Insulin resistance is related with oxidative stress in systemic lupus erythematosus

Sistemik lupus eritematozda insülin direnci oksidatif stres ile ilişkilidir

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ABSTRACT

Objective: Systemic lupus erythematosus (SLE) patients have increased risk of coronary heart disease (CHD) that cannot be fully explained by the traditional risk factors. Metabolic alterations like oxidative stress and insulin resistance may be additional risk factors to contribute early and accelerated atherosclerosis in SLE. Our aim was to evaluate malondialdehyde (MDA) level, oxidative stress indicator, and homeostasis model assessment of insulin resistance (HOMA-IR), and possible relationship between oxidative stress and insulin resistance, in SLE.

Methods: This cross-sectional controlled study included 30 SLE patients (SLE group) and 15 age- and sex-matched healthy controls (HC group). The SLE patients were classified into subgroups based on the disease activity index as active or inactive. Serum MDA, insulin, C-peptide, fasting blood glucose, lipid profile, acute phase reactants, tumor necrosis factor (TNF)-α, interleukin (IL)-6 and HOMA-IR were determined. Statistical analyses were performed using Kruskal-Wallis, Mann-Whitney U and Pearson tests.

Results: In the SLE group, TNF-α (7.9 [0.5-57.8] vs. 3.9 [0.3-6.3] pg/ml, p<0.01), IL-6 (9.2 [0.1-33.9] vs. 2.2 [0.1-4.8] pg/ml, p<0.01), MDA (2.3 [0.1-6.7] vs. 0.95 [0.5-2.96] nmol/ml, p<0.01) and C-peptide (1.9 [0.9-3.5] vs. 1.5 [1.1-2.4] ng/ml, p<0.01) levels were higher than in the HC group, while HOMA-IR index (1.7 [0.5-6.5] vs. 1.2 [0.8-2.9], p>0.05) was nonsignificantly higher. In the SLE group, MDA levels were correlated with insulin (r=0.614, p<0.05) and HOMA-IR (r=0.601, p<0.05).

Conclusion: In inflammatory diseases, relations between oxidative stress and insulin resistance, each of them triggers or enhances the other one, come to an impasse. In conclusion, this modifiable impasse might be important to prevent the development of atherosclerosis in SLE. *(Anadolu Kardiyol Derg 2009; 9: 23-8)*

Key words: Insulin resistance, HOMA-IR, oxidative stress, malondialdehyde, inflammation, systemic lupus erythematosus

ÖZET

Amaç: Sistemik lupus eritematoz (SLE) hastalarında, koroner kalp hastalığı (KKH) riskinde artış olduğu kanıtlanmıştır. Ancak KKH riskindeki bu artış çoğu zaman klasik risk faktörleri ile açıklanamamaktadır. Sistemik lupus eritematozdaki erken ve hızlanmış aterosklerozdan, ek risk faktörleri olarak, oksidatif stres ve/veya insülin direnci gibi metabolik değişiklikler sorumlu olabilir. Bu çalışmada, SLE hastalarında, oksidatif stres indikatörü malondialdehit (MDA) düzeyi ve ``homeostasis model assessment of insulin resistance`` (HOMA-IR) indeksinin belirlenmesi ve oksidatif stres ile insülin direnci arasındaki olasılı ilişkinin değerlendirilmesi amaçlandı.

Yöntemler: Bu enine kesitli kontrollü çalışmaya, 30 SLE hastası (SLE grubu) ile yaş ve cinsiyet uyumlu 15 sağlıklı gönüllü (kontrol grubu) alındı. Sistemik lupus eritematoz hastaları, hastalık aktivite indeksi skoruna göre, aktif ve inaktif olarak alt gruplara ayrıldı. Serum MDA, insülin, C-peptid, açlık kan glukozu, lipit profili, akut faz reaktanları, tumor nekrozis alpha faktör (TNF-α) ve interlökin (IL)-6 düzeyleri belirlendi ve HOMA-IR indeksi hesaplandı. İstatistiksel analizlerde Kruskal Wallis, Mann-Whitney U ve Pearson testleri kullanıldı.

