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Original Article

Comparative analysis of plasma total antioxidant capacity in patients with hyperglycemia and hyperglycemia plus dyslipidemia

Virun Vichaibun [a, *], Kamonwan Khananurak [b], Thanet Sophonnithiprasert [a]

[a] Biochemistry Unit, Department of Medical Science, Faculty of Science, Rangsit University, Patumthani, 12000, Thailand
[b] Laboratory of Clinical Chemistry, Klang Hospital, Bangkok, 10100, Thailand

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ABSTRACT

Aims: The aim of this study was to measure plasma total antioxidant capacity (TAC) level and superoxide dismutase (SOD) activity in order to assess the oxidative stress status and the antioxidant defense system in patients with hyperglycemia and both hyperglycemia and dyslipidemia.
Materials and methods: Sixty blood samples of hyperglycemia, 60 blood samples of both hyperglycemia and dyslipidemia and 60 blood samples of normoglycemia and normolipidemia (controls) were collected into study. All samples were measured for the levels of plasma TAC and SOD by colorimetric method using microtiter-plate reader.
Results: Plasma TAC significantly decreased in patients with hyperglycemia (0.42 ± 0.1 mM) and both hyperglycemia and dyslipidemia 0.41 ± 0.1 mM) compared to those of controls (0.47 ± 0.14) ($P < 0.05$), whereas plasma SOD significantly increased in patients with hyperglycemia (81.0 ± 17.9 U/ml) and both hyperglycemia and dyslipidemia (83.7 ± 21.3 U/ml) compared to those of controls (73.7 ± 17.4 U/ml) ($P < 0.05$). However, the levels of plasma TAC and SOD had no significant difference between patients with hyperglycemia and both hyperglycemia and dyslipidemia ($P > 0.05$).
Conclusions: The present study showed the significant difference of plasma TAC and SOD levels in hyperglycemic patients with and without dyslipidemia compared to those of controls. There was no additive or synergistic effect in terms of decreased plasma TAC levels and elevated SOD activities between hyperglycemic patients with and without dyslipidemia.

1. Introduction

Hyperglycemia and dyslipidemia are groups of metabolic disorders characterized by elevated levels of plasma glucose [1] and by the lipid profiles of elevated levels of plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) including reduced high-density lipoprotein cholesterol (HDL-C) [2]. Diabetic hyperglycemia can lead to many complications including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and diabetic cardiovascular disease, whereas hypercholesterolemia can cause atherosclerosis [3]. High levels of glucose and/or cholesterol in blood may damage the cells through oxidative stress [4].

Studies have shown that hyperglycemia promotes the overproduction of reactive oxygen species (ROS) and induces oxidative stress causing the pathogenesis of diabetic complications [5]. However, oxidative stress can also decrease insulin sensitivity and damage the β-cells of pancreas resulting in the onset of diabetes mellitus [6]. The different cell types in hyperglycemia can also increase ROS production [6]. There are many evidences to show the correlation between diabetes and oxidative stress by measuring biomarkers [3]. Oxidative stress and activation of polyol pathway can be increased by hyperglycemia, which can provide inflammation and renal damage [7]. In addition to hyperglycemia, there have been reports that hypercholesterolemia may raise the risk for atherosclerosis [8]. Atherosclerosis involves in inflammatory and oxidative stress process on the arterial wall [9]. Oxidative stress and inflammation are interrelated because oxidative stress can cause inflammation; on the other hand inflammation can induce oxidative stress leading to cell injury [10]. Studies indicate that high levels of glucose and cholesterol lead to atherosclerotic vascular damage in patients with pathologic condition of insulin resistant [11]. The oxidation of low density lipoprotein (LDL) plays a vital role in atherosclerosis. High levels of oxidized LDL may damage blood

* Corresponding author.
E-mail addresses: virun.v@rsu.ac.th (V. Vichaibun), chemistry.klang@gmail.com (K. Khananurak), thanet.s@rsu.ac.th (T. Sophonnithiprasert).

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vessel and lead to produce foam cells and plaque resulting in atherosclerosis [12].

Antioxidant defense mechanisms consist of both enzymatic and non-enzymatic systems which show working as a team to prevent and attenuate the harmful effects of oxidative stress [13]. The measurement of each antioxidant is complex and very time-consuming as well as high-cost experiments. For this reason, the measurement of total antioxidant capacity (TAC) in serum or plasma can provide information of antioxidant status in patients [14]. Studies on antioxidant systems, the enzymatic antioxidant system plays a major role in controlling ROS levels [15]. SOD is the first line of defense superoxide radicals. SOD catalyzes the conversion of superoxide radical to hydrogen peroxide which is then reduced to water by catalase and glutathione peroxidase [16].

