Comparison of serum oxidant and antioxidant parameters in familial Mediterranean fever patients with attack free period

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is an autoinflammatory, autosomal recessive, inherited disease characterized by recurrent self-limiting attacks of serosal surfaces. The imbalance of oxidants/antioxidants may play a role in such attacks. In this study, we aimed to evaluate the relationship between serum paraoxonase (PON1) activity, PON1 phenotype, and other parameters in patients with FMF and healthy controls.
Methods: A total of 120 FMF patients with an attack-free period (AFP) and 65 healthy subjects were included in this study. The serum PON1 activity, stimulated paraoxonase (SPON) activity, PON1 phenotype (representing Q192R polymorphism; QQ, QR, RR), arylesterase activity, total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI), advanced oxidative protein products (AOPP), total thiols (TTL), and ischemia-modified albumin (IMA) and cystatin-c (CYS-C) levels were measured.
Results: For the QQ phenotype, the median TTL and AOPP levels of the control group were 264.50 (57.75) μmol/L and 21.26 (21.17) mmol/L, respectively, whereas the median TTL, AOPP levels of the patients were 309.00 (47.00) μmol/L and 12.98 (6.96) mmol/L, respectively. There was a statistically significant difference between the patients and controls with the QQ phenotype in terms of TTL and AOPP ($p< 0.001$ and $p= 0.004$, respectively). However, there were no statistically significant differences between the QQ and QR+RR phenotypes with respect to TAC, TOS, OSI, or the other parameters.
Conclusions: The FMF patients with AFP had higher TTL and lower AOPP levels than the controls. However, other oxidant and antioxidant parameters were similar among the patients during AFP and the controls.

Keywords: Familial Mediterranean Fever; Antioxidant; Oxidant; Status

INTRODUCTION

Familial Mediterranean Fever (FMF) is an autoinflammatory disease with periodic fever accompanied by abdominal pain, pleuritis, arthritis, erysipelas-like skin lesions, and recurrent self-limiting attacks[1]. It is known that ongoing persistent subclinical inflammation may be found in FMF patients during an attack-free period (AFP), and oxidative stress and oxidant/antioxidant imbalance can play a role in this persistent subclinical inflammation. Oxidative stress produces increasing oxidants levels and free radicals and/or decreasing antioxidant capacity in organisms, and oxidant damage to cellular and extracellular structures have harmful effects on cellular molecules. Free radicals play an important role in the development and pathogenesis of certain diseases, including cardiovascular disorders, cancer, allergy (or symptoms thereof), some neurological diseases, diabetes, and diabetic cataract/retinopathy[2, 3].

Therefore, we aimed to investigate the relationship between PON and arylesterase (ARE) activity, cystatin-c (CYS-C) levels, other oxidant/antioxidant parameters, and paraoxonase phenotypes in patients with FMF during an AFP and healthy controls.

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MATERIALS AND METHODS

A total of 120 FMF patients fulfilling Tel Hashomer criteria[4] (75 female, 45 male) with AFP and 65 healthy subjects (43 female, 22 male) were included in this study. The study protocol was approved by the local ethics committee and was in accordance with the Declaration of Helsinki 2008. Informed consent was obtained from all subjects. A total of 106 patients had Mediterranean Fever (MEFV) mutations: 19 had M694V homozygosity, 39 had M694V heterozygosity (single or compound heterozygote with another mutation), and 48 had mutations other than M694V. Fourteen patients had no mutation. All of the FMF patients were under treatment with colchicine (1-1.5 gr daily). Patients with other inflammatory, autoimmune, acute or chronic infectious diseases and diabetes mellitus were not included in the study. Normal healthy volunteers without chronic systemic disease and with normal physical examination and laboratory findings were selected as the control group.

The serum PON1 activity, stimulated paraoxonase (SPON) activity, PON1 phenotype (representing Q192R polymorphism; QQ, QR, RR), ARE, total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI), advanced oxidative protein products (AOPP), total thiols (TTL), and ischemia-modified albumin (IMA) and CYS-C levels were measured.