Bulgular: Sistemik lupus eritematoz grubunda, kontrol grubuna göre TNF-α (7.9 [0.5-57.8] karşın 3.9 [0.3-6.3] pg/ml, p<0.01), IL-6 (9.2 [0.1-33.9] karşın 2.2 [0.1-4.8] pg/ml, p<0.01), MDA (2.3 [0.1-6.7] karşın 0.95 [0.5-2.96] nmol/ml, p<0.01) ve C-peptid (1.9 [0.9-3.5] karşın 1.5 [1.1-2.4] ng/ml, p<0.01) düzeyleri yüksekti; HOMA-IR indeksi (1.7 [0.5-6.5] karşın 1.2 [0.8-2.9], p>0.05) ise göreceli artmıştı. Sistemik lupus eritematoz grubunda, MDA düzeyleri, insülin (r=0.614, p<0.05) ve HOMA-IR (r=0.601, p<0.05) düzeyleri ile ilişkiliydi.

Sonuç: İnflamatuvar hastalıklarda, oksidatif stres ve insülin direnci arasındaki ilişki, biri diğerini tetikleyebilen veya düzeyini artırabilen, bir kısır döngü haline gelmektedir. Sistemik lupus eritematozda gelişebilen aterosklerotik hastalıkların önlenmesinde, bu modifiye edilebilir kısır döngü oldukça önemli olabilir. *(Anadolu Kardiyol Derg 2009; 9: 23-8)*

Anahtar kelimeler: İnsülin direnci, HOMA-IR, oksidatif stres, malondialdehit, inflamasyon, sistemik lupus eritematoz

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Introduction

Systemic lupus erythematosus (SLE) is a systemic chronic inflammatory disorder characterized by a wide range of immunological hyperactivity, autoantibody production and multi-organ damages. In an epidemiologic study (1), women with SLE have been demonstrated to have 50-fold increased risk of developing myocardial infarction than women in general population. The relative risk for coronary heart disease (CHD) has been still 7 to 17-fold higher, even after adjusting for traditional risk factors in SLE (2). Therefore, these reports have suggested that patients with SLE possess additional risks in addition to the traditional risk factors for the development of accelerated atherosclerosis, and these risk factors might be metabolic changes like oxidative stress and/or insulin resistance.

Oxidants, especially lipid and lipoprotein peroxidation products, are well known to trigger the endothelial dysfunction and subsequent atherosclerotic process (3). Impaired oxidant/antioxidant balance has been shown in various inflammatory rheumatic diseases (4, 5). The chronic inflammatory process of SLE leads to a state of oxidative stress, and increased oxidants and oxidative stress have been shown in patient with SLE (6, 7). Furthermore, increased oxidative stress has been found to be a risk factor for accelerated atherosclerosis in SLE (6, 7).

In addition to effects of oxidants and oxidative stress on atherosclerosis (3), they contribute to poor insulin action, and thus can be associated with insulin resistance (8-10). Several clinical and experimental trials have demonstrated improved insulin sensitivity in insulin-resistant and/or diabetic patients treated with the antioxidants vitamin C, vitamin E, α-lipoic acid and glutathione (11-14).

Insulin resistance, which plays an important role in the pathogenesis to atherosclerosis is a common metabolic state defined as a subnormal biologic response to insulin (15). In non-obese subjects without diabetes, insulin resistance has predicted the development of CHD independently of the other known risk factors (16). In another group of subjects without diabetes or impaired glucose tolerance, those in the highest quintile of insulin resistance had a 2.5-fold increase in the risk of CHD compared with those in the lowest quintile (17).

Oxidative stress and insulin resistance are established risk factors for CHD in the general populations. Though, the relationship between HOMA-IR and inflammation markers have been established few is known on the relationship between oxidative stress indices and insulin resistance in SLE.

In this study, we aimed to investigate the level of malondialdehyde (MDA), which is a product of lipid peroxidation, HOMA-IR index and the possible relationship between oxidative stress and insulin resistance, in patients with SLE with no major traditional risk factors.

