BLOOD CHOLINESTERASE ACTIVITY AND OXIDATIVE STRESS IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Background: Type 2 diabetes mellitus is a metabolic disorder that affects functional aspects of many enzymatic systems, including those of blood cholinesterases. The aim of the present study was to assess the association between oxidative stress and blood plasma cholinesterase activities in patients with type 2 diabetes.

Subjects and methods: A total of 200 subjects (100) apparently healthy individuals and 100 type 2 diabetic patients) of both sexes (50/gender) were enrolled in this study. Their ages ranged between 30 to 70 years. The enrolled participants were not exposed to organophosphate insecticides or any medication that is known to interfere with cholinesterase activity. The criteria of WHO for diagnosis of type 2 diabetes were applied for confirming the diagnosis. Plasma malondialdehyde concentration, an oxidative stress marker and both plasma and erythrocyte cholinesterase activities were measured in all subjects.

Results: Significantly ($P< 0.05$) higher plasma malondialdehyde concentrations with both plasma and erythrocyte cholinesterase activities were found in type 2 diabetic patients, compared to respective healthy individuals. Plasma malondialdehyde concentrations significantly increased in both male and female type 2 diabetic patients in comparison with healthy individuals. Plasma cholinesterase activity significantly increased in type 2 diabetic male patients, whereas that of the erythrocyte significantly increased in type 2 diabetic females compared to healthy individuals' respective values.

Conclusions: Elevated malondialdehyde concentrations in conjunction with increased blood cholinesterase activities may render type 2 diabetic patients more susceptible to oxidative stress; this might impact therapy with cholinesterase inhibitors when there is exposure to anticholinesterase pesticides.

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Keywords: Cholinesterase,Malondialdehyde,Organophosphate,Oxidativestress,Type2 iabetes

Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused by impairment of insulin secretion and/or peripheral insulin resistance leading to dysfunctions of glucose utilization by the liver, skeletal muscles, and adipose tissues[1]. The most apparent manifestation of T2DM is fasting and postprandial hyperglycemia, which is the primary contributor to the induction of further metabolic disturbances[1,2]. Hyperglycemia in association with diabetes mellitus strongly correlates with increased production of free radicals, especially reactive oxygen species in tissues and subsequently oxidative stress[3,4]. The oxidative stress in diabetes mellitus further compromises insulin secretion and insulin action with metabolic derangements in the cardiovascular system[1,3,4]. Elevated lipid peroxidation biomarker in the plasma malondialdehyde (MDA) is directly linked

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to oxidative stress in diabetic patients[1-4].

Cholinesterases (ChEs) are enzymes that hydrolyze acetylcholine into choline and acetate at the nerve endings[5, 6]. There are two types of ChEs in the blood, true ChE, which is present in the red blood cells as well as in platelet and white blood cells, whereas in the plasma, atypical or pseudo-ChE is present[5,6]. The role of these enzymes in the blood is not elucidated very well till now; however, they are useful for biomonitoring exposure to ChE inhibiting pesticides[6-11]. Many reports have indicated that blood ChEs are modulated by diabetes-induced metabolic changes[12-23]. The majority of the studies reported increases in plasma, serum or erythrocyte ChEs[14-18,23]. Whereas others showed a decrease in the enzyme activity[19-21]. However, regardless of the nature of the change in enzyme activity, hyperglycemia was the most common and the most important factor found in diabetic patients, which led to the speculations that hyperglycemia affects the activities of blood ChEs[1,5,14,18,23-25]. Even in laboratory animals rendered diabetic experimentally, similar findings of increased ChE activity and hyperglycemia were reported[22,26]. A recent report in type 2 diabetic patients showed increases in plasma and erythrocyte ChEs, coupled with increased susceptibility of the enzyme to the ChE inhibiting organophosphate dichlorvos[23]. This finding and others reported earlier raised the speculations that type 2 diabetic patients might be more prone to side effects of antiChEs[23,27,28].

Limited information is available about the combined effects of T2DM on blood ChEs and the status of oxidative stress in patients[17,29]. The aim of the present study was to identify any association between oxidative status and blood ChE activities in type 2 diabetic patients in Duhok governorate, Iraq.

SUBJECTS AND METHODS

Recruitment of patients who agreed to participate in the study was from Azadi Hospital, Duhok, Iraq, between September 2017 to March 2018. Their ages were between 30 to 70 years. All participants were briefed about the aim of the study. Written consent forms were obtained from all of them. According to WHO criteria, the final participants in the study were 100 (50 of each gender) patients diagnosed with T2DM[30]. For comparison purposes, healthy and age-matched 100 subjects (50 of each gender) were selected from non-smokers, alcohol-free, had no history of chronic diseases, and had a fasting glucose level (60-125 mg/dL). The enrolled participants were not exposed to organophosphate insecticides or any medication known to interfere with ChE activity. Blood glucose levels were determined by using a conventional certified assay procedure recommended by local health authorities.

