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Urinary Malondialdehyde as a Biomarker of Type 2 Diabetes Mellitus Treatment in the Primary Care Unit of a Tertiary Care Hospital

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Abstract

Introduction/Objectives: The examination of Urinary Malondialdehyde (UMDA) as a biomarker in the involvement of inflammatory response and oxidative stress, as a mechanism underlying the development of diabetes; in addition to complications in followed-up patients at a primary healthcare unit. The level of UMDA and its related factors in T2DM patients, between good and poor glycemic control was investigated. **Methods:** This analytical cross-sectional study was conducted at the primary care unit, of Songklanagarind Hospital; from May 2020 to August 2020. The voluntary patients were divided into 2 groups, by using a percentage of HbA1c $\leq$7% as a good control T2DM group, and higher than 7% as a poor control T2DM group. The comparison statistics and logistic regression analysis were performed by using R Program. **Results:** A total of 71 patients voluntarily participated in this study, and consisted of: 38 patients with poor glycemic control and 33 patients with good glycemic control. There were no significant differences between the patients; with the exception of smoking habits. The average levels of UMDA of the good control group (2.43 ± 0.91 μg/mL) were slightly lower than the poor control group (2.60 ± 0.96 μg/mL): *P*-value $>$.05. Patients who had underlying diseases, smoking, or drinking habits displayed significantly different levels of UMDA. Being a non-smoking patients, and having a higher level of HDL-C with significant protective factors, while having increased level of FBS and triglyceride were pointedly negative factors of oxidative stress status. **Conclusion:** Patients who had good control of T2DM produced better health outcomes than the poor control group. UMDA, FBS, HDL-C, and triglyceride levels could be applied as follow-up criteria in T2DM patients within a primary healthcare setting.

Keywords

biomarker, urinary malondialdehyde, type 2 diabetes, primary care, glycemic control

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Introduction

A common chronic metabolic disease in Thailand is Diabetes mellitus Type 2 (T2DM). More than 95% of DM patient are T2DM, which develops when the body becomes resistant to insulin, or has relative insulin deficiency.[1] In Thai people, the prevalence of diabetes increased from 7.7% in 2004 to 7.8% in 2009, and 9.9% in 2014 (8.9% among men and 10.8% among women).[2] The mechanism of body resistance to insulin, or having a relative insulin deficiency, causes T2DM to develop. A hemoglobin A1C (HbA1c) of $\leq$7.0% has been suggested as a good control diabetic condition in T2DM patients, while a poor control is HbA1c higher than 7.0%.[1,3] Patients with T2DM are at a high risk of developing debilitating complications, which include: cardiovascular diseases, peripheral vascular disease, microvascular complications, nephropathy, retinopathy, and neuropathy, that can

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lead to disability and premature death; especially in poorly-controlled hyperglycemia T2DM. It also imposes significant medical and economic burdens on the health care system. Hyperglycemia promotes reactive oxygen species (ROS) accumulation, for example the metabolic pathways,[4] in T2DM patients that can induce individual oxidative stress conditions and also decrease antioxidants.[5] The most associated factors for development of this condition are genetic susceptibility and environmental influences. However, physical inactivity and obesity, in T2DM patients has been more observed. Many researchers hypothesized that obesity as well as physical inactivity may be the main reasons of importance for the increasing burden of T2DM in developed countries. Howbeit, diabetic patients often die from macrovascular disease; wherein, correlation between chronic hyperglycemia and long-term complications in diabetics were reported.[6-8]

Oxidative stress is an imbalance of the individual level of a cellular structure between oxidants and antioxidants, which can cause negative effects; such as, membranes, lipids, proteins, lipoproteins, DNA, and lipid peroxidation. Therefore, the oxidative stress mechanism can be an important factor for several diseases. Various studies have found higher oxidative stress levels in poor glycemic control groups than in good glycemic control groups, which may be due to several potential mechanisms; including, chronic inflammation, hyperglycemia, and impairment of antioxidant defense.[7-9]

