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The Relation Of Malondialdehyde And Superoxide Dismutase To The Pathogenesis Of Systemic Lupus Erythematosus And Effect Of Antioxidants On The Disease Activity

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Abstract

Background:

Systemic lupus erythematosus (SLE) is a chronic complex multifactorial autoimmune disease. Reactive oxygen species (ROS) are claimed to play a role in this disease.

Objective:

To disclose the effect of oxidants represented by malondialdehyde (MDA) and the antioxidant activity represented by superoxide dismutase (SOD) on SLE activity and the possible role of antioxidants in the treatment of the disease.

Patients and methods:

The level of SOD and MDA were measured in 52 persons; 20 patients with active SLE and 17 SLE patients in remission as measured by Systemic Lupus Activity Measure (SLAM), plus 15 control persons of matched age and sex. The active group received a course of antioxidants (800 IU of vitamin E daily and 500 mg of vitamin C twice daily) plus 20 mg of prednisolone daily. The activity is remeasured after three months of treatment.

Results:

Serum MDA was significantly elevated in the active group as compared to the remission group. Both groups showed higher level of MDA when compared to the control group. The level of SOD was higher in control and remission groups than in the active group. There was an inverse relation between the level of MDA and SOD in both the active and remission groups. There was no significant correlation between MDA and SOD in the control group. The SLAM score and MDA level decreased significantly in the active group after receiving the aforementioned treatment while there was non significant increase in SOD.

Conclusion:

The oxidative burden - represented by MDA - is involved in the pathogenesis of SLE, and SOD acts as a protective agent against this damage. Antioxidants; as vitamins E and C can be used as adjunctive treatment for SLE.

Introduction

Systemic lupus erythematosus is a chronic complex autoimmune disease with variable manifestations, course and prognosis[1,2]. Pathogenesis of SLE remains unclear. It involves interaction of a complex of genetic, hormonal and environmental factors which act altogether[3,4]. There is loss of immune tolerance to self antigens with the activation of T helper and B cells and autoantibodies production[3,4,5]. Complement system defects are also incorporated including C4,C2 and C1q[6,7].

Reactive oxygen species is a collective term including oxygen free radicals such as superoxide and hydrogen peroxide and some nonradical derivatives which may yield free radicals in the presence of transitional metal ions[8,9].They may be molecules like hydrogen peroxide(H_2O_2)or ions like hypochlorite ions (OCl-)[10,11].

Reactive oxygen species result from endogenous sources via mitochondrial respiratory chain reactions in neutrophils and macrophages, peroxisomes or degradation of heme products[8,9]. Exogenous sources of ROS include radiation, drugs, cigarette smoke and transitional metal ions[12,13].

Antioxidants are substances that inhibit the oxidation of a target molecule by a free radical attack. They are either preventive inhibitors (prevent the initiation of free radical attack) as catalase and SOD or chain breakers[14] as vitamin E and ascorbic acid which convert free radicals to stable products, thus block free radical chain reactions[15].

Oxidative stress is the shift in ratio between oxidants and antioxidants either due to excessive ROS generation and / or decrease in

antioxidant defences[16]. This state is associated with various forms of pathological tissue injury. The most important is lipid peroxidation of various membranes especially the mitochondrial membranes[17]

Moreover, ROS cause cross linking of proteins or oxidative inactivation of certain enzymes causing functional impairment of cells and liberation of cytoplasm proteases[10]. They can also induce damages in DNA. This results in new antigenic determinants, stimulation of anti DNA antibody formation and autoimmunity[18,19].

In addition, endothelial dysfunction with increased vascular permeability and edema is observed in conditions associated with increased oxidative stress. This is due to inactivation of endothelial derived nitric oxide - a pivotal molecule in the regulation of vasomotor tone and homeostasis - by superoxide radicals[15,17]. Intracellular messages, protein kinases and transcription factors are also inactivated[4].

Malondialdehyde is the most abundant aldehyde resulting from lipid peroxidation. It was reported that high level of MDA in SLE patients indicates that ROS damage might play a role in SLE[11,20].