Methods

This cross-sectional controlled study enrolled 30 patients with SLE in the SLE group (median age 35 [17-62] years; 29 females, 1 male), and sex-and age-matched 15 healthy controls (HC) in the HC group (median age 33 [22-58] years; 12 females, 3 males). The diagnosis of SLE was made according to the latest criteria of the American College of Rheumatology for the classification of SLE (18). The SLE disease activity index (SLEDAI) was determined as described previously (19). The SLE patients were classified into subgroups based on SLEDAI scores; SLEDAI $\geq$5 as active and SLEDAI <5 as inactive, and 18 patients were in active phase while 12 patients were in inactive phase.

All the participants, included in the study, were informed about the study, and their consents were taken. This study protocol was approved by the ethical committee of Firat University.

Detailed histories of all the participants were obtained and their systemic and rheumatologic examinations were performed. Disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids treatments given to patients was also recorded in the SLE group. Prior history of hypertension, diabetes mellitus, hyperlipidemia, smoking, myocardial infarction, angina pectoris, congestive heart failure, peripheral vascular disease, thyroid dysfunction, severe liver disease, chronic alcohol abuse, current pregnancy or delivery within 3 months, current acute or chronic infection and malignancy were the exclusion criteria for both groups. Participants who were taking antioxidants supplements, lipid lowering and antihypertensive medications and who were with electrocardiographic abnormalities were also excluded.

In all the participants, body height (BH) and body weight (BW) were measured to determine the body mass index (BMI).

Blood samples were drawn from all the participants who had fasted overnight. The samples were centrifuged at 3000 rpm for 10 minutes to obtain sera and stored at -20^{o}C for subsequent measurement of some markers. Routine laboratory evaluation of complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting plasma glucose, hepatic and renal function tests, lipid profile , urine microscopy were studied in SLE patients and controls. In addition, resting 12-lead electrocardiograms were obtained.

Antinuclear antibody (ANA), anti-dsDNA and anticardiolipin (aCL) antibodies, complement levels were also determined. The ANA and anti-dsDNA antibody were detected by indirect immunofluorescence using as a substrate Hep-2 cells and *Chrithidia luciliae,* respectively. The titters of ANA, anti-dsDNA and aCL antibodies were measured by ELISA method.

Serum insulin and C-peptide levels were determined by chemiluminescent assay using appropriate commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA). We used the homeostasis model assessment of insulin resistance (HOMA-IR) to detect insulin resistance. The HOMA-IR index was calculated using the following equation: HOMA-IR=[fasting blood insulin (μu/ml)) x fasting blood glucose (mmol/l)/22.5] (20).

Measurement of serum MDA level was carried out using the thiobarbituric acid method as modified by Yagi (21). Serum tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) levels were measured using appropriate commercial kits (Medgenix, Biosource International, Camarillo, USA) by the ELISA method.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 11.0 (Chicago, IL, USA). Data are presented as median (minimum-maximum) values. The comparisons of the variables of more than two groups were performed with Kruskal-Wallis test, while the comparisons for two groups were performed with Mann-Whitney U test. The

relationships among the variables were analyzed using Pearson product-moment correlation test. Differences were considered as statistically significant at p<0.05.

Results

In the SLE group median disease duration was 3 (0.1-14) years. The median BMI was 22.3 (16.5-29.3) kg/m^2 and 24.1 (18.9-28.8) kg/m^2 in the SLE and HC groups, respectively (p>0.05). The laboratory characteristics of the SLE and HC groups are given in the Table 1.

Table 1. Laboratory characteristics of patients with SLE and control subjects

Variables$^{\Delta}$	SLE group (n=30)	Control group (n=15)	p$^{\blacklozenge}$
Hb, gr/dl	12.2 (8.5-16.6)	13.1 (9.9-16.4)	0.054
WBC, 10^3/µl	5.3 (3.2-12)	6.7 (4.8-9.6)	0.040
ESR, mm/h	16.5 (3-97)	11.5 (2-46)	0.100
CRP, mg/l	3.33 (3.13-35)	3.16 (3.13-31)	0.448
TNF-α, pg/ml	7.9 (0.5-57.8)	3.9 (0.3-6.3)	0.011
IL-6, pg/ml	9.2 (0.1-33,9)	2.2 (0.1-4.8)	0.006
Serum MDA, nmol/ml	2.3 (0.1-6.7)	0.95 (0.5-2.96)	0.001
FBG, mg/dl	84.5 (70-99)	85 (75-100)	0.987
Insulin, µu/ml	7.3 (2.9-31.2)	6.5 (3.8-13.6)	0.217
C-peptide, ng/ml	1.9 (0.9-3.5)	1.5 (1.1-2.4)	0.007
HOMA-IR	1.7 (0.5-6.5)	1.2 (0.8-2.9)	0.254
Total cholesterol, mg/dl	164.5 (77-227)	174 (130-249)	0.319
LDL cholesterol, mg/dl	96 (50-147)	113 (75-158)	0.048
HDL cholesterol, mg/dl	39 (25-66)	49 (39-70)	0.089
Triglyceride, mg/dl	86 (58-222)	93 (49-317)	0.624