The most important biomarker of lipid peroxidation is Malondialdehyde (MDA), which is generated as an end product from oxidative degradation of polyunsaturated fatty acids. Diabetes has several mechanisms that can contribute to systemic hyperinflammatory status, and an increase of oxidative stress metabolism, with enhanced production of ROS, that contributes to injury of the host tissue by several mechanisms; including, DNA damage, and lipid peroxidation.[8,9]

Several studies[5,7,10,11] have been conducted in different settings to evaluate oxidative stress, by measuring plasma MDA as an end product of lipid peroxidation. They reported that the level of plasma MDA in poorly controlled T2DM (fasting plasma glucose, FPG >180 mg/dL)[7] was significantly higher when compared with a normal group of patients (FPG <110 mg/dL), who were followed up at a university hospital.[10] In addition, MDA levels in T2DM patients were significantly higher than non-diabetics at the primary healthcare unit of a tertiary hospital.[5] In a diabetic clinic setting, there was no significant difference between good control (normal HbA1c) and poor control T2DM patients (HbA1c levels $>6.5\%$).[11]

To improve the glycemic control management in T2DM, the biomarker and also related factor should be investigated; even if the glycemic control was defined by using the cut-off point of HbA1c level at 7.0%, as per the standard guideline.[1,3] This study aimed to determine the difference of urinary malondialdehyde (UMDA) levels, as a biomarker of oxidative stress, using a non-invasive technique, and the factors related to glycemic control in T2DM patients, at the primary healthcare unit of a tertiary care hospital. The MDA level may act as the early detector of a patients' glycemic control and be used to further monitor the development of this disease.

Materials and Methods

This cross-sectional descriptive study aimed to determine the difference between urinary malondialdehyde and glycemic control in T2DM patients at the primary care unit, of Songklanagarind Hospital; from May 2020 to August 2020. The study was conducted in line with the Belmont Report, and was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University (Ref no: REC 63-144-9-1).

The sample size for each group was 42, calculated by following 2 independent means formula

$$n_1 = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left[\sigma_1^2 + \left(\frac{\sigma_2^2}{r}\right)\right]}{\Delta^2},$$

$$\alpha = 0.05, \beta = 0.20, r = 1$$

Where:

Mean and standard deviation of group 1 was 4.7 and 3.5, respectively while for group 2 it was 2.9 and 2.2 respectively.[11]

The study's population inclusion criteria: T2DM patients aged between 35 and 65 years were selected, by purposive sampling, from those who had regular follow-up appointments at the Diabetes Clinic, in the primary healthcare unit, Songklanagarind hospital. T2DM patients who had cardiovascular, liver, kidney diseases, and other endocrine disorders were excluded from this study, as per the exclusion criteria. The voluntary patients signed a consent form and were then divided into 2 groups, by using the percentage of HbA1c as $\leq 7\%$ as a good control T2DM group, and a higher than 7% as a poor control T2DM group.

After the volunteer recruitment process was concluded, the family physician, researcher, declared the patients' laboratory data using their latest visit, as collected from the Hospital Information System (HIS) of Songklanagarind hospitals database. Biochemical data included: HbA1c, fasting blood sugar (FBS), plasma total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides.

UMDA Collection and Analysis

Urine samples (40 mL) were collected from all voluntary patients at the PCU, so as to reduce possibility confounder factors[12,13]; such as, food intake and smoking. All urine sample were collected before noon, within the day of their hospital visit. An aliquot of 10 mL was separated into

Table 1. General Characteristics of Subjects in the 2 Study Groups (N = 71).