Superoxide dismutase is one of the most important of antioxidant enzymes. It catalyses the dismutation of superoxide radicals to hydrogen peroxide and molecular oxygen. It acts with a rate of 10000 times faster than the spontaneous rate of superoxide radical dismutation[21].

Inhibition of SOD activity is associated with cellular dysfunction and human diseases and the activity of this enzyme can be utilized as a measure of the activity of some diseases as SLE[12,22,23].

Aim Of The Work

The aim of this study is to measure the extent of the effect of ROS- as measured by the lipid peroxidation product MDA- and the efficient antioxidant activity represented by SOD, in cases of SLE and their relation to the pathogenesis and activity of the disease. In addition the role of antioxidants in ameliorating the course of the disease is studied.

Patients And Methods

This study involved 37 patients and 15 healthy controls of matched age and sex, table(1). They were classified into three main groups:

" Group I [control group]: included 14 healthy normal females and one male. Their age ranged from 16 to 43 years.

" Group II [remission group]: included 17 female SLE patients diagnosed according to American Rheumatism Association (ARA) criteria[24] but all have inactive SLE according to Systemic Lupus

Activity Measure (SLAM)[25]. Their age ranged from 19 to 39 years.

" Group III [active group]: included 17 female patients and one male patient with active SLE disease according to SLAM. Their age ranged from 18 to 42 years.

Patients were selected from the outpatient clinics and inpatient wards of Dermatology, Rheumatology and General Medicine Departments in Faculty of Medicine, Zagazig University. They were subjected to complete history taking, thorough clinical examination and related laboratory investigations including:

1-antinuclear antibody (ANA) and anti native DNA antibody (anti-nDNA).

2-kidney function tests, complete urine analysis, and protein level in 24 hour urine.

3-complete blood picture, ESR and C reactive protein.

The activity of the disease was assessed according to SLAM which is based on 24 clinical criteria and 7 laboratory criteria. The score of SLAM ranges from 0 to 85. the higher the score, the more active and extensive the disease[25].

Any finding in grading should be attributable to SLE. It should have been present within a month prior to the examination date. The finding is listed as inactive or active. If active ,then it is assigned points based on intensity with 1 point for mild, 2 points for moderate and 3 points for severe.

Investigations to detect oxidative stress

1. Determination of lipid peroxidation through estimation of MDA in the serum

2. Determination of SOD in red blood cells.

Determination of serum MDA

This method implies the measurement of MDA as one of the main products of lipid peroxidation by the thiobarbituric acid method. The principle of the method is based on the reaction of MDA with thiobarbituric acid (TBA) with the resulting pink colored tri-methyl complex with a maximum absorption at 530-532 nm. The samples were analyzed by spectrophotometer (Milton Roy spectronic 3000 ARRAY double beam spectrometer, USA)[26].

Determination of SOD

This was measured using commercial kits supplied by (Randox, Antrim, Northern Ireland) depending on the principle that SOD accelerates the dismutation of the toxic superoxide radical (O.-), produced during oxidative energy processes , to hydrogen peroxide and molecular oxygen.

This method employs xanthine and xanthine oxidase (XOD) to generate superoxide radicals which react with 2- (4-iodophenyl) - 3 - (4-nitrophenol) -5-phenyltetraxolium chloride (I.N.T) to form a red formazan dye. The superoxide activity is then measured by the degree of inhibition of this reaction. Normal range=1102-1601 U/g Hb.

After measurement of MDA and SOD, the active group was given a course of treatment of 800 IU of vitamin E per day and 500 mg twice daily of vitamin C plus 20 mg prednisolone daily for three months. Thereafter, the SLAM, the level of MDA and SOD were remeasured for this group.

