

In Vitro Effect of Zinc Sulphate on Granulocytes Functional Activity in Diabetic Patients Measured by mean of Luminal-dependent Chemiluminescence in Human Whole Blood

ISSN -1817 -2695

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((Received 10/2/2009, Accepted 23/12/2009))

Abstract

Diabetes mellitus is one of the most widely distributed metabolic disorders and occurs in almost all populations of the world at a variable prevalence. Diabetic patients commonly have a decreased activity of granulocytes. The aim of this study is to evaluate the activity of granulocytes and assess the effectiveness of zinc sulphate on the activity of granulocytes in diabetic patients.

The study includes one-hundred and forty subjects, eighty had diabetes mellitus (forty males and forty females), and sixty healthy subjects (forty-nine males and eleven females). The activity of granulocytes was studied by the chemiluminescence technique for diabetic patients and healthy subjects. There was highly significant difference ($P < 0.001$) in the activity of granulocytes between the healthy subjects and diabetic patients, also there was a significant difference ($P < 0.01$) in the activity of granulocytes between males and females diabetic patients and males and females healthy subjects.

We studied the influence of zinc sulphate on phagocytic activity of granulocytes of diabetic patients and healthy subjects, the study shows that the mean and SD for granulocytes activity and low concentrations of zinc sulphate (0.1, 1, 5 and 10) $\mu\text{g/ml}$ for diabetic patients and healthy subjects, there were no significant differences in the activity of granulocytes between the control (zinc concentration = 0) and the test sample (with zinc sulphate) at different low concentrations of zinc sulphate. The study included effect of different concentrations of zinc (0.68 mg/ml, 1.36 mg/ml, 2.05 mg/ml, 2.73 mg/ml and 3.41 mg/ml), there were significant differences ($P < 0.01$) in the phagocytic activity of granulocytes between the control (zinc concentration = 0) and the test sample (with zinc sulphate) at different concentrations of zinc (0.68, 1.36, 2.05, 2.73 and 3.41) mg/ml for diabetic patients and healthy subjects. Also, we studied the effect of zinc sulphate on the activity of granulocytes for diabetic patients with and without recurrent infections, there were significant differences ($P < 0.01$) in phagocytic activity of granulocytes between the control (zinc concentration = 0) and the test sample (with zinc sulphate) at different concentrations of zinc (0.68, 1.36, 2.05, 2.73 and 3.41) mg/ml for both groups of patients (with recurrent infections and without recurrent infections).

Conclusion: It is concluded that there is a significant decrease in the activity of granulocytes in patients with diabetes mellitus and supplementation with zinc may benefit the activity of granulocytes in these patients.

Keywords: Diabetes mellitus, zinc, granulocytes, chemiluminescence.

Introduction

Zinc is one of the essential trace elements that is required to maintain the normal physiological function of all forms of life [1]. Zinc occurs within a great variety of foods of both animal and plant origin. Zinc within animal products is more readily available than that within plant products [2]. Zinc is present in every cell of the body & essential for many physiological processes such as protein synthesis, tissue repair, glucose metabolism and immunological functions [3, 4]. It plays a role in the protection against infections [5] and stimulates the activity of approximately 100 enzymes, which are substances that promote biochemical reaction in our body [6]. This element has been linked to carbohydrate and insulin metabolism through the pancreatic β -cell, in direct relationship with insulin microinclusions [7]. A previous study demonstrated a 50% drop in pancreatic zinc in diabetic patients as compared to healthy subjects [8]. Furthermore, granulation of the islet β -cell is decreased in zinc-deficient animals, a condition which implies impaired glucose tolerance [9]. Similarly, zinc is thought to play a role in regulating the synthesis, storage and secretion of insulin [10].

Diabetes mellitus is one such disorder, which is associated with altered granulocyte function [11]. Zinc deficiency is associated with depression of a number of cellular immune functions, including delayed type hypersensitivity, T helper cell activity development of cytotoxic T cells and mitogen T-lymphocyte proliferation [12, 13].

Phagocytes play a crucial role in host protection by combating infection. For this purpose they have a molecular mechanism that is able to generate toxic oxygen derivatives. The signaling pathways involved in the stimulus-response of the plasma membrane oxidase system. The initial product of NADPH oxidase mediated oxygen reduction is primarily superoxide anion (O_2^-), a very potent free radical. The superoxide is converted to H_2O_2 either spontaneously or by superoxide dismutase. The electron donor for NADPH oxidase is cytosolic NADPH. The O_2^- generated by the respiratory burst is released at the outer surface of the granulocyte membrane, or into the phagocytic vacuole when bacteria are engulfed [14-18].