In this work, we choose one of the antioxidant enzymes on the basis of data in scientific literature to evaluate the enzymatic antioxidant system. There are few studies to compare antioxidant status between patients with hyperglycemia and both hyperglycemia and dyslipidemia. In our study, we measured plasma TAC level and SOD activity to assess the oxidative stress status and the antioxidant defense system in patients with hyperglycemia and both hyperglycemia and dyslipidemia.

2. Materials and methods

2.1. Subjected and study design

A random sample of sixty patients (27 men, 33 women) with hyperglycemia (glucose > 120 mg/dL, HbA1c > 6%), average age 62.1 ± 10.5 years and normal lipid profiles (TC < 200 mg/dL, LDL-C < 140 mg/dL, TG < 150 mg/dL), and sixty patients (28 men, 32 women) with both hyperglycemia and dyslipidemia (glucose > 120 mg/dL, HbA1c > 6%, TC > 200 mg/dL, LDL-C >140 mg/dL, TG > 140 mg/dL), average age 59.8 ± 10.4 years, were collected for plasma measurements of TAC and SOD.

Samples of control consisted of 28 men and 32 women, average age 63.7 ± 9.6 years, showed normal blood glucose (glucose < 110 mg/dL)and lipid profiles (TC < 200 mg/dL, LDL-C < 140 mg/dL, TG < 150 mg/dL). The sample with upper limit of creatinine and bilirubin were excluded from the study.

2.2. Specimens

Blood samples were drawn from an antecubital vein after overnight fasting and collected into Li-heparin tubes. The plasma was separated from whole blood by centrifuging blood samples at 3000 xg for 20 min at 4 °C. The plasma was then collected and stored at −80 °C until analysis. Samples with hemolysis were excluded. This study was approved by Ethics Committee of Research Institute of Rangsit University.

2.3. Plasma TAC analysis

Total antioxidant capacity in plasma was determined using antioxidant assay kit (Sigma-Aldrich). The assay is based on the inhibition of the oxidation of ABTS (2, 2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) to a radical cation, $ABTS^{+}$. The antioxidants in the sample prevent $ABTS^{+}$ formation and the color intensity decreases proportionally depending on the amount of antioxidants. The absorbance was read at 405 nm using a microtiter-plate reader, EZ Read 2000 (Biochrom). All samples were assayed in duplicate following manufacturer's instruction manual. Plasma TAC value is quantified as Trolox equivalent antioxidant capacity and expressed in the millimolar (mM) concentration.

2.4. Antioxidant enzyme assay

SOD was selected as the parameter for assessment of the enzymatic antioxidant system. SOD in plasma was measured using SOD determination kit (Sigma-Aldrich). The reaction based on the inhibition of the production of a water-soluble formazan dye which is produced by WST-1 (2-(4-Iodophenyl)-3-(4-nitrophenyl)-5-(2, 4-disulfophenyl)-2H-tetrazolium, monosodium salt) and superoxide anion. The rate of inhibition was proportional to the concentration of SOD. The absorbance was read at 450 nm using a microtiter-plate reader, EZ Read 2000 (Biochrom). All samples were assayed in duplicate following manufacturer's instruction manual. 1 U of SOD activity is defined as the amount of SOD required to inhibit the reduction of a water-soluble formazan dye by 50% under the assay conditions.

2.5. Biochemical analysis

Plasma glucose, TC, LDL-C, HDL-C and TG levels were assayed by colorimetric method using commercially available kits (Roche Diagnostics, Switzerland). Glycated hemoglobin (HbA1c) was determined on the basis of the turbidimetric inhibition immunoassay for hemolyzed whole blood using kit and assayed as described by the supplier (Roche Diagnostics). All tests were done on Cobas C 501 analyzer (Roche Diagnostics, Switzerland).

2.6. Statistical analysis

Statistical analysis of the data was performed using Microsoft Excel version 2010 software (Microsoft Corporation, Redmond, WA, USA). All variables were expressed as mean ± SD (standard deviation). Differences between the three groups were compared for significant by Student's unpaired two-tailed *t*-test. All statistical tests were 2-sided at the 5% significant level.