Blood samples from the FMF patients and control group were collected and immediately placed on ice at 4ºC. The plasma was separated from the cells by centrifugation (Hettich Lab Technology, Tuttlingen, Germany) at 2509 x g for 10 min and stored at -80ºC until analyzed. Plasma TOS and TAC were assessed using the automated measurement method of Erel[5, 6].

Serum TOS was determined using the novel automated measurement method developed by Erel[6]. The oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion, and the oxidation reaction is enhanced by the glycerol molecules that are abundant in the reaction medium. The ferric ion generates a colored complex with Xylenol Orange in an acidic medium. Thus, the color intensity, which can be measured spectrophotometrically, is related to the quantity of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide, and the results are expressed in terms of micro-molar hydrogen peroxide equivalents per liter (mmol H2O2 equiv./L).

Serum TAC was also determined using a novel automated measurement method[6]. In this method, hydroxyl radical, the most potent biological radical, is produced. In the assay, a ferrous ion solution, present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequentially produced radicals, such as the brown-colored dianisidinyl radical cation produced by the hydroxyl radical, are also potent radicals. Using this method, the anti-oxidative effect of the sample against potent free-radical reactions, which are initiated by the produced hydroxyl radical, can be measured. The assay has excellent precision values of greater than 97%. The results are expressed as mmol Trolox® (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) equivalents/L.

OSI is defined as the ratio of TOS to TAC and is expressed as a percentage. For the calculation, the TAC units were changed to mmol/L, and the OSI value was calculated according to the following formula[5]: OSI (arbitrary units)= TOS (µmol H2O2 equivalents/L)/ TAC (mmol Trolox® equivalents/L)x10^{-1}.

PON1 polymorphism and the ARE activities were examined using previously described methods[3,7,8].

STATISTICAL ANALYSIS

The data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). The normality of the distributions of continuous variables was determined by the Shapiro-Wilk test. The Levene test was used for the evaluation of the homogeneity of the variances. The data are shown as the median (IQR). The differences in the median values between groups (case vs control or QQ vs QR+RR) were compared using the Bonferroni Adjusted Mann-Whitney U test. The Bonferroni correction was applied for controlling type I errors for all possible multiple comparisons. A value of $p< 0.025$ was considered statistically significant.

RESULTS

For the FMF patients, 61 (50.8%) had a QQ phenotype, 47 (39.2%) had a QR phenotype, and 12 (10%) had an RR phenotype. For the controls, 30 (46.2%) had a QQ phenotype, 31 (47.7%) had a QR phenotype, and 4 (6.2%) had an RR phenotype (Table I). The mean age of the groups, and the sex distribution was similar ($p> 0.05$).

The median level of PON was 94.18 (31.21) U/L in

TABLE I. DISTRIBUTION OF GROUPS ACCORDING TO PARAOXONASE PHENOTYPE

	Control	FMF	Total
QQ	30 (46.2%)	61 (50.8%)	91 (49.2%)
QR	31 (47.7%)	47 (39.2%)	78 (42.2%)
RR*	4 (6.2%)	12 (10.0%)	16 (8.6%)
Total	65 (100%)	120 (100%)	185 (100%)

*Because the RR phenotype was not frequently found in the FMF and control groups, the QR and RR phenotype groups were combined for the statistical analysis. FMF, familial Mediterranean fever

the controls and 77.22 (27.27) U/L in the FMF patients with the QQ phenotype, whereas the median level of PON was 282.08 (122.19) U/L in the controls and 272.46 (146.82) U/L in the FMF patients with the QR+RR phenotype. For the QQ phenotype, the median level of SPON was 279.35 (101.65) U/L in the controls and 238.50 (98.18) U/L in the FMF patients (Table II).