Aim of the study

The aim of this study is to evaluate the activity of granulocytes and assess the effectiveness of zinc

sulphate on the activity of granulocytes in diabetic patients.

Subjects and Methods

Eighty patients had diabetes mellitus, forty males and forty females age ranged (17-70) years were referred to Al-Sader Teaching Hospital in Basrah city. Seventeen of these patients with type I diabetes mellitus (IDDM) and sixty-three patients with type II diabetes mellitus (NIDDM). Twenty-two patients had a history of recurrent infections.

Sixty healthy volunteers were used as controls, forty-nine males and eleven females age ranged (16-47) years.

Ethical consent was obtained from the local area Ethical committee (Al-Sader Teaching Hospital).

All subjects were questioned about their past medical history, a pre-tested questionnaire was used, which was designed to obtain information on gender, birth date, duration of disease, history of disease, exposure to inflammations, exposure to diseases, drugs taken and insulin taken. After an overnight fast, we drew 3 ml of venous blood for hematological study (white blood cells count), biochemical study (glucose) and Luminol-dependent chemiluminescence Measurements (granulocytes functional activity in whole blood).

Blood samples were incubated with different concentrations of zinc sulphate (0.68 mg/ml, 1.36 mg/ml, 2.05 mg/ml, 2.73 mg/ml and 3.41 mg/ml) for 30 minutes. 10 μ l from each concentration of zinc sulphate was added to 0.2 ml of whole blood.

The phagocytosis of neutrophil was measured by the chemiluminescence technique, the reaction mixture consisted of 1 ml chemiluminescence inducer ($BaSO_4$ suspension), 0.1 ml of NaOH and 0.1 ml of luminal in a 5 ml beaker, 0.01 ml of whole blood was added to the above mixture and agitated to mix well before it was poured into the measuring cuvette of photon counting system. Chemiluminescence was continuously recorded on a chart recorder, until the chemiluminescence peaked and demonstrated a definite decline, whole blood was used to mirror the in vivo situation [19].

Statistical analysis:-using one-way analysis of variance (ANOVA) to compare the results between diabetic patients and healthy subjects, $P < 0.01$ was considered as significant.

Results

Table (1) shows the activity of granulocytes in healthy subjects and diabetic patients. There was significant differences between healthy subjects and diabetic patients in functional activity of granulocytes (P<0.001). Also Table 1 shows the activity of granulocytes in healthy subjects and diabetic patients according to the gender; there was significant differences between healthy male subjects and diabetic male patients in functional activity of granulocytes, also there were differences between healthy female subjects and diabetic female patients in functional activity of granulocytes (P<0.01).

Test values for healthy subjects and diabetic patients are presented in table 2. This table includes the effect of low concentrations of zinc sulphate on the activity of granulocytes in diabetic patients and healthy subjects {final concentrations in the blood were (0.1, 1, 5 and 10) µg/ml}, there were no significant differences in phagocytic activity of granulocytes (P>0.01) between control (zinc concentration = 0) and test sample {zinc sulphate, different concentrations (0.1, 1, 5 and 10) µg/ml} for both groups (diabetic patients and healthy subjects).

Table (3) shows the effect of different concentrations of zinc sulphate on the activity of granulocytes in diabetic patients and healthy subjects {final concentrations in the blood is (0.68, 1.36, 2.05, 2.73 and 3.41) mg/ml}, there were significant differences

in phagocytic activity of granulocytes (P<0.01) between the control (zinc concentration = 0) and the test sample (with zinc sulphate) different concentrations of zinc (0.68, 1.36, 2.05, 2.73 and 3.41) mg/ml for both two groups (diabetic patients and healthy subjects). The percentage of enhancement of granulocytes functional activity for both groups (diabetic patients and healthy subjects) was similar in pattern.

Zinc ion caused enhancement of the chemiluminescence functional activity of granulocytes for each group (group of healthy subjects and group of diabetic patients) as shown in (figure 1).

Table (4) shows the effect of different concentrations of zinc sulphate on the activity of granulocytes in the diabetic patients (with & without history of recurrent infections), there were significant differences in phagocytic activity of granulocytes (P<0.01) between blood without zinc (concentration = 0) and blood with zinc sulphate {different concentrations of zinc (0.68, 1.36, 2.05, 2.73 and 3.41) mg/ml} for both groups of patients (with recurrent infections and without recurrent infections). The percentage of enhancement of granulocytes functional activity for both groups of patients (with recurrent infections and without recurrent infections) was similar in pattern.