Variables general characteristics	Poor-control type 2 DM	Well-control type 2 DM	Chi-square test (*P* value)
	N (%)		
Subjects (n)	38 (53.5)	33 (46.5)	—
Gender (n)			
Male	16 (53.3)	14 (46.7)	>.05
Female	22 (53.7)	19 (46.3)	
BMI (kg/m^2)			
<25	10 (38.5)	16 (61.5)	.09
≥25	28 (62.2)	17 (37.8)	
Waist circumference (cm)			
Beyond standard	9 (39.1)	14 (60.9)	.15
Over standard	29 (60.4)	19 (39.6)	
Smoking (n)			
Active	3 (60.0)	2 (40.0)	.03*
Never	31 (62.0)	19 (38.0)	
Ex-smoker	4 (25.0)	12 (75.0)	
Drinking (n)			
Active	8 (53.3)	7 (46.7)	.46
Never	25 (58.1)	18 (41.9)	
Ex-drinker	5 (38.5)	8 (61.5)	
Underlying disease (n)			
DM	2 (50.0)	2 (50.0)	.82*
DM and DLP	19 (57.6)	14 (42.4)	
DM, DLP, and HT	17 (50.0)	17 (50.0)	

Abbreviations: DLP, dyslipidemia; DM, diabetes mellitus; HT, hypertension.
Waist circumference: over standard means waist circumference ≥90 in men while ≥80 in women and beyond standard means waist circumference <90 in men while <80 in women.
*Fisher's exact test.

another tube to determine the urinary creatinine, via CREP2 (creatinine plus version 2).[14] The remaining spot urine samples (30 mL) were stored in a polypropylene tube, and frozen at −80°C before preparation and analysis.

A small portion of the urine sample (200 µL) was mixed with DNPH solution (500 µL), in a 15 mL conical tube. The mixture was placed in an incubator for 1 h at 50°C, in the dark. At the end of the incubation, extraction with hexane (5 mL) was carried out for the derivatized samples. The tubes were shaken on a rotator for 30 min, and centrifuged at 14 000 rpm for 10 min. The supernatants were dried under vacuum using a rotary evaporator at 40°C. The residue was dissolved in 200 µL of 50% (vol/vol) acetonitrile-water solution. The reconstituted solution was analyzed for MDA by high-performance liquid chromatography (HPLC).

HPLC (1100 Series; Agilent, Foster City, CA, USA) with diode array detector (DAD), UV detector (310 nm for Excitation wavelength and 510 nm for Emission wavelength), and Agilent ZORBAX columns (4.6 × 250 mm ID, 5 µm particle size) was set in this study. The 25% aqueous 1,5-pentane dialdehyde solution was used as an internal standard: with the limit of detection of the method being 0.15 nmol/L. The recovery of MDA was 85% to 115%, obtained by the addition of 8 concentrations of standard solutions (0.1-50 µg/mL) to the urine samples. The reproducibility was 90% to 110%, and the concentration of metabolites was presented in µmol/mol creatinine.

Statistical Analysis

Data analysis was performed by using R program 4.0.0. Shapiro-Wilk test was performed to determine the normality of each data. This included descriptive analysis, percentage, mean, and standard deviation; for the comparison statistical analysis Chi-square-test, Fisher's exact test, *T*-test, and Wilcoxon rank-sum test were used to explain the difference of independent variables between poor-control and well-control groups. Finally, Bivariate and Multivariate Linear Regression analysis were used to explain, as well as to predict, the relationship between independent variables and UMDA: a *P*-value <.05 was considered as the statistically significant level.

Results

There were a total of 71, T2DM patients that met the criteria for this study; 38 patients with good glycemic control and

Table 2. The Biochemical Data of Subjects in the 2 Study Groups (N = 71).