Results

There was a non significant difference in age and sex between patients (active and remission groups) and the control group (P>0.05). There was also a non significant difference in duration of the disease between active and remission groups (P>0.05),**table (1).**

	Control *n=15*	**Remission** *n=17*	**Active** *n=20*	**P value**
Age range	(16-43)	(19-39)	(18-42)	0.5
mean ± SD	27.6 ± 8.3	30 ± 6.0	30.5 ± 7.3	(N sig)
Duration				
Range (in months)	-----	(3-44)	(5-48)	0.65
mean ± SD		19.3 ± 13.91	21.3 ± 12.5	(N sig)
Gender : male	1	------	1	0.1
female	14	17	19	(N sig)

Table (1): Demographic data of the studied groups

As regards SLAM score, there was a significant difference between remission and control groups (P<0.01), a highly significant difference between active and control groups (P<0.001) and a highly significant difference between active and remission groups (P<0.001), **table(2).**

	Control *n=15*	Remission *n=17*	Active *n=20*
SLAM (range)	0	(0 - 3)	(16 – 45)
Mean±SD		0.529 ± 0.01	22.2 ± 7.8
P value	P<0.01*	P<0.001**	P<0.001***
MDA (range in **µ mol/L**)	(2.451-4.928)	(4.739-6.109)	(5.006-7.865)
mean±SD	3.4 ± 0.96	5.19 ± 0.62	6.36 ± 0.9
P value	P<0.001*	P<0.001**	P<0.001***
SOD (range in **u/g Hb**)	1102-1519	1218.1-1638.5	37.3 – 785.6
mean±SD	1334.8±169.3	1364.0±172.5	357.6±328.1
P value	P>0.05*	P<0.01**	P<0.001**

* relation between control and remission groups
** relation between remission and active groups
*** relation between active and control groups

Table (2): Results of SLAM, MDA and SOD in the studied groups and relations between the three groups

The level of MDA showed a highly significant difference between the remission and active groups (P<0.001), between the remission and the control group (P<0.001), and between the active and the control groups (P<0.001), **table(2)**.

The level of SOD showed a statistically significant difference between the remission and active groups (P<0.01) and between the active and the control groups (P<0.01). However, there was a non significant difference in SOD level between the remission and control groups (P>0.05), **table(2)**.

Correlation between the level of MDA and SOD within each group revealed a statistically highly significant inverse correlation between MDA and SOD in the active group (r = - 0.66, P<0.001). There was also a highly significant inverse correlation between MDA and SOD in the remission group (r = -0.46, P<0.005). There was no statistically significant correlation between MDA and SOD in the control group (r = - 0.2, P>0.05), **table(3)**.

	r	P	correlation
Control	-0.2	P>0.05	N sig
Remission	-0.46	P<0.005	H sig
Active	-0.66	P<0.001	H sig

Table (3): Correlation between MDA and SOD in the studied groups

There was a significant relation between SLAM score and MDA and a significant inverse relation between SLAM and SOD in the active group, but there was a non significant relation in the remission group (P>0.05), **table(4)**.

	Remission			Active		
	r	P	significance	r	P	significance
MDA	0.01	>0.05	N sig	0.46	<0.05	sig
SOD	0.02	>0.05	N sig	-0.5	<0.01	sig

Table (4): Correlation between SLAM and MDA / SOD in both remission and active groups

By comparing the normal control subjects with all SLE patients (active and in remission); there was a highly statistically significant difference in MDA level in the patient group compared to the control group (P<0.001), **table(5)**.

	Control [n=15]	Cases [n=37]	t	P value
MDA (range in **µmol/L**)	2.451-4.928	4.739-7.865		
mean±SD	3.4 ± 0.96	5.86 ± 0.9	8.5	<0.001
SOD (range in **u/g Hb**)	1102-1519	24.8-1636.8		
mean±SD	1334.8±169.3	819.76±573.2	3.4	<0.01

Table (5): Comparison between total cases and control group in MDA and SOD

There was a statistically significant difference in SOD level in patient group compared to control group (P<0.01), **table(5)**.

After treatment:

There was a significant decrease both in MDA serum level and SLAM score in the active group after the course of treatment (P<0.01). On the contrary, the increase of SOD level was not significant (P>0.05),**table (6)**.

	Before [mean±SD]	After [mean±SD]	P value
SLAM	22.2 ± 7.8	7.5 ± 1.3	<0.01
MDA	6.36 ± 0.9	5.1 ± 0.7	<0.01
SOD	357.6±328.1	450.8±325.5	>0.05

Table (6): Changes of SLAM, MDA and SOD in the active group after treatment

Statistics

Data were checked , entered and analyzed using Epi- Info (2000). F test (ANOVA) , t test, Chi squared (X2), paired t test and correlation coefficient (r) were used when appropriate. P value <0.05 was considered significant.