The median level of SPON was 678.00 (259.00) U/L in the controls and 687.00 (291.00) U/L in the FMF patients with the QR+RR phenotype. There were statistically significant differences between the QQ and QR+RR phenotypes for PON and SPON in each group ($p< 0.001$ and $p< 0.001$, respectively). The median level of TTL in the QQ control group was 264.50 (57.75) μmol/L, whereas the median level of TTL in the QQ FMF patients was 309.00 (47.00) μmol/L. The median level of AOPP in the QQ control group was 21.26 (21.17) mmol/L and was 12.98 (6.96) mmol/L the QQ FMF patient group. There was a statistically significant difference between the patients and controls with the QQ phenotype with respect to TTL and AOPP ($p< 0.001$ and $p= 0.004$, respectively). However, there was no statistically significant difference between the patients and controls with the QQ and QR+RR phenotype for the other parameters (Table II).

The mean level of TAC was 3.48 (0.63) mol Trolox eqv./L in the QQ control group and 3.54 (0.35) mol Trolox eqv./L in the QQ FMF patients (Table II). The mean level of TAC was 3.40 (0.56) μmol Trolox eqv./L in the QR+RR control group and 3.53 (0.53) in the QR+RR FMF patients. For the QQ phenotype, the mean level of TOS was 2.96 (3.88) μmol H2O2 eqv./L in the controls and 2.44 (1.73) μmol H2O2 eqv./L in the FMF patients, whereas the mean level of TOS was 2.51 (2.02) μmol H2O2 eqv./L in the controls and 2.67 (1.89) μmol H2O2 eqv./L in the FMF patients with the QR+RR phenotype (Table II). There were no statistically significant differences between the QQ and QR+RR phenotypes for TAC, TOS, OSI, or the other parameters (Table II).

DISCUSSION

Serum TTLs bearing sulfhydryl groups have antioxidant properties, and the patients with a QQ phenotype had higher TTL levels than the controls. However, it is not known whether this situation is defensive or compensative. In this study, we found that the patients with a QQ phenotype exhibited lower AOPP levels than the controls.

FMF is an autoinflammatory, autosomal recessive, inherited disease characterized by recurrent self-limiting attacks of serosal surfaces. Several factors might trigger these attacks, including infection, surgery, various stresses, and menses[9]. It is known that subclinical inflammation may persist during AFP[9].

Free radicals have deleterious effects on cell membranes, causing damage through lipid peroxidation under conditions of oxidative stress. Activated neutrophils play an important role in inflammatory reactions by producing reactive oxygen species (ROS). Although ROS can be neutralized by antioxidant mechanisms, nucleic acids, lipids, and proteins can be damaged by the harmful effects of oxidants when the oxidant/ /antioxidant balance is disturbed[10]. Antioxidants are derived by two ways in the body: they are synthesized endogenously by such enzymes as superoxide dismutase, catalase, and glutathione peroxidase and are supplied exogenously in the diet, such as with vitamins E and C[10].

PON1 is able to metabolize organophosphate pesticides (i.e., Paraoxon). Two exonic amino acid polymorphisms have been detected in PON 1, one at position 192 [a glutamine (Q) / arginine (R) substitution] and the other at position 55 [a methionine (M) / leucine (L) substitution][3]. PON 1 alloenzymes have effects on both organophosphate detoxification and lipoprotein oxidation[3]. Humans who have different PON1 activity are capable of balancing oxidants/ /antioxidants. The PON gene family is located on chromosome 7q21.3-22.1 and consists of three members: PON1, PON2, and PON3[11].

Saygili *et al.* demonstrated that TOS and OSI levels were increased in diabetic cataract patients in compa-

