients that under following up at hospital USM.

There are various factors associated with serum UA in DM patients such as age, sex, obesity, blood pressure and lipid profile (Dehghan *et al.*, 2008; Modan *et al.*, 1987; Sudhindra Rao and Sahayo, 2012).

From our study, age was found to be significantly associated with serum UA in DM patients. Results from general linear regression analysis has shown that there is a significant linear negative relationship between age and serum UA level. Those who are 1 year older have 1.66 unit lower in serum UA level. However, other study done in Rotterdam, the Netherlands showed that there is a significant positive correlation between age and serum UA level in diabetic patients (Dehghan *et al.*, 2008). This could be explained by different study population and it's prospective in design.

Our study also found out that there was a significant linear positive relationship between gender and serum UA level .When comparing male and female, male have serum UA 55.19 unit more than female. This is different from another study that was done on a large, contemporary, multiethnic sample of United State adults whereby they showed that there was an inverse association between increasing serum UA levels and DM which was consistently present among men and women (Bandaru and Shankar, 2011). However, the similarity was that they also showed that the association was stronger in men.

Furthermore, our study found that there was a significant linear positive relationship between WC and serum UA. For every increase of 1 cm in WC, there is a 2.04 unit increase of serum UA level. This finding is almost similar with the study done by Dehghan *et al*., 2008 whereby there is a positive correlation between WC and serum UA with a correlation coefficient of 0.35.

Moreover, our study also found that there was a significant linear positive relationship between diabetic status and serum UA. Good controlled patients have serum UA level 40.40 unit higher than poorly controlled patients. This finding is almost similar with the study done by Ioachimescu *et al.*, 2007. Their study showed that hyperglycemia as reflected by mean HbA1c levels was associated with lower serum uric acid levels. Patients with HbA1c $\geq$ 9.0% had significantly lower serum UA level compared to those with HbA1c < 9.0% (342.2 ± 106.2 versus 383.5 ± 106.2, $p = 0.003$). Serum UA level was similar in patients with HbA1c < 7.0% versus those with HbA1c between 7.0 and 8.9% (383.5 ± 88.5 versus 383.5 ± 123.9, $p = 0.86$). Our finding is consistent with previous study that showed serum UA level was higher in good controlled diabetic patients (Choi and Ford, 2008; Liu *et al.*, 2010). This type of patients are usually in pre diabetes state or newly diagnosed diabetes.

There was a significant linear positive relationship between TG and serum UA in our study. For every increase of 1 unit in serum TG level, there is a 30.80 unit increase of serum UA level. This is in agreement with a previous study that showed serum UA levels were positively correlated with TG (Kim *et al.*, 2012). Contra with our study, there were no association between serum UA level and TC level. This could be due to small sample size of our study that requires further evaluation. Furthermore, variations in genetic makeup and different life style between populations may also contribute to the results.

There are several limitations in this study. Data integrity and quality issues often arise in the collection of retrospective data. This method depends on interviews between doctors and patients. Certain information might not be obtained from patients and it is not possible to avoid recall bias or lying patients. Majority of Kelantan populations are Malay and it could contribute to the limitation in determining the associated factors for serum UA and races.

Conclusion

As a conclusion, this study suggests a positive association between the serum concentration of UA and good controlled diabetic mellitus. Our study also found out that age, gender, duration of T2DM, WC and serum TG were significant associated factors with serum UA level in T2DM patients. Prospective studies should be done in multi-ethnic population so that it could represent our population.

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