Discussion

Systemic lupus erythematosus is a puzzling disease due to its multifactorial etiology and wide spread clinical presentation[1].

This study was based upon previous findings showing that oxidative stress markers are significantly higher in SLE patients compared to healthy controls[11,27,28]. Similar results were found here where MDA level was significantly elevated in the active group when compared to the remission group (P<0.01). In addition, serum MDA was significantly elevated in all patients compared to the control group (P<0.001).

Serum MDA level in the active group correlated positively with the SLAM score. This is in agreement with other authors[15,22,29,30] who found an increase in the generation of MDA along with the increase in the activity of the disease and supported the proposal that serum MDA level

could be helpful in predicting the prognosis of SLE.

In this study, SOD level was significantly decreased in the active group as compared to either the remission or control group ($P<0.01$). There was no statistically significant difference in the level of SOD between the remission and control groups ($P>0.05$).

After summation of the active and remission groups; the level of SOD was significantly decreased when compared to the control group ($P<0.01$) while it was inversely correlated to SLAM score. Similar results had been reported[22,28]. The decreased level of SOD could be due to its direct inactivation by its products H_2O_2 or O.- 2 anion itself and / or development of autoantibodies against SOD[11].

The decreased activity of SOD leads to excessive accumulation of the superoxide radical which would otherwise have been enzymatically converted to hydrogen peroxide. Increased superoxide levels have the potential to initiate the lipid peroxidation chain reaction leading to peroxidation of membrane lipids and other tissue lipids with increase in the MDA level[11,15].

We found a significant inverse correlation between the SOD and MDA in both active and remission groups ($P<0.05$). This opposite relation is a reflection of oxidative stress due to consumption of SOD in the process of detoxification of superoxide radicals.

Accordingly, since ROS are elevated in patients with SLE than in normal controls and their level correlated with the disease activity, we can conclude that oxidative stress does have a role in the pathogenesis of SLE disease.

We found that the addition of antioxidants, vitamins E and C, to treatment of SLE has led to a significant remission in active cases with improvement of the MDA level and SLAM score. Meanwhile; the dose of steroid was reduced thus decreasing the potential side effects of prolonged steroid therapy.

On the other side; SOD did not increase to a significant level which could be explained by the sharing of multiple factors affecting SOD level other than ROS. These factors like autoantibodies against the enzyme could still be working in spite of the decrease in the level of ROS by the aforementioned treatment[11,15].

The combination of antioxidants may be of benefit due to possible synergistic interaction between vitamins C and E since vitamin C reduces the potentially harmful radicals resulting from oxidation of vitamin E[15].

Antioxidants as beta carotene, vitamins E & C and selenium were studied on animal models with significant immune regulatory effects on the pathogenesis of autoimmune diseases and lupus nephritis[31].

Captopril was found to prolong survival in murine SLE due to its antioxidant effects[27,32].

Similarly, naturally occurring dietary preparations as high dietary omega - 3 fatty acids have been shown to decrease anti-ds DNA and anticardiolipin antibodies and to reduce kidney damage in murine lupus[33].

Treatment trials have been launched in this issue and many of them revealed encouraging results. Antioxidants may prevent renal dysfunction in SLE patients independent of their ability to inhibit lipid peroxidation[11,34].

It was found that vitamin C intake is associated with decreased vascular damage (ischemic heart disease, cerebrovascular accidents, thrombotic events) in SLE patients and is inversely associated with the activity of the disease [11,15,35,36] .

Moreover, antioxidants as vitamin E and C prevent sun damaging effect on SLE patients by acting as systemic sunscreens[23,28].

Pharmacological agents used in treatment of SLE include both immunosuppressive and ani-inflammatory drugs most notably the corticosteroids. While these drugs are often effective in retarding the development of the disease and prolongation of the life span of SLE patients, their long term use is associated with a considerable number of side effects[34,35,36].