3. Results

The characteristics of the study groups are shown in Table 1. No differences were observed regarding age, sex distribution in between groups. Whereas, glucose and HbA1c levels in patients with hyperglycemia and both hyperglycemia and dyslipidemia were significantly elevated compared to those of controls ($P < 0.001$). There have been significant increases in TC, LDL-C and TG and decrease in HDL levels in patients with both hyperglycemia and dyslipidemia in comparison to controls and hyperglycemic patients without dyslipidemia ($P < 0.001$). However, there were no significant differences in TC, LDL-C, HDL-C and TG levels between controls and hyperglycemic patients without dyslipidemia ($P > 0.05$).

Level of plasma TAC was found to be decreased in patients with hyperglycemia (0.42 ± 0.1 mM) and both hyperglycemia and dyslipidemia (0.41 ± 0.1 mM) compared to those of controls (0.47 ± 0.14 mM) (Table 2). As shown in Fig. 1, the analysis of TAC levels in the plasma revealed significant differences in hyperglycemic patients with and without dyslipidemia as compared to those of controls ($P = 0.023$ and 0.043 respectively). However, there was no significant difference in plasma TAC levels between hyperglycemic and both hyperglycemic and dyslipidemic groups ($P = 0.74$). SOD levels in the plasma of patients with hyperglycemia (81.0 ± 17.0 U/ml) and patients with both hyperglycemia and dyslipidemia (83.7 ± 21.3 U/ml) were significantly higher than those of controls (73.7 ± 17.4 U/ml) ($P = 0.21$ and 0.005 respectively) but there was no significant difference between hyperglycemic and both hyperglycemic and dyslipidemic groups ($P = 0.45$) (Fig. 2).

Table 1
Characteristics of the studied blood samples.

Parameters	Control group	Hyperglycemic group	Hyperglycemic and dyslipidemic group	*P*-Value
Sex (Male/Female)	28/32	27/33	28/32	>0.05
Age ((Years)	63.78 ± 9.6	62.12 ± 10.5	59.87 ± 10.4	>0.05
Glucose (mg/dL)	96.58 ± 10.7	159.28 ± 37.7	172.37 ± 47.7	<0.01
HbA1c (%)	5.29 ± 0.4	6.90 ± 0.8	7.65 ± 1.6	<0.01
TC (mg/dL)	162.97 ± 23.2	162.08 ± 24.7	242.75 ± 33.6	<0.01*
LDL-C (mg/dL)	100.35 ± 21.6	101.10 ± 26.6	175.85 ± 35.7	<0.01*
HDL-C (mg/dL)	57.63 ± 12.1	55.02 ± 12.5	50.10 ± 12.9	<0.05*
TG (mg/dL)	113.38 ± 35.5	117.82 ± 36.2	226.00 ± 83.5	<0.01*

AbbreviationsHbA1c, Glycated hemoglobin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride.
Data presented as mean ± SD.
Asterisk (*) indicated the *P*-value between control and both hyperglycemic and dyslipidermic group.

Table 2
Assessment of TAC and SOD values in the blood samples.

Parameters	Control group	Hyperglycemic group	Hyperglycemic and dyslipidemic group	*P*-Value
TAC (mM)	0.47 ± 0.14	0.42 ± 0.1	0.41 ± 0.1	<0.05
SOD (U/ml)	73.7 ± 17.4	81.0 ± 17.0	83.7 ± 21.3	<0.05

AbbreviationTAC, total antioxidant capacity; SOD, superoxide dismutase.
Data presented as mean ± SD.

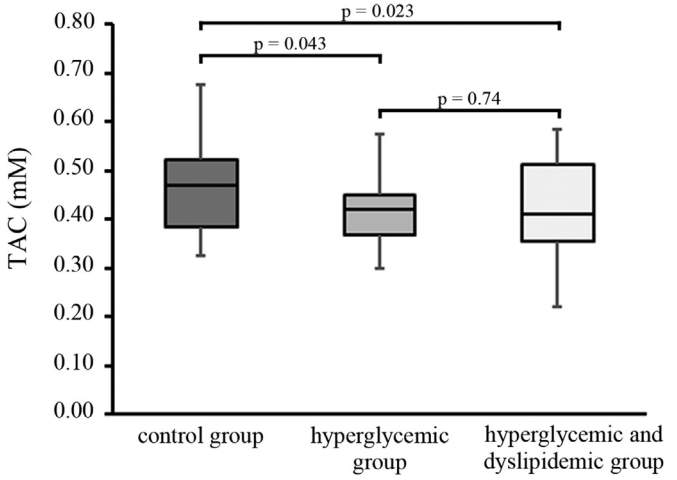

Fig. 1. Comparison of TAC levels in the blood samples among different study groups: Box and Whisker plot shows median, upper median, lower median and minimum to maximum range of plasma TAC.