Five mL venous blood samples were collected from each subject. The plasma and erythrocytes were separated using a centrifuge (4 ^{0}C) at 3000 rpm, for 15 minutes. The plasma and erythrocyte aliquots were harvested and kept at -30 °C for later analysis within one week of blood collection. A colorimetric method was used to determine plasma MDA concentration at 535 nm[31]. Plasma and erythrocyte ChE activities were determined by Ellman's spectrophotometric method[32], which is

based on yellow color development after hydrolysis of the substrate acetylthiocholine to form thiocholine which combines with the coloring agent dithiobisnitrobenzoate. The developed yellow color was measured spectrophotometrically at 410 nm.

Data were analyzed using IBM Corp. Released 2019. IBM SPSS Statistic for Windows, Version 26.0. Armonk, NY: IBM Corp. The student's t-test was used to estimate differences between the groups. The level of significant difference was at $P < 0.05$.

RESULTS AND DISCUSSION

Plasma MDA concentrations and both plasma and erythrocyte ChE activities significantly increased in type 2 diabetic patients, regardless of gender, when compared to respective control values of the healthy individuals (Table1). No statistically significant correlation was found between MDA concentrations and the ChE activities in the plasma and erythrocytes ($r = 0.015$ and 0.16, respectively). Elevated plasma MDA concentration is a convenient biomarker of oxidative stress and lipid peroxidation induced in many metabolic diseases, including both types 1 and 2 diabetes mellitus[1-4,33]. It is commonly used to assess the status of oxidative stress clinically in T2DM[1-4,33]. This finding of increased plasma MDA of type 2 diabetic patients (Table 1) further supports previous reports on the occurrence of oxidative stress in patients with T2DM.1-4,33 However, in contrast to the present study, some studies have reported increased MDA in only one gender suffering from T2DM34-37. The reason for this discrepancy is not fully known. It is possible that contributing factors to such an effect include but are not limited to age, alcohol use, smoking, and disease conditions34-36. Further, females may have inherently higher plasma MDA levels compared to males38.

Table 2 shows that plasma MDA concentrations significantly increased in both male and female type 2 diabetic patients compared to those of the respective healthy individuals. However, plasma ChE activity significantly increased in type 2 diabetic male patients, whereas erythrocyte ChE activity significantly increased in type 2 diabetic females when compared with respective values of healthy individuals.

Table 1: Plasma malondialdehyde (MDA) concentrations and plasma and erythrocyte cholinesterase (ChE) activities in the studied subjects

Groups	MDA (µmol/L)	Plasma ChE (mM/min)	Erythrocyte ChE (mM/min)
Healthy individuals	0.223 ± 0.133	0.201± 0.041	0.229 ± 0.054
Diabetic patients	0.305 ± 0.182*	0.217 ± 0.069*	0.262 ± 0.088*

* Significantly different from the corresponding value of the healthy individuals, $p \leq 0.05$.
Values are mean + SD of 100 subjects/group.

Table 2: Plasma malondialdehyde (MDA) concentrations and plasma and erythrocyte cholinesterase (ChE) activities in type 2 diabetic male and female patients

Gender	Group	MDA (µmol/L)	Plasma ChE (mM/min)	Erythrocyte ChE (mM/min)
Males	Healthy	0.257 ± 0.143	0.212 ± 0.043	0.213 ± 0.055
	Patients	0.356± 0.228*	0.246 ± 0.066*	0.206 ± 0.069
Females	Healthy	0.190± 0.114	0.189 ± 0.035	0.246 ± 0.048
	Patients	0.254±0.992*	0.188 ± 0.058	0.318 ± 0.066*

* Significantly different from the corresponding value of the healthy individuals, $p \leq 0.05$.
Values are mean + SD of 50 subjects/gender/group.

Measurement of blood ChE activities is used for biomonitoring exposure to ChE inhibiting pesticides.6-9,39,40 Further, many metabolic diseases affect plasma (serum) and erythrocyte ChE activities5,12. T2DM was also reported to affect ChE activities in the blood, producing an increase,14-18,23 or even a decrease19-21 in plasma (serum) or erythrocyte ChE activities. In the present study, both blood ChE activities significantly increased in type 2 diabetic patients regardless of gender (Table 1). However, any gender-related increase in blood ChE activity (Table 2) could be attributed to inherently sex differences in ChE activity and possibly to the differences in the status of T2DM in patients and different therapeutic regimens applied on them.1,5,12-15,25,41 Nevertheless, the overall increase in blood ChE activities in the present study (Tables 1 and 2), further supports the recently reported elevation in blood ChE activities in diabetic patients.14-18,23 The reason for this increase in enzyme activity is not fully known. It could be associated with increases in serum triglycerides levels and lipoprotein metabolism,12,15,25 and furthermore, the status of hyperglycemia possibly increases the catalytic mechanisms of serum ChE.25 In this context, our findings of increases in plasma MDA and blood ChE activities are in accordance with the notion that changes in enzyme activity and the associated cardiovascular complication are seen in T2DM1,2,14-18. Furthermore, increases in blood ChE activities could be related to low-grade systemic inflammations, which are also found in diabetes.42

The elevated plasma MDA in the diabetic group in this study (Tables 1 and 2) further supports the notion that chronic hyperglycemia in diabetes mellitus favors the production of reactive oxygen species, which is a common finding in T2DM.1-4,33 In this context, together with alterations in ChE activity of the diabetics, there are speculations that oxidative stress modulates plasma or erythrocyte ChE activities, and this, in turn, might impact the enzyme reactivity to ChE inhibiting drugs or pesticides.29,40,43,44

CONCLUSIONS

Changes in blood ChE activities should be expected in type 2 diabetic patients suffering from hyperglycemia and oxidative stress. This enzymatic effect could have an impact on therapy with ChE

inhibitors and may modulate the outcome of exposure to antiChE pesticides.