We can conclude that the addition of antioxidants as adjunctive treatment in concert with this conventional drug therapy might offer an advantage over the drug therapy alone. The drug dosages could be reduced, thus minimizing their side effects. This could be an important research field for amelioration of SLE.

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الملخص العربي

علاقة المالون داىألدهايد وأنزيم سوبرأكسيد ديسميوتيز بمرض الذئبة الحمراء الجهازى وتأثير مضادات الأكسدة على نشاط المرض

يعتبر مرض الذئبة الحمراء الجهازى من الأمراض المزمنة ذات الخلل في المناعة الذاتية و يعتقد أن لشوارد الأكسجين الحرة دور فى نشوء هذا المرض ودرجة نشاطه . و الغرض من هذا البحث هو اظهار العلاقة بين الشوارد الحرة و مسببات مرض الذئبة الحمراء عن طريق قياس مادة المالون داي ألدهايد و هى تعتبر مقياسا مهما لنشاط المؤكسدات ودرجة أكسدة الدهون ، بالاضافة الى قياس أنزيم سوبر أكسيد ديسميوتيز الذى يعتبر من أهم الأنزيمات المقاومة للأكسدة. كما يدرس تأثير استعمال مضادات الأكسدة كعلاج مساعد فى

هذا المرض.

و قد ضمت الدراسة عدد 52 شخصا مقسمة الى ثلاث مجموعات:

1 – المجموعة الأولى ، وتضم عشرين مريضا-19 مريضة ومريضا واحدا- بالذئبة الحمراء الجهازى فى الحالة النشطة للمرض حسب مقياس SLAM)مقياس نشاط الذئبة الحمراء).

2-المجموعة الثانية ، وتضم سبع عشرة مريضة فى الحالة غير النشطة للمرض حسب مقياس SLAM.

3- المجوعة الضابطة ، وتضم خمس عشرة امرأة و رجلا واحدا من الأصحاء فى نفس الفئة العمرية.

النتائج:

1)كان مستوى مادة المالون داى ألدهايد فى المصل مرتفعا بصورة ذات دلالة احصائية عالية فى المجموعتين الأولى و الثانية (المرضى) بالمقارنة بالمجموعة الضابطة. كما وجد أن هناك علاقة طردية بين مستوى المادة ودرجة نشاط المرض.

2)كان مستوى أنزيم سوبر اكسيد ديسميوتيز منخفضا بدرجة احصائية عالية فى المجموعة النشطة مقارنة بالمجموعة غير النشطة والمجموعة الضابطة،

كما وجد علاقة عكسية ذات دلالة احصائية عالية بين مستوى الأنزيم ودرجة نشاط المرض فى المجموعة النشطة . بالاضافة الى العلاقة العكسية بين مستوى الأنزيم و المالون داى ألدهايد فى كل من المجموعة النشطة و غير النشطة من المرضى.

تشير هذة النتائج الى وجود علاقة ين التلف الناتج عن المؤكسدات وانخفاض درجة نشاط الانزيم سوبر أكسيد ديسميوتيز و بين نشاط المرض.

وقد تم اعطاء مضادات الأكسدة (فيتامين ج 500مجم مرتين يوميا وفيتامين هاء 800 وحدة يوميا مع جرعة منخفضة من الكورتيزون(20 مجم يوميا) للمجموعة النشطة لمدة 3 شهور ثم أعيدت القياسات.

لوحظ انخفاض نسبة المالون داى ألدهايد وانخفاض مقياس نشاط المرض بدرجة عالية الدلالة الاحصائية فى المجموعة النشطة بعد العلاج السابق. على الناحية الأخرى لم يرتفع مستوى الأنزيم بدرجة احصائية فى نفس المجموعة بعد العلاج.

الاستنتاج:

نستدل من هذة النتائج أن للمؤكسدات دور كأحد المسببات لمرض الذئبة

الحمراء الجهازى ومن هنا يمكن استخدم مضادات الأكسدة كعلاج مساعد للمرض لتخفيض جرعة مثبطات المناعة مثل الكورتيزون و بالتالى لتفادى الآثار الجانبية لطول فترة العلاج.