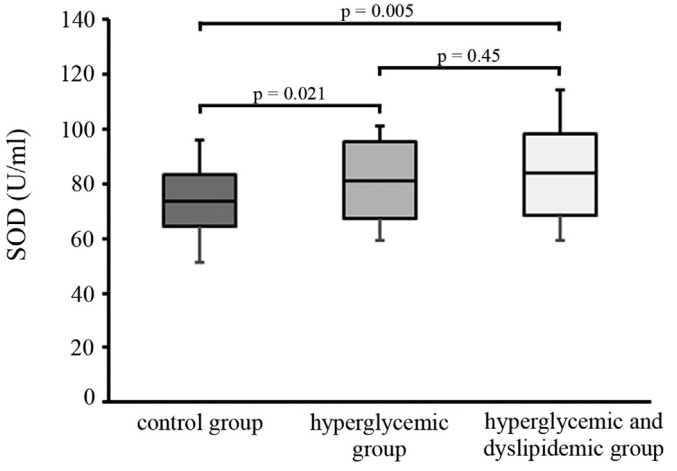

Fig. 2. Comparison of SOD activity in the blood samples among different study groups: Box and Whisker plot shows median, upper median, lower median and minimum to maximum range of plasma SOD activity.

4. Discussion

Oxidative stress plays a major role in the pathogenesis in many diseases. Hyperglycemia and dyslipidemia can induce oxidative stress leading to endothelial dysfunction [17]. In addition to hyperglycemia, patients with both hyperglycemia and dyslipidemia showed significantly increased TC, LDL-C, and TG and decreased HDL-C when compared to those of controls. Whereas, hyperglycemic patients without dyslipidemia showed no significant differences in lipid profiles compared to those of controls. Patients with both hyperglycemia and dyslipidemia tend to have a higher risk of the complications. Increase in glucose and insulin levels along with dyslipidemia in patients developing macroangiopathies caused oxidative stress leading to atherosclerosis [11]. Therefore, we were interested in measuring the plasma TAC levels in patients with hyperglycemia and both hyperglycemia and dyslipidemia as an appropriate marker of oxidative stress. Besides, we measured SOD activity and compared between groups in order to explore the enzymatic antioxidant defense system. This is the first study to evaluate the comparative between TAC values and SOD activity in hyperglycemic patients with and without dyslipidemia. The plasma TAC level in our study was significantly decreased in patients with hyperglycemia and both hyperglycemia and dyslipidemia as compared to those of controls. However, there was no significant difference in plasma TAC level between hyperglycemic and both hyperglycemic and dyslipidemic groups although plasma TAC level in patients with both hyperglycemia and dyslipidemia slightly decreased when compared to patients with hyperglycemia. A lower TAC level might reflect oxidative stress status in the patients. Consistent with our results, previous studies have shown that patients with diabetes have reduced TAC levels in plasma or serum [18]. In addition, TAC level was significantly decreased in impaired fasting glucose group as compared to normal [19]. There was report an association between diabetic patients and oxidative stress, which demonstrated that diabetic patients with complications have increased oxidative stress and reduced TAC levels compared to those of diabetic patients without complications [20]. Hyperglycemia induced several pathways to produce ROS leading to

decreased plasma TAC levels [21]. The reduction of plasma TAC levels in patients with hyperglycemia and both hyperglycemia and dyslipidemia may be a result of high levels of ROS. Different studies have demonstrated that hyperglycemia induced the overproduction of ROS such as superoxide anion leading to complications [22]. From our results, hyperglycemic patients with dyslipidemia had no additive or synergistic effect in terms of decreased plasma TAC levels compared to those of hyperglycemic patients without dyslipidemia. However, hyperglycemia and dyslipidemia in patients lead to increase risk factor for cardiovascular events [23].