TABLE II. DISTRIBUTION OF MEASUREMENTS ACCORDING TO GROUP AND PON 1 PHENOTYPE

	Control	FMF Patients	p-value[a]
CYS-C (mg/L)			
QQ	0.68 (0.19)	0.64 (0.25)	0.344
QR+RR	0.61 (0.18)	0.63 (0.28)	0.032
p-value[b]	0.042	0.290	
TAC (µmol Trolox eqv./L)			
QQ	3.48 (0.63)	3.54 (0.35)	0.289
QR+RR	3.40 (0.56)	3.53 (0.53)	0.506
p-value[b]	0.974	0.661	
TOS (µmol H2O2 eqv./L)			
QQ	2.96 (3.88)	2.44 (1.73)	0.109
QR+RR	2.51 (2.02)	2.67 (1.89)	0.894
p-value[b]	0.385	0.367	
PON (U/L)			
QQ	94.18 (31.21)	77.22 (27.27)	0.060
QR+RR	282.08 (122.19)	272.46 (146.82)	0.740
p-value[b]	<0.001	<0.001	
SPON (U/L)			
QQ	279.35 (101.65)	238.50 (98.18)	0.044
QR+RR	678.00 (259.00)	687.00 (291.00)	0.664
p-value[b]	<0.001	<0.001	
TTL (µmol/L)			
QQ	284.50 (57.75)	309.00 (47.00)	<0.001
QR+RR	296.00 (63.00)	321.00 (82.00)	0.047
p-value[b]	0.155	0.775	
ARES (U/L)			
QQ	207.62 (86.80)	186.79 (61.51)	0.234
QR+RR	217.93 (87.16)	214.10 (72.78)	0.978
p-value[b]	0.528	0.005	
OSI (AU; arbitrary unit)			
QQ	0.08 (0.16)	0.07 (0.05)	0.161
QR+RR	0.07 (0.07)	0.08 (0.06)	0.805
p-value[b]	0.385	0.265	
AOPP (mmol/L)			
QQ	21.26 (21.17)	12.98 (6.96)	0.004
QR+RR	17.79 (15.06)	15.74 (13.32)	0.375
p-value[b]	0.407	0.065	
IMA (U/mL)			
QQ	6415 (4850.62)	5252.50 (3271.25)	0.423
QR+RR	6105 (3697.5)	5290.00 (3532.5)	0.198
p-value[b]	0.854	0.663	
SPONAR (U/L)			
QQ	1.50 (0.40)	1.27 (0.40)	0.179
QR+RR	3.20 (0.79)	3.19 (0.96)	0.242
p-value[b]	<0.001	<0.001	
PONAR (U/L)			
QQ	0.47 (0.13)	0.44 (0.11)	0.307
QR+RR	1.32 (0.40)	1.30 (0.61)	0.722
p-value[b]	<0.001	<0.001	

a. Comparison between the control and FMF groups according to PON 1 phenotype. A Bonferroni correction was applied for controlling Type I errors. p< 0.025 was considered statistically significant. b. Comparison of groups according to PON 1 phenotype. A Bonferroni correction was applied for controlling type I errors. p< 0.025 was considered statistically significant. Because the RR phenotype was not frequently found in the FMF and control groups, the QR and RR phenotype groups were combined for the statistical analysis.
AOPP, advanced oxidative protein products; ARE, arylesterase; CYS-C, cystatin-c; IMA, ischemia-modified albumin; OSI, oxidative stress index; PON, paraoxonase, SPON, stimulated paraoxonase; TAC, total antioxidant capacity; TTL, total thiols; TOS, total oxidant status; FMF, familial Mediterranean fever.

rison to senile cataract patients. These authors demonstrated that TAC, TOS, and OSI can represent the antioxidant compounds in the body (e.g., superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase) and oxidant parameters[12].

Turgay *et al.* showed that the levels of oxidative stress and antioxidant parameters in erythrocytes and plasma of Turkish patients with systemic lupus erythematosus (SLE) were not significantly different between active and inactive SLE. These authors found that these parameters did not influence SLE disease severity but could be pathogenetic factors for SLE etiology. Moreover, there were statistically significant differences between the SLE and control groups, though the most important limitation of the study was the small cohort size[13].

It has been suggested that endothelial dysfunction caused by free radical-mediated injury and vasospasm due to episodes of ischemia-reperfusion injury may play a role in the pathogenesis of some rheumatic diseases, such as systemic sclerosis (SSc). It was found that PON activity was higher in anti-centromere autoantibody-positive SSc patients than in healthy controls and autoantibody-negative patients[14]; it was, therefore, proposed that free radical injury may be involved[14]. Furthermore, the authors showed that oxidative stress plays a role in the pathogenesis of some connective tissue diseases[15,16].