Variables general characteristics	Poor-control type 2 DM (Mean ± SD)	Well-control type 2 DM (Mean ± SD)	*t*-Test (*P* value)
HbA1c (%)	8.49 ± 1.23	6.22 ± 0.64	<.01
FBS (mg/dL)			
<130	111.88 ± 11.10 (N = 8)	109.25 ± 11.92 (N = 24)	.58
≥130	176.93 ± 45.83 (N = 29)	156.88 ± 21.64 (N = 8)	.09
LDL-C (mg/dL)			
<100	78.94 ± 12.21 (N = 17)	83.41 ± 7.80 (N = 19)	.24
≥100	141.63 ± 37.15 (N = 20)	125.24 ± 21.01 (N = 14)	.27*
HDL-C (mg/dL)	47.97 ± 8.83	55.41 ± 12.20	
Male			
<40	34.17 ± 3.52 (N = 3)	38.2 ± 1.95 (N = 4)	.07*
≥40	52.63 ± 9.53 (N = 12)	61.94 ± 13.62 (N = 10)	.17
Female			
<50	43.94 ± 4.59 (N = 14)	45.3 ± 3.06 (N = 5)	.66*
≥50	55.08 ± 4.31 (N = 8)	58.12 ± 8.56 (N = 14)	.47
Triglyceride (mg/dL)			
<150	99.90 ± 20.80 (N = 19)	98.21 ± 31.60 (N = 28)	.83
≥150	238.83 ± 97.85 (N = 18)	193.0 ± 48.39 (N = 5)	.35*
TC (mg/dL)			
<200	155.5 ± 23.59 (N = 28)	154.7 ± 21.22 (N = 30)	.04
≥200	241.56 ± 29.98 (N = 9)	228 ± 38.12 (N = 3)	.04
MDA (μg/mL)	2.52 ± 0.94		
	2.60 ± 0.96	2.43 ± 0.91	.45
Urine creatinine (mg/dL)	101.27 ± 70.81		
	91.91 ± 53.56	112.05 ± 86.18	.73*

A well-control type 2 DM group means HbA1c ≤7% as, and a poor-control type 2 DM group means HbA1c higher than 7%.
*Wilcoxon rank sum test.

33 patients with poor glycemic control. There were 30 males and 41 females who participated in this study. They were 54.06 ± 5.57 years of age. However, the average age of the well-control T2DM group (55.33 ± 4.94 years old) was significantly higher than the poor-control T2DM (52.95 ± 5.90 years-old), *P*-value <.05. Table 1 shows the general characteristic of the patients. There were no significant differences between gender, Body Mass Index (BMI), waist circumference, underlying diseases, or alcohol consumption between the good control and poor control groups; with the exception of smoking habits.

The general biochemical data and UMDA level in T2DM were compared between both well-control and poor-control groups. The average UMDA level of the good control group (2.43 ± 0.91 μg/mL) was slightly lower than the poor control group (2.60 ± 0.96 μg/mL), but without any significant difference. For subgroup analysis, the level of FBS, LDL-C, HDL-C, triglyceride, and TC between good and poor control groups presented no significant difference; however, the HbA1c level did (Table 2).

The subgroup analysis of UMDA between the well-control and poor-control groups was conducted. Table 3 shows the UMDA level of patients with underlying diseases, smoking habits, and alcohol consumption habits, which presented a significant difference between the good and poor control groups ($P < .05$). In addition, the UMDA levels were increased in the poor control patients; especially for those whom had higher BMI scores, LDL-C, and triglyceride levels, active smoking habits, and underlying diseases ($P > .05$). In contrast, the UMDA level was decreased in patients who had a higher HDL-C level ($P > .05$).

Bivariate and Multivariate Linear Regression analysis were performed to explain the relationship among individual factors, biochemical data, and UMDA level, Multivariate regression analysis (Table 4) showed non-smoking patients (−1.32, 95% CI: −2.23 to −0.41) and patients who had a higher level of HDL-C (−0.003, 95% CI: −0.05 to −0.01) were significant protective factors, while increased level of FBS (0.005, 95% CI: 0.0001 to 0.009) and triglyceride (0.003, 95% CI: −0.006 to 0.0004) were significantly negative factors of oxidative stress status, when using UMDA as the biomarker.

Discussion

Urinary MDA Level in T2DM Patients

In this present study, we aimed to present UMDA levels, a known oxidative stress marker, as a screening tool for

Table 3. The Subgroup Analysis of Urinary Malondialdehyde Level (μg/mL) Between 2 Study Groups (N = 71).