$^{\Delta}$Data are expressed as median (minimum-maximum)
$^{\blacklozenge}$Mann-Whitney U test
CRP- C-reactive protein, ESR- erythrocyte sedimentation ratio, FBG- fasting blood glucose, Hb- hemoglobin, HDL - high-density lipoprotein cholesterol, HOMA-IR- homeostasis model assessment of insulin resistance, IL 6- interleukin-6, LDL - low density lipoprotein cholesterol, MDA- malondialdehyde, TNF-α- tumor necrosis factor alpha, WBC- white blood cell count

In the SLE group, serum levels of MDA, C-peptide, TNF-α and IL-6 were higher when compared with the HC group (p<0.01 for each, Table 1).

The level of MDA was correlated with age (r=0.488, p<0.05), fasting insulin (r=0.614, p<0.05), HOMA-IR (r=0.601, p<0.05, Fig. 1), total cholesterol (r=0.582, p<0.01), LDL cholesterol (r=0.639, p<0.01) and triglyceride (r=0.514, p<0.05), and HOMA-IR index was correlated with total cholesterol (r=0.561, p<0.05) and LDL cholesterol (r=0.824, p<0.001), in addition to MDA, in the SLE group.

In the HC group, MDA level and HOMA-IR index were correlated with triglyceride level (r=0.761, p<0.01 and r=0.591, p<0.05, respectively).

In the SLE group (n=30), two patients had aCL antibody positivity, 5 patients had lupus nephritis, and 6 patients were newly diagnosed and they were not receiving any DMARDs or corticosteroids. At the time of the study, 14 of the 30 SLE patients were taking corticosteroid (median dose 2.5, range 0-15 mg/day), 10 were taking antimalarial, 10 were taking azathioprine, one was taking cyclophosphamide, and one was taking mycophenolate mofetil. There were no statistical differences in terms of laboratory findings between aCL-positive and -negative patients, between patients with and without lupus nephritis, between patients receiving and not receiving drugs.

In the SLE group, median SLEDAI score was 10 (0-30); median levels of C_3 and C_4 were 0.81 (0.41-1.21) and 0.09 (0.01-0.18) g/l, respectively. Overall, 27 (90%) of the 30 SLE patients had ANA positivity and 24 (80%) had anti-dsDNA antibody positivity, and the median titers of ANA and anti-dsDNA antibody were 2.5 (0-6.2) and 49 (0-434) U/ml, respectively. The level of MDA and HOMA-IR index were not correlated with levels of acute phase reactants and complements, titers of autoantibodies and SLEDAI score (data not shown).

The levels of MDA, fasting insulin, HOMA-IR, TNF-α and IL-6 were relatively higher in the active subgroup (n=18) than inactive subgroup (n=12, Table 2). The levels of MDA, C-peptide, HOMA-IR, TNF-α and IL-6 were significantly higher (p<0.001, p<0.05, p<0.05, p<0.05, p<0.01, respectively) in the active subgroup compared to HC group (Table 2, Fig. 2, 3).