Erdem *et al.* found no statistically significant differences among PON1 and ARE activity, disease activity (BASDAI), and functional status (BASFI) measures between ankylosing spondylitis patients and healthy controls[17]. Human PON1 activity and phenotype distribution were studied in patients with Sjögren's syndrome (SS) using a dual-substrate method[18], and a correlation between phenotype distribution and decreased PON activity was found in SS patients. Accordingly, in our study, we found that the PON1 phenotype was associated with TAC and TOS levels in patients with FMF.

Yildirim *et al.* studied the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Cu/Zn-Superoxide dismutase (SOD), and Malondialdehyde (MDA) levels, and PON1 and ARE activities in patients with FMF during AFP and found that the serum ARE activity was decreased in these patients, though no statistically significant associations were found between the groups[19]. Additionally, PON1 and ARE activities have been evaluated in other rheumatic diseases, such as rheumatoid arthritis[20,21], psoriasis[22], systemic lupus erythematosus[23,24], and Behçet's disease[25].

Savran *et al.* demonstrated that increased oxidative stress, CRP and TOS levels were found higher fifty one FMF patients with AFP compared with 30 healthy subjects[26]. In another study, authors showed that TOS, OSI levels were higher in attack-period (AP) with FMF patients[27]. Nevertheless, serum TAC and Zn levels were lower in FMF patients during AP and AFP than in healthy controls[27]. We found similar TAC, TOS, and OSI levels in FMF patients during AFP and healthy controls according to PON1 phenotypes.

CONCLUSION

It is known that ongoing persistent subclinical inflammation may be found in FMF patients during AFP[28] and that persistent subclinical inflammation can be caused by an imbalance of oxidant/antioxidant, TAC, TOS, and OSI levels. It should be noted that the present study had some limitations, as we could not compare the oxidant/antioxidant, ESR, CRP, and fibrinogen levels. However, we did evaluate oxidant/ /antioxidant parameters in FMF patients with AFP and healthy individuals according to PON 1 phenotypes. Further studies of attack and attack-free patients and those with renal involvement (amyloidosis) need to be performed to evaluate these findings.

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REFERENCES

1. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet 1998;351:659-664.
2. Keskin M, Dolar E, Dirican M, Kiyici M, Yilmaz Y, Gurel S, Nak SG, Erdinc S, Gulten M. Baseline and salt-stimulated paraoxonase and arylesterase activities in patients with chronic liver disease: relation to disease severity. Intern Med J 2009;39:243--248.
3. Browne RW, Koury ST, Marion S, Wilding G, Muti P, Trevisan M. Accuracy and biological variation of human serum paraoxonase 1 activity and polymorphism (Q192R) by kinetic enzyme assay. Clin Chem 2007;53:310-317.
4. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40:1879–1885.
5. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112-119.
6. Erel O. A new automated colorimetric method for measuring