Superoxide anion is thought to be one of the important ROS causing the pathogenesis of many diseases. SOD is often the first line of defense against oxidative stress and responsible for the dismutation of superoxide anion. There are three isoforms of SOD that have been identified and characterized in humans. SOD1 (CuZn-SOD) is found in the cytoplasm and nucleus; SOD2 (Mn-SOD) is found in the mitochondria; and SOD3 (extracellular SOD, EC-SOD) is found in extracellular matrix of tissues [24]. Our studies found a significant increase of plasma SOD activity in hyperglycemic patients with and without dyslipidemia as compared to those of controls. Plasma SOD activity in hyperglycemic patients with dyslipidemia slightly increased when compared to hyperglycemic patients without dyslipidemia, but there was no significant difference between groups. Several studies examined the association between SOD activity and diabetic patients and reported that SOD activity in patients with hyperglycemia decreased significantly as compared to normal [25,26]. Whereas some studies found elevated SOD activity in diabetic patients compared to controls which were consistent with our findings [27–29]. Few studies found no significant difference in SOD activity between hyperglycemic and normoglycemic groups [30]. The variation in results might be due to the duration and the amount of ROS presenting in patients. From previous reports, hyperglycemia induced oxidative stress and inflammation resulting in enhancing the SOD production by leukocytes and monocytes [31]. The increased ROS also induced higher activities of the main enzymes such as SOD CAT and GPx that metabolized them [32]. SOD activity could be also increased in response to several conditions such as heat shock, shear stress and oxidative stress [33]. In our results, it is possible to consider the increase of plasma SOD levels as compensatory mechanism in order to attenuate oxidative stress levels and restore homeostatic balance. Therefore, SOD levels may serve as a marker of the balance between ROS production and antioxidant defense system. In general, EC-SOD had an affinity for heparin-like substance [34] and glycoaminoglycans on the endothelial cell surface [35]. Patients with hyperglycemia showed a higher glycated SOD [36] and glycation changed the affinity for heparin leading to a decrease amount of SOD binding to the cell surface [37]. Another plausible explanation is that the decrease in binding of EC-SOD leads to an increase in plasma SOD levels. The appearance of EC-SOD on the endothelial cell surface at a high level might play an important role in protecting damage from superoxide anion in the vascular wall and preventing LDL oxidation [38].

Several studies reported that hypercholesterolemia was associated with increase cellular superoxide anion production [39]. Different studies demonstrated that one of the important steps in the process of atherosclerosis was macrophages uptake oxidized LDL in the arterial wall, whereas native LDL particles were recognized by LDL receptor in normal metabolic pathway [40]. Previous studies showed that dyslipidemia increased the oxidation of LDL which was associated with high levels of native LDL [41]. Likewise, there was report that elevated levels of LDL-C and TG can enhance circulating oxidized LDL levels [42], whereas HDL-C protects LDL particles from oxidation [43]. Other studies demonstrated that patients with high LDL-C levels led to increase oxidized LDL-C and SOD levels which high SOD activity was likely to scavenge superoxide anion overproduction [44]. In our studies, plasma SOD activity in hyperglycemic patients with dyslipidemia slightly increased when compared with hyperglycemic patients without dyslipidemia. There was no additive or synergistic effect in terms of increased SOD activity between hyperglycemic patients with and without dyslipidemia. Consistent with our findings, there was study in patients with familial hypercholesterolemia and found the increase of oxidative stress in circulating mononuclear cells in the absence of elevated antioxidant enzymes such as SOD CAT and GPx [39]. The association of high SOD activities and oxidative stress situations such as hyperglycemia and dyslipidemia could be interpreted as a defense mechanism against oxidative injury. There are some limitations in our studies that should be considered. Our studies were done in a small group of samples, thus the results should be confirmed in the larger sample groups. The results should be interpreted carefully because the possibility of interference by medication could occur in the plasma of patients.

5. Conclusions

The present study showed that plasma TAC levels in hyperglycemic patients with and without dyslipidemia significantly decreased in comparison with those of controls. In addition, plasma SOD activities in hyperglycemic patients with and without dyslipidemia significantly increased compared to those of controls. However, there was no additive or synergistic effect in terms of decreased plasma TAC levels and elevated SOD activities between hyperglycemic patients with and without dyslipidemia. So now the important of TAC levels and SOD activities could be necessary markers while dealing with criteria for hyperglycemia and both hyperglycemia and dyslipidemia. From our finding, however, diabetic patients should control not only glucose levels but also lipid levels in order to decrease oxidative stress.

Conflicts of interest

The authors state no conflict of interest.

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