Variables general characteristics	Poor-control type 2 DM (Mean ± SD)	Well-control type 2 DM (Mean ± SD)	*t*-Test (*P* value)
BMI (kg/m^2)			
<25	2.32 ± 1.08 (N = 10)	2.30 ± 0.88 (N = 16)	.96
≥25	2.70 ± 0.92 (N = 28)	2.55 ± 0.95 (N = 17)	.62
Underlying disease (n)	1.14 ± 0.32	1.16 ± 0.33	<.01
DM	2.29 ± 2.08 (N = 2)	1.88 ± 1.82 (N = 2)	.85
DM and DLP	2.43 ± 0.92 (N = 19)	2.58 ± 0.92 (N = 14)	.65
DM, DLP, and HT	2.83 ± 0.91 (N = 17)	2.37 ± 0.83 (N = 17)	.14
Smoking (n)	1.09 ± 0.39	1.13 ± 0.34	<.01
Never	2.51 ± 1.00 (N = 31)	2.23 ± 0.83 (N = 19)	.23
Ex-smoker	2.67 ± 0.71 (N = 4)	2.66 ± 1.05 (N = 12)	.29
Active	3.45 ± 0.53 (N = 3)	2.93 ± 0.22 (N = 2)	.99
Drinking (n)	1.28 ± 0.58	1.31 ± 0.57	<.01
Never	2.66 ± 0.94 (N = 25)	2.23 ± 0.93 (N = 18)	.78*
Ex-drinker	2.02 ± 1.04 (N = 5)	2.51 ± 1.03 (N = 8)	.14
Active	2.76 ± 0.98 (N = 8)	2.85 ± 0.63 (N = 7)	.43
LDL-C (mg/dL)			
<100	2.46 ± 1.07 (N = 17)	2.35 ± 0.94 (N = 19)	.77
≥100	2.66 ± 0.86 (N = 20)	2.53 ± 0.88 (N = 14)	.68
HDL-C (mg/dL)			
Male			
<40	3.00 ± 0.95 (N = 3)	3.86 ± 0.49 (N = 4)	.25
≥40	2.01 ± 1.02 (N = 12)	2.44 ± 0.63 (N = 10)	.24
Female			
<50	2.93 ± 0.83 (N = 14)	2.39 ± 1.10 (N = 5)	.36
≥50	2.60 ± 0.81 (N = 8)	2.03 ± 0.73 (N = 14)	.12
TC (mg/dL)			
<200	2.58 ± 1.01 (N = 28)	2.45 ± 0.88 (N = 30)	.63
≥200	2.54 ± 0.83 (N = 9)	2.18 ± 1.39 (N = 3)	.70
Triglyceride (mg/dL)			
<150	2.47 ± 0.98 (N = 19)	2.50 ± 0.86 (N = 28)	.91
≥150	2.67 ± 0.95 (N = 18)	2.02 ± 1.19 (N = 5)	.30
FBS (mg/dL)			
<130	2.81 ± 0.88 (N = 8)	2.54 ± 0.80 (N = 24)	.46
≥130	2.60 ± 0.97 (N = 29)	2.30 ± 1.11 (N = 8)	.52

Abbreviations: DLP, dyslipidemia; DM, diabetes mellitus; HT, hypertension.
*Wilcoxon rank sum test.

optimal management of T2DM patients.[6] We demonstrated that the UMDA level was not significantly associated with glycemic control in our T2DM patients when using HbA1c of ≤7%, representing a well control group.[3] Our findings were inconsistent with previously published studies that showed poor control T2DM patients who have a HbA1c of more than 6.5% as being more likely to have high plasma MDA levels.[11] Patients with poor control T2DM had significantly higher levels of plasma MDA when compared with both good control patients and healthy people.[6] These inconsistent results might have occurred via the use of different criterions such as the percentage of HbA1c, level of FBS and previous studies using serum MDA, whereas, our study used urinary MDA.[5,7,10,11,15]

The factors related to glycemic control in T2DM patients oxidative stress is considered as a crucial factor, because this is an early indicator of metabolic syndrome and a contributor to the development of long-term vascular complications in DM. The lipid profile of patients in our study found that triglyceride and HDL-C of the poor control group were higher than the good control group ($P > .05$), while another study[16] reported that there is a significant correlation between HbA1c and dyslipidemia; particularly serum triglyceride. The increasing mechanism of triglyceride levels in hyperglycemic patients was involved in the reduction of lipoprotein lipase activity.[16] However, these results showed the importance of glycemic control in diabetes patients and the importance of

Table 4. Bivariate and Multiple Regression Analysis of Associations Between Urinary MDA and Factors.