total oxidant status. Clin Biochem 2005;38:1103-1111.
7. Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 1983;35:1126-1138.
8. La Du BN, Eckerson HW. The polymorphic paraoxonase/arylesterase isozymes of human serum. Fed Proc 1984;43:2338.
9. Karadag O, Tufan A, Yazisiz V, et al. The factors considered as trigger for the attacks in patients with familial Mediterranean fever. Rheumatol Int 2013;33:893-897.
10. Mutlu B, Aksoy N, Cakır H, Celik H, Erel O. The effects of the mode of delivery on oxidative-antioxidative balance. J Matern Fetal Neonatal Med 2011;24:1367-1370.
11. Draganov DI, Teiber JF, Speelman A, Osawa Y, Sunahara R, La Du BN. Human paraoxonase (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities. J Lipid Res 2005;46:1239-1247.
12. Saygili EI, Aksoy SN, Gurler B, Aksoy A, Erel O, Ozaslan M. Oxidant/antioxidant status of patients with diabetic and senile cataract. Biotechnol Biotechnol Eq 2010;24:1648-1652.
13. Turgay M, Durak I, Erten S, Ertugrul E, Devrim E, Avci A, Turgay F. Oxidative stress and antioxidant parameters in a Turkish group of patients with active and inactive systemic lupus erythematosus. APLAR J Rheumatol 2007;10:101-106.
14. Ergüder IB, Erten S, Devrim E, Turgay M, Durak I. Plasma paraoxonase activity in patients with systemic sclerosis. Indian J Med Res 2009;129:609-612.
15. Devrim E, Erten S, Ergüder IB, Namuslu M, Turgay M, Durak I. Malondialdehyde and nitric oxide levels in erythrocytes from patients with systemic sclerosis. Med Princ Pract 2008;17:349--350.
16. Bodolay E, Seres I, Szodoray P, Csipo I, Jakap Z, Vegh J, Szilagyi A, Szegedi G, Paragh G. Evaluation of paraoxonase activity in patients with mixed connective tissue disease. J Rheumatol 2008;35:237-243.
17. Erdem FH, Karatay S, Yildirim K, Kiziltunc A. Evaluation of serum paraoxonase and arylesterase activities in Ankylosing Spondylitis patients. Clinics 2010;65:175-179.
18. Szanto A, Harangi M, Seres I, Paragh G, Zeher M. Decreased human paraoxonase-1 activity in patients with Sjögren's syndrome. Intern Immunol 2010;22:605-609.
19. Yildirim K, Uzkeser H, Keles M, Yildirim S, Karatay S, Kiziltunc A, Ugur M. Cu/Zn-superoxide dismutase, paraoxonase and arylesterase activities and malondialdehyde levels in patients with familial Mediterranean fever. Bratisl Lek Listy 2012; 113:561--564
20. Isık A, Koca SS, Ustundag B, Celik H, Yildirim A. Paraoxonase and arylesterase levels in rheumatoid arthritis. Clin Rheumatol 2007;26:342-348.
21. Tanimoto N, Kumon Y, Suehiro T, Ohkubo S, Ikeda Y, Nishiya K, Hashimoto K. Serum paraoxonase activity decreases in rheumatoid arthritis. Life Sci 2003;72:2877-2885.
22. Toker A, Kadi M, Yildirim AK, Aksoy H, Akçay F. Serum lipid profile paraoxonase and arylesterase activities in psoriasis. Cell Biochem Funct 2009;27:176-180.
23. Delgado Alves J, Ames PR, Donohue S, Stanyer L, Nourooz-Zadeh J, Ravirajan C, Isenberg DA. Antibodies to high-density lipoprotein and beta2-glycoprotein I are inversely correlated with paraoxonase activity in systemic lupus erythematosus and primary antiphospholipid syndrome. Arthritis Rheum 2002;46:2686-2694.
24. Kiss E, Seres I, Tarr T, Kocsis Z, Szegedi G, Paragh G. Reduced paraoxonase 1 activity is a risk for atherosclerosis in patients with systemic lupus erythematosus. Ann N Y Acad Sci 2007;1108:83-91.
25. Karakucuk S, Baskol G, Oner AO, Baskol M, Mirza E, Ustdal M. Serum paraoxonase activity is decreased in the active stage of Behçet's disease. Br J Ophthalmol 2004;88:1256-1258.
26. Savran Y, Sari I, Kozaci DL, Gunay N, Onen F, Akar S. Increased Levels of Macrophage Migration Inhibitory Factor in Patients with Familial Mediterranean Fever. Int J Med Sci 2013;10:836-839. doi:10.7150/ijms.6116.
27. Deveci K, Senel S, Deveci H, Sancakdar E, Deniz A, Uslu AU, Aydin H. Do serum Zn levels and oxidative status change in familial Mediterranean fever patients during attack and attack--free periods? Health Med 2013;Vol. 7 Issue 4, p1307.
28. Erten S, Altunoglu A, Ceylan GG, Maras Y, Koca C, Yuksel A. Low plasma vitamin D levels in patients with familial Mediterranean fever. Rheumatol Int 2012;32:3845-3849.