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ETHICAL CLEARANCE

Ethical approval and informed consent
The Postgraduate Committee approved this study of the College of Medicine, University of Duhok, and by the Local Research Ethics Committee at the Duhok Health Office, Duhok, Iraq.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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پوختە

چالاکییا کولین ئستیرێز و ئەوکسێدێتڤ ستریس ل دەف نەخوشێن ئێشا شەکری جورێ دووێ

پێشەکی: ئێشا شەکری جۆرێ دووێ ئێك ژوان نەخوشییێن میتابولزمیە ژئەگەرێ کێمبۆنا سێکریشنا ئەنسولینێ یان ریزێستنا وێ چێدبیت لگەل هندەك فاکتەرێن دی یێن مەترسی وەك قەلەوبون، انورمالیا جێنیتیکی، دبیت ئەگەر بۆ کێم وەرگرتنا کلوکوزی ل کەزەبێ ,ماسولکێت سکێلیتەل ,وتەڤنێن ئەدیبوس.
ئارمەناجا ئەڤێ ڤەکولینێ خواندنا رێژا تەئەکسدێ و چالاکییا کولین ئستیرێز ل دەف نەخوشێن ئێشا شەکری جورێ دووێ.
رێکێن ڤەکولینێ: ل ڤێ ڤەکولینێ کومەك پێکهاتی ژ 200 کەسان هاتیە تومارکرن (کوما کەسێن ساخلەم پێکهێت ژ100 کەسان، کوما کەسێن توشی نەخوشییا شەکری ژ جورێ 2 پێکهاتیە ژ100 کەسان) ژهەردوو رەگەزا بو هەر کومەکی 50. تەمەنێ وان ناڤبەرا 30 تا 70 سالی، نەخوشییا شەکری هاتە دەستنیشانکرن ل دویف پیڤەرێن رێکخراوا ساخلەمیا جیهانێ .
ئەنجام: رێژا چریا ئەلمالوندیهاید ل پلازما کەسێن توشبویی ب نەخوشییا شەکری ژ جورێ دووێ ژ نێر و مێیا زێدەبونەکا زۆر بخوڤە دیتیە ببەراوەرد دگەل کوما کەسێن ساخلەم.
هەر وەسا زێدەبونەکا مەزن ل چالاکییا پلازما وگوگێن سور ل کەسێن توشبویی ب نەخوشییا شەکری ژ جورێ دووێ دیتیە ببەراوەرد دگەل کوما کەسێن ساخلەم.
دەرئەنجام: ژبەر زێدەبونا بەرچاڤ یا کولێنستریز و رێژا تەئەکسدێ ل دەف نەخوشێن شەکری، دبیت ئەونەخوشان پتر حەساسییەت هەبن بو نەخوشێن دی وەك ئەلزهایمەر و مەسێنیە گراڤێز بەرامبەر کروبێن ساخلەم.

الخلاصة

نشاط الكولينستراز والإجهاد التأكسدي في مرضى السكري من النوع 2

الخلفية والأهداف: داء السكري من النوع الثاني هو أحد الاضطرابات الأيضية الناتجة عن ضعف إفراز الأنسولين و / أو مقاومة الأنسولين المحيطية إلى جانب عوامل الخطر الأخرى مثل السمنة والشذوذ الوراثي ، مما يؤدي إلى خلل في استخدام الجلوكوز من قبل الكبد والعضلات الهيكلية والأنسجة الدهنية. كان الهدف من هذه الدراسة هو فحص الإجهاد التأكسدي ونشاط أستيل كولينستراز في مرضى السكري من النوع 2.

طرق البحث: تم تسجيل ما مجموعه 200 شخص (100 مجموعة تحكم و 100 مصاب بالسكري من النوع 2) من كلا الجنسين (50 / مجموعة) في هذه الدراسة. تراوحت أعمارهم بين 30 و 70 سنة. تم تشخيص مرضى السكري وفقا لمعايير منظمة الصحة العالمية.

النتائج: زيادة ملحوظة في نسبة البلازما للمالونديهايد في مرضى السكري من النوع 2 من الذكور والإناث مقارنة بمجموعات التحكم المقابلة. كذلك حدثت زيادة معنوية في نشاط إنزيم الكولينستريز في البلازما وكريات الدم الحمراء في مرضى السكري من النوع 2 مقارنة بمجموعة التحكم.

الاستنتاج: إن مرضى السكري أكثر حساسية للإصابة بأمراض مثل مرض الزهايمر والوهن العضلي من الأفراد العاديين و ذلك بسبب زيادة الإجهاد التأكسدي ونشاط الكولينستريز لديهم.