Tablo 2. Laboratory data of the active- and inactive-SLE subgroups and control group

Variables$^{\Delta}$	SLE group (n=30)		Control group (n=15)	p$^{\blacklozenge}$
	Active subgroup (n=18)	Inactive subgroup (n=12)		
Serum MDA, nmol/ml	2.65 (0.19-7.67)*	1.73 (0.08-4.91)	0.95 (0.5-2.96)	0.005
FBG, mg/dl	86 (70-98)	83.5 (78-99)	85 (75-100)	0.315
Insulin, µu/ml	9.4 (2.9-31.2)	6.4 (4.1-9.9)	6.5 (3.8-13.6)	0.429
C-peptide, ng/ml	2.9 (0.9-3.5)§	1.8 (1.4-3.1)	1.5 (1.1-2.4)	0.024
HOMA-IR	1.99 (0.5-6.5)§	1.37 (0.9-1.9)	1.2 (0.8-2.9)	0.429
TNF-α, pg/ml	7.9 (0.5-57.8)§	5.4 (1.1-18.7)	3.9 (0.3-6.3)	0.107
IL-6, pg/ml	9.3 (0.4-26.9)†	4.5 (0.1-28.2)	2.2 (0.1-4.8)	0.093

$^{\Delta}$Data are expressed as median (minimum-maximum)
$^{\blacklozenge}$Kruskal-Wallis test
The active subgroup of SLE vs. the control group; §p<0.05, †p<0.01, *p<0.001- Mann-Whitney U test
FBG- fasting blood glucose, HOMA-IR- homeostasis model assessment of insulin resistance, IL-6- interleukin-6, MDA- malondialdehyde, TNF-α- tumor necrosis factor alpha

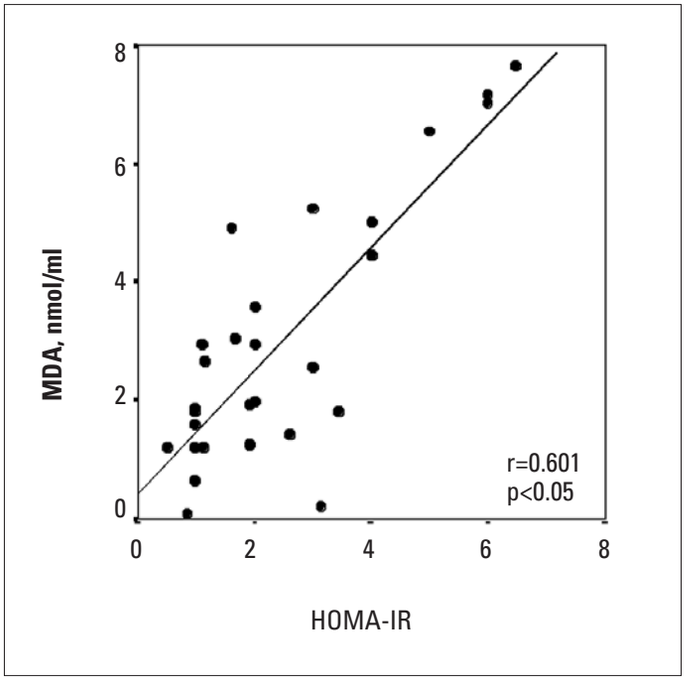

Figure 1. Correlation of serum MDA level with HOMA-IR in the SLE group
HOMA-IR- homeostasis model assessment of insulin resistance,
MDA- malondialdehyde, SLE- systemic lupus erythematosus

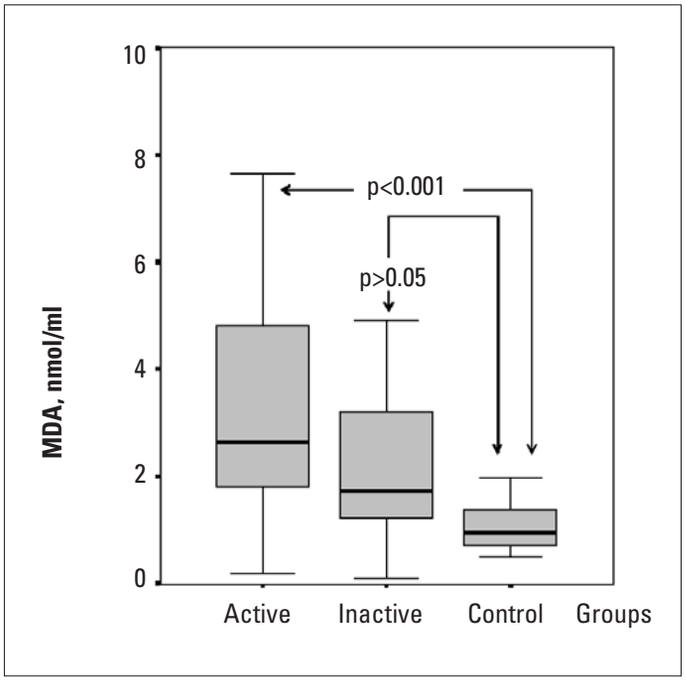

Figure 2. Serum MDA level in patients with active and inactive SLE and healthy subjects
MDA- malondialdehyde, SLE- systemic lupus erythematosus