Table .1: Chemiluminescence functional activity of granulocytes for healthy subjects and diabetic patients measured by mean of luminol–dependent chemiluminescence at 37°C.

Subjects	Granulocytes functional activity yield in whole blood		
	n	(M ± S.E) × 10 ⁻³	
		Males	Females
Healthy subjects	60	584.8 ± 28.5	405.1 ± 29.7
		n=49 608.0 ± 32.8	n=11 405.1 ± 29.7
Diabetic patients	80	400.9 ± 18.4	481.5 ± 41.8
		n=40 396.6 ± 22.1	n=40 481.5 ± 41.8

P < 0.001

P < 0.01

Table. 2: Effect of different low concentrations of zinc sulphate on chemiluminescence functional activity of granulocytes in vitro of healthy subjects and diabetic patients.

Concentration of zinc sulphate µg / ml	Diabetic Patients n=8 (M ± S.E) × 10 ⁻³	Healthy Subjects n=8 (M ± S.E) × 10 ⁻³
0	473.37 ± 79.1	710.00 ± 47.8
0.1	397.00 ± 59.3	758.87 ± 37.2
1	373.00 ± 46.5	753.75 ± 46.5
5	349.12 ± 40.1	751.75 ± 42.7
10	356.75 ± 27.7	761.50 ± 78.1

P > 0.01

P > 0.01

Table .3: Effect of of zinc sulphate on chemiluminescence functional activity of granulocytes of diabetic patients and healthy subjects.

Concentration of zinc sulphate mg / ml	Diabetic Patients n=37 (M ± S.E) × 10 ⁻³	The % of enhancement of granulocytes activity	Healthy Subjects n=21 (M ± S.E) × 10 ⁻³	The % of enhancement of granulocytes activity
0	341.1 ± 60.0	0	543.10 ± 88.5	0
0.68	460.4 ± 56.8	34.9	711.1 ± 117.9	30.9
1.36	567.1 ± 59.9	66.2	921.6 ± 154.2	69.6
2.05	735.8 ± 79.1	115.7	1164.6 ± 190.5	114.4
2.73	792.0 ± 78.8	132.1	1304.6 ± 197.1	140.2
3.41	924.5 ± 103.9	171.0	1472.4 ± 227.9	171.1

P < 0.01

P < 0.01

Figure .1: A typical luminal-dependent chemiluminescence (CL.) response of diabetic patient granulocytes activity in whole blood stimulated by barium sulphate showing enhancement response with zinc ion. (A) Control response and (B) a CL. response for test sample final concentration 0.68 mg/ml. Measurements were made in triplicate and the mean was taken for calculation.

Table 4: Effect of zinc sulphate on chemiluminescence functional activity of granulocytes of diabetic patients with and without recurrent infections.

Concentration of zinc sulphate mg / ml	Diabetic patients with recurrent infections n=22 (M ± S.E) × 10 ⁻³	The % of enhancement of granulocytes activity	Diabetic patients without recurrent infections n=15 (M ± S.E) × 10 ⁻³	The % of enhancement of granulocytes activity
0	212.8 ± 33.2	0	394.5 ± 49.4	0
0.68	289.4 ± 20.9	35.9	535.8 ± 70.4	35.8
1.36	368.2 ± 31.7	73.0	649.9 ± 71.5	64.7
2.05	482.0 ± 49.3	126.5	843.2 ± 95.0	113.7
2.73	522.0 ± 41.3	145.3	934.7 ± 101.4	136.9
3.41	570.2 ± 46.4	168.1	1072.2 ± 123.3	171.7

P < 0.01

P < 0.01

Discussion

The granulocytes are involved in the innate immunity against bacterial infection. The tendency of patients with diabetes mellitus to develop a variety of infections may be due to defects in host defences. Impaired granulocyte activity in diabetes mellitus is partly responsible for the increased susceptibility to infection [20]. The activity of granulocytes was evaluated in eighty diabetic patients and sixty healthy subjects. The result of our study showed that there is a significant difference between healthy subjects and diabetic ones in the activity of granulocytes; the data obtained demonstrate impaired granulocyte phagocytic activity functions and chemiluminescence response in diabetic patients. Previous studies observed that phagocytosis is decreased in patients with diabetes mellitus [11, 21].