	Bivariate		Multivariate		
Variables	Coefficient	95% CI	Coefficient	95% CI	*P* Value
Sex (n), Male = Ref.					
Female	0.05	−0.39, 0.5	0.2	−0.4, 0.8	.50
BMI (kg/m^2)	0.03	−0.02, 0.08	0.02	−0.03, 0.07	.40
Underlying disease (n), DM = Ref.					
DM and DLP	0.96	−0.1, 2.03	0.35	−0.63, 1.32	.48
DM, DLP, and HT	1.17	0.11, 2.24	0.54	−0.49, 1.57	.30
Smoking (n), active = Ref.					
Never	−0.64	−1.58, 0.29	−1.32	−2.23, −0.41	.005
Ex-smoker	−0.44	−1.45, 0.56	−0.7	−1.59, 0.19	.119
Drinking (n), active = Ref.					
Never	−0.17	−0.73, 0.39	0.31	−0.42, 1.04	.40
Ex-drinker	−0.41	−1.11, 0.29	−0.55	−1.2, 0.11	.10
Urine creatinine (μg/dL)	0.004	0.001, 0.007	0.004	0.001, 0.007	.01
HDL-C (mg/dL)	−0.04	−0.05, −0.02	−0.03	−0.05, −0.01	.002
Triglyceride (mg/dL)	0.0004	−0.0023, 0.003	0.003	−0.006, 0.0004	.03
TC (mg/dL)	−0.01	−0.01, 0.0003	−0.003	−0.008, 0.003	.39
FBS (mg/dL)	0.002	−0.0031, 0.0068	0.005	0.0001, 0.009	.04

Abbreviations: DLP, dyslipidemia; DM, diabetes mellitus; HT, hypertension.

increasing HDL-C values, because the mechanism of dyslipidemia in type 2 diabetes is dependent on insulin resistance, which distorts the lipoprotein lipase to hepatic lipase ratio; resulting in decreased HDL-C levels.[15]

Multivariate analysis was performed in this study to clarify the factors related to UMDA and glycemic control in T2DM patients. Smoking habits, HDL-C, triglyceride, and FBS levels were correlated between urinary Malonaldehyde and glycemic control in our T2DM patients. These might occur from hyperglycemia and fluctuation in blood glucose levels leading to the generation of ROS levels.[17] Smoking habits had a positive correlation with the level of MDA, as smoking is a risk factor for Coronary Artery Disease and is closely associated with increased oxidative stress. Additionally, the number of cigarettes smoked plays an important role in increasing the level of oxidative damage and reducing antioxidant defense.[18]

Limitations of This Study

There were several limitations for this study. First, there was no data concerning the laboratory's quality control (QC) data between plasma MDA and UMDA analysis. Second, patient medication; such as, Atorvastatin[15] might interfere with the results of our study, in that poor control T2DM patients who use a combination therapy with insulin may have Urinary MDA less than well controlled T2DM patients who use a single drug. Therefore, Laboratory QC and the medication should be considered in the next study.

Conclusion

The UMDA between well-control and poor-control T2DM was not different. However, patients who had good control of T2DM are expected to have better health outcomes than those in a poor control group. Non-smoking habits and increasing HDL-C levels were the protective factors, while increasing levels of FBS and triglyceride were negative factors of oxidative stress status. Therefore, UMDA, FBS, HDL-C, and triglyceride levels could be applied as follow-up criteria in T2DM patients, within primary healthcare settings.

Authors' Note

This research was conducted in the Primary Health Care Unit, at the Faculty of Medicine, Prince of Songkla University, Thailand.

Declaration of Conflicting Interests

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