Discussion

In this study, indicators of inflammation, oxidative stress and insulin resistance in the patients with SLE were evaluated. Serum MDA and cytokines levels were higher in the SLE group. HOMA-IR was higher in the active SLE subgroup, compared to the HC group, although only C-peptide level was higher through insulin resistance indicators in the SLE group. Moreover, oxidative stress and insulin resistance were positively related in the SLE group, although their indicators were not correlated with any inflammatory parameters in the neither SLE nor HC groups.

In patients with SLE, because accelerated atherosclerosis and premature CHD cannot be explained by traditional risk factors alone, it has been attributed to complex interactions between traditional risk factors and factors associated with the disease itself or its treatment (22).

Studies have shown that lipid peroxidation products, superoxide and hydrogen peroxide (H_2O_2) are significantly higher in patients with SLE than in healthy subjects (6, 7). Tam et al. (23) have reported increased level of MDA, which is a product of lipid peroxidation in SLE patients. In our study, MDA level was higher in the SLE group than in the HC group. There is an accumulating evidence that lipid peroxidation accounts for endothelial dysfunction (3). Furthermore, oxidative stress has been reported to be a risk factor for cardiovascular diseases in patients with SLE (6, 7).

Oxidative stress leads to the activation of multiple serine kinase cascades (8). There are a number of potential targets of these kinases in the insulin-signaling pathway, including the insulin receptor (IR) and the insulin receptor substrate (IRS) family of proteins (8-10). Increased phosphorylation of the IR or IRS on discrete serine or threonine sites decreases the extent of their tyrosine phosphorylation, and is consistent with impaired insulin action (9). The activation of each pathway (nuclear factor-κB [NF-κB], p38 map kinase [MAPK], and N-terminal JUN kinase [JNK]), which can affect insulin action, is sensitive to oxidative stress (10). Activation of these pathways is linked to impaired insulin action, suggesting that they may play a role in oxidative stress-induced insulin resistance (10).

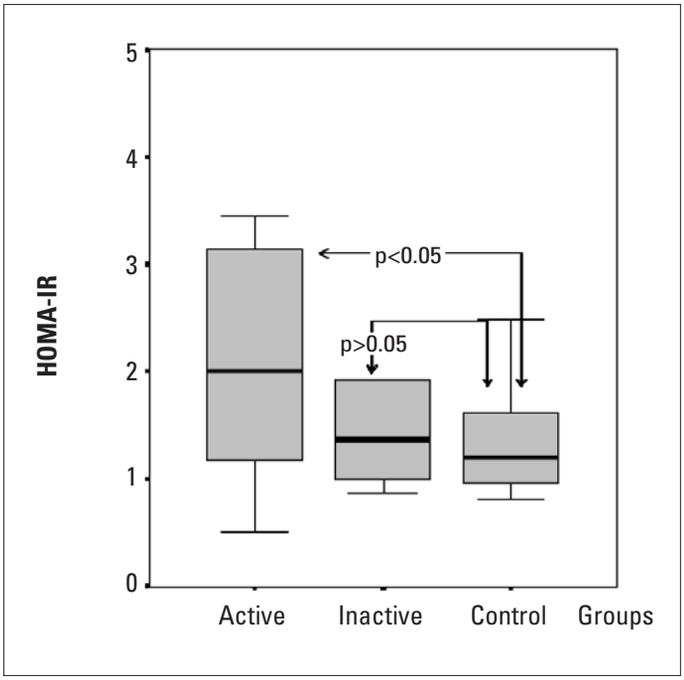

Figure 3. HOMA-IR index in patients with active and inactive SLE and healthy subjects
HOMA-IR-homeostasis model assessment of insulin resistance, SLE- systemic lupus erythematosus