Chemotaxis, adherence and phagocytosis are impaired in diabetics and each of these important granulocyte functions is an energy-dependent process [22]. Granulocytes normally derive energy almost exclusively from the metabolism of glucose [23]. The mechanisms responsible for these defects are not certain, but in general they correlate with the poor control of the diabetes and are corrected by reversal of the hyperglycaemia, hyperosmolarity and ketoacidosis with insulin [24]. The enhanced metabolic activity of stimulated polymorphonuclear neutrophils is reflected by the fact that, during phagocytosis their glycogen concentrations fall and oxygen consumption, glucose utilization, and lactate production all increase [25]. The fact that these parameters of metabolic activity all have been shown to be impaired in leukocytes from poorly controlled diabetic patients [23, 25]. It is known, that the presence of insulin deficiency, polymorphonuclear neutrophil glycogen content and the activity of glycogen synthetase are both reduced [26]. While most enzymatic steps in the glycolytic pathway are reversible, the hexokinase, phosphofructokinase and pyruvatekinase reactions are not; of these, the latter two are closely regulated by insulin availability [27]. The combined findings in the diabetic polymorphonuclear neutrophil of an inhibition of the hexokinase reaction, an accumulation of fructose-6-phosphate and a reduction of pyruvatekinase activity are consistent with blocks in the glycolytic pathway at these critical insulin-dependent steps [28].

The present study examined the effect of low concentrations of zinc sulphate on the activity of granulocytes in eight diabetic patients and eight healthy subjects. There were no significant differences between control and test samples at all low concentrations of zinc for both groups.

Thirty-seven patients and twenty-one healthy subjects were subjected to the effect of zinc sulphate.

These have significant differences regarding the phagocytic activity after addition of zinc sulphate. A large body of experimental and clinical proof with diabetes mellitus, especially in developed countries, supported alteration of zinc metabolism in patients with diabetes mellitus [29]. However, few studies examine the effect of zinc on diabetes in developing countries [30].

Diabetes mellitus is one of the diseases, which affects zinc homeostasis in different ways. The relationship between diabetes, insulin and zinc is complex with no clear cause and effect relationship. The predominant effect of diabetes on zinc homeostasis is hypozincemia, which may be the result of hyperzincuria or decreased intestinal absorption of zinc or both [29]. Zinc has an important role in the glucose utilization by muscles and fat cells [31]. It is required as a co-factor for the function of intracellular enzymes that may be involved in protein, lipid, and glucose metabolism [32]. Zinc also plays a key role in the synthesis, storage, and secretion of insulin by pancreatic tissue, and it accounts for the conformation integrity of insulin in its hexameric crystalline form [33]. Zinc may participate as an integral component of several antioxidant enzymes. Several of the complications of diabetes may relate to an increase in intracellular oxidant and free radicals associated with a decrease in intracellular zinc and zinc dependent antioxidant enzymes [29]. The hypothesized zinc deficit in patients with diabetes has been confirmed by Pai and Prasad, who reported decreased levels of zinc in neutrophils, lymphocytes, and platelets, as well as a decline in the activity of nucleoside phosphorylase, a zinc-dependent purine catabolic pathway enzyme, in patients with type II diabetes mellitus (NIDDM).

Many studies showed that certain clinical features such as slow healing of ulcers, neurosensory changes, decreased serum testosterone, and cell-mediated immune disorders, which are shared by both zinc-deficient subjects and diabetics, may be related to abnormal zinc metabolism in patients with diabetes mellitus [35, 36]. Zinc affects multiple aspects of the immune system [37]. Zinc is crucial for normal development and function of cells mediating innate immunity, neutrophils and natural killer cells. Macrophages are also affected by zinc deficiency. Phagocytosis, intracellular killing, and cytokine production are all affected by zinc deficiency. Zinc deficiency affects adversely the growth and function of T and B cells. Zinc may play a direct role in the maintenance of membrane structure and function by stabilizing or otherwise protecting the membranes [38] and changes in tissular or cellular concentrations of this trace

element are likely to affect the utilization of glucose in peripheral tissues [39], as well as impeding the synthesis, storage, and secretion of insulin [9, 10]. In one of the studies, administration of the zinc sulphate solution intramuscularly to the diabetic animals replaces the zinc which is deficient due to the lack of insulin, and also may increase phagocytic activity of neutrophils and monocytes so that they can control the wound region in a better way, since diabetics are more prone to infections [40]. The study found that the concentration (0.68 mg/ml) was considered the threshold. The shape of chemiluminescence curve reached to plateau at concentration 3.41 mg/ml for both diabetic and healthy blood samples, the percentage of enhancement was not changed at concentrations more than 3.41 mg/ml (data was not shown). The ability of zinc to function as an

antioxidant and stabilize membranes suggests that it has a role in the prevention of free radical induced injury during inflammatory processes [41]. Zinc is a co-enzyme of superoxide dismutase (SOD), an antioxidant enzyme that works with catalase (an enzyme) to scavenge and neutralize free radicals that protects against free radical damage; essential to formation of insulin and helps and accelerates healing [6]. The recommended daily allowance for adults is 11 mg [42].