An increased phosphorylation of IRS1, which can cause insulin resistance, induced by H_2O_2 has been reported (24). Moreover, treatment of 3T3-L1 adipocytes with high dose of H_2O_2 (25) or with agents that induce reactive oxygen species (ROS) accumulation (26) have been reported to induce insulin resistance via inhibiting insulin-stimulated glucose transport. Glucose utilization and glucose oxidation are inhibited when islet cells are exposed to lipid peroxidation products (27). In our study, HOMA-IR index was higher in the SLE group, and it was positively correlated with serum MDA level. Oxidative stress might contribute to atherosclerotic process via not only direct effects on endothelial dysfunction but also effects insulin resistance.

Relations between insulin resistance and atherosclerosis are well documented in previous studies (15-17). Increased prevalence of insulin resistance has been reported in patients with SLE (28). Levels of cytokines are elevated both in active and inactive periods of SLE (29), indicating that there is a chronic low-grade inflammation, which can increase during exacerbation in SLE. Systemic chronic inflammation has been proposed to have a prominent role in the pathogenesis of insulin resistance (30). Relations between TNF-α and insulin resistance are well documented (31, 32). Uysal et al. (31) have reported that mice show impaired insulin sensitivity in response to TNF-α administration, and they were protected from insulin resistance by the blockade of TNF-α. Cultured 3T3-L1 adipocytes exposed to TNF-α are shown to become insulin resistant in several days (30). The TNF-α leads to insulin resistance via increasing of inhibitor kappa kinase-beta (IKKβ) and JNK activities, which are important regulators of insulin resistance (32). Moreover, IL-6 mediates inhibition of lipoprotein lipase activity, and thus, contributes to dyslipidemia and insulin resistance (reviewed in 33).

In our study, enhanced levels of serum cytokines are accompanied with increased HOMA-IR index. In the SLE group, in addition to oxidative stress, insulin resistance may be induced by increased cytokines. Chung et al. (34) have also reported that HOMA index is associated with ESR and CRP in SLE, and with TNF-α, IL-6, CRP and ESR in rheumatoid arthritis.

In the state of insulin resistance, free fatty acids (FFA) release from adipocytes is increased due to resistance of insulin's anti-lipolytic effects (reviewed in 10). Thus, oxidations of FFA enhance in the peripheral tissues. Enhanced FFA contribute to oxidative stress due to increased mitochondrial uncoupling and β-oxidation, which can increase ROS production (10). Moreover, increased FFA conversely contribute to insulin resistance through inhibiting insulin-induced glucose uptake to muscular tissue (35). Hyperglycemia has been found to cause overproduction of superoxide by the mitochondrial electron transport via inhibiting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity, and thus, decreases many antioxidants (3536). In addition, hyperglycemia leads to oxidative stress via increased production of mitochondrial ROS, glycation of proteins and glucose autoxidation (10). In the state of insulin resistance, hyperglycemia and FFA induced oxidative stress damages the sensitivity and action of insulin (10). In patients with SLE, the presence of insulin resistance may be in part a cause and/or consequence of this oxidative stress.

Though, it has been known that glucocorticoids increase insulin resistance in connective tissue diseases, prednisolone treatment has been shown to ameliorate insulin resistance via its anti-inflammatory effects (37-39). There was no difference between patients receiving corticosteroids and not receiving in terms of insulin resistance, in our study. Therefore it may be speculated that corticosteroids are not as important as thought in the pathogenesis of insulin resistance in SLE.

Limitations of the Study

Relatively small sample size and absence of determining the other oxidant and antioxidant parameters of patients with SLE might be the limitations of our study. Other limitations of our study might be the fact that we did not assess endothelial dysfunction by flow-mediated dilations, carotid intima-media thickness and the presence of carotid plaques, and did not consider menopause status of the female participants.

Conclusion

Inflammation in SLE leads to tissue injury, and thus, increases ROS and reactive nitrogen species, and subsequent oxidative stress. Oxidants and oxidative stress may contribute to the pathogenesis of insulin resistance or vice versa. More attention should be given to low-grade inflammation and metabolic risk factors in the management of SLE patients to prevent the development of cardiovascular events.

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