In conclusion, diabetic patients have significantly lower activity of granulocytes than healthy subjects. Zinc supplementation for diabetic patients has beneficial effects in improving the activity of granulocytes.

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تأثير كبريتات الخارصين في الفعالية الوظيفية لكريات الدم البيضاء الحبيبية في مرضى السكري مقاسة بطريقه اللعان الكيمائي المنوط اللومينول في دم الإنسان

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الخلاصة

يعد داء السكري هو أحد الاضطرابات الأيضية المنتشرة على نحو واسع ويحدث تقريبا في كل كان العالم في انتشار متغير. وتشير الدراسات الى ان لمرضى السكري انخفاض في فعالية الكريات الدم البيضاء لهذا هدفت الدراسة الحالية الى تقييم نشاط كريات الدم البيضاء الحبيبية وتقيم فعالية كبريتات الخارصين على نشاط كريات الدم البيضاء الحبيبية في المرضى المصابين بالسكري.

تضمنت الدراسة 140 شخصا، 80 شخصا مصابين بمرض السكري (40 ذكور، 40 إناث)، و 60 شخصا أصحاء (48 ذكور، 12 إناث). تمت دراسة فعالية الكريات الدم البيضاء الحبيبية بتقنيه اللعان الكيمائي لمرضى السكري والأشخاص الأصحاء.

أظهرت النتائج أن هناك فارقا معنويا ($P < 0.001$) في الفعالية الوظيفية لكريات الدم البيضاء الحبيبية بين الأشخاص الأصحاء ومرضى السكري، وظهر أيضا فرق معنوي ($P < 0.01$) في الفعالية الوظيفية لكريات الدم البيضاء الحبيبية بين ذكور وإناث مرضى السكري وذكور وإناث الأشخاص الأصحاء.

تمت دراسة تأثير كبريتات الخارصين على الفعالية الوظيفية لكريات الدم البيضاء الحبيبية لمرضى السكري والأشخاص الأصحاء، وأوضحت الدراسة قيم المعدل والانحراف المعياري لفعالية الكريات الدم البيضاء الحبيبية وتراكيز الزنك الواطئة (0.1، 1، 5، 10) مايكروغرام/مل، على التوالي ولم تظهر فروقات معنوية في الفعالية الوظيفية لكريات الدم البيضاء الحبيبية بين الدم الخالي من كبريتات الخارصين (تركيز الخارصين = 0) والدم الحاوي على التراكيز الواطئة المختلفة من كبريتات الخارصين (0.1، 1، 5، 10) مايكروغرام/مل. تضمنت الدراسة تراكيز مختلفة من الزنك (0.68، 1.36، 2.05، 2.73، 3.41) ملغرام/مل، وظهر هناك اختلافات معنوية ($P < 0.01$) في الفعالية الوظيفية لكريات الدم البيضاء الحبيبية بين الدم الخالي من كبريتات الخارصين (تركيز الخارصين = 0) والدم الحاوي على كبريتات الخارصين تراكيز مختلفة من كبريتات الخارصين (0.68، 1.36، 2.05، 2.73، 3.41) ملغرام/مل مرضى السكري والأشخاص الأصحاء.

أيضا تمت دراسة تأثير كبريتات الخارصين على الفعالية الوظيفية لكريات الدم البيضاء الحبيبية لمرضى السكري الذين يعانون من التهابات المتكررة والمرضى الذين لا يعانون من التهابات المتكررة، وتبين هناك اختلافات معنوية ($P < 0.01$) في الفعالية البلعمية لكريات الدم البيضاء الحبيبية بين الدم الخالي من كبريتات الخارصين (تركيز الخارصين = 0) والدم الحاوي على كبريتات الخارصين تراكيز مختلفة من كبريتات الخارصين (0.68، 1.36، 2.05، 2.73، 3.41) ملغرام/مل { لكلا المجموعتين من مرضى السكري (المرضى الذين يعانون من التهابات المتكررة والمرضى الذين لا يعانون من التهابات المتكررة).

يمكن الاستنتاج من هذه الدراسة بان فعالية كريات الدم البيضاء الحبيبية تقل في مرضى السكري وان إعطاء ايون الزنك قد يحسن فعاليه ووظائف هذه الكريات.