Comparison of Oxidant and Antioxidant Parameters in Patients with Sjögren's Syndrome and Healthy Subjects

Vergleich der Oxidations- und Antioxidationsparameter bei Patienten mit Sjögren-Syndrom und gesunden Probanden

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ABSTRACT

Objective Oxidative stress may have an effect on the pathogenesis of diseases, including autoimmune rheumatic diseases. We aimed to investigate the serum paraoxonase activity and other oxidant/antioxidant parameters in patients with Sjögren's syndrome (SS) and healthy controls.

Methods 85 patients with SS and 65 healthy subjects were included in the study. Groups were age and gender-matched and had no liver disease. Serum paraoxonase (PON)-1 activity, stimulated paraoxonase (SPON), PON-1 phenotypes that represent polymorphism (Q192R; QQ, QR, RR), arylesterase (ARE), total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI), advanced oxidative protein products (AOPP), total thioles (TTL) and ischaemia-modified albumin (IMA) were measured in all study participants.

Results Statistically significant differences were found in the QQ and QR + RR phenotype of PON-1 for TAC, TOS and TTL ($p < 0.001$) between SS and healthy groups. The other parameters were statistically insignificant.

Conclusion Antioxidant parameters were lower in SS patients compared with healthy controls. Conversely, oxidant parameters were higher. This imbalance may play a role in SS pathogenesis.

ZUSAMMENFASSUNG

Ziel Oxidativer Stress kann die Pathogenese von Krankheiten, einschließlich rheumatischer Autoimmunerkrankungen, beeinflussen. Wir wollten die Paraoxonase-Aktivität im Serum und andere oxidative / antioxidative Parameter bei Patienten mit Sjögren-Syndrom (SS) und gesunden Kontrollpersonen untersuchen.

Methode 85 Patienten mit SS und 65 gesunde Probanden wurden in die Studie eingeschlossen. Die Gruppen waren alters- und geschlechtsgleich und hatten keine Lebererkrankungen. Bei allen Studienteilnehmern wurden Serum-Paraoxonase (PON) 1-Aktivität, stimulierte Paraoxonase (SPON), PON 1-Phänotypen, die Polymorphismus darstellen (Q192R; QQ, QR, RR), Arylesterase (ARE), Gesamtoxidationsstatus (TOS), Gesamtantioxidationskapazität (TAC), oxidativer Stress-Index (OSI), fortgeschrittene oxidative Proteinprodukte (AOPP), Gesamtthiole (TTL) und Ischämie-modifiziertes Albumin (IMA) gemessen.

Ergebnisse Es gab statistisch signifikante Unterschiede im QQ- und QR + RR-Phänotyp von PON-1 für TAC, TOS und TTL ($p < 0{,}001$) zwischen SS- und gesunden Gruppen. Die anderen Parameter waren statistisch nicht signifikant.

Schlussfolgerung Die Antioxidationsparameter waren bei SS-Patienten im Vergleich zu gesunden Kontrollen niedriger, und umgekehrt waren die Oxidationsparameter höher. Dieses Ungleichgewicht kann eine Rolle bei der SS-Pathogenese spielen.

Introduction

Sjogren's syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation of the salivary and lacrimal glands. Xerostomia and keratoconjunctivitis sicca are seen in about 95 % of the patients [1].

Oxidative stress develops by increasing oxidants levels and/or decreasing antioxidant capacity in organisms. The oxidants may damage cellular and extracellular structures, and impair the genetic structures by having harmful effects on DNA [2].Reactive oxygen species play a role in the development and pathogenesis of diseases including cardiovascular disorders (ie. atherosclerosis), some neurological diseases, cancer, allergic symtomps, diabetes and diabetic cataract, retinopathy, and also in autoimmune rheumatic diseases like sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus and scleroderma [2, 3].

Paraoxanases enzymes (PON 1, 2, 3) have roles in protection against oxidative damage and lipid peroxidation, contribution to innate immunity, detoxification of reactive molecules, bioactivation of drugs, modulation of endoplasmic reticulum stress and regulation of cell proliferation/apoptosis [4]. PON 1 is an antioxidant, negative acute phase protein; and mostly used enzyme in studies. It is synthesized from liver and can be used as a biomarker in oxidative stress, inflammation, and liver diseases. PON 1 has 3 phenotypes; QQ representing low, QR intermediate and RR high enzyme activity of PON1 [4].

There is very little literature regarding the role of oxidative stress in Sjögren's syndrome.We aimed to investigate serum paraoxonase activity, and other oxidant/antioxidant parameters in patients with SS and healthy controls.

Materials and Methods

Eighty five (76 female, 9 male) patients, age above 18 years old, without any liver disease,with Sjögren's syndrome according to American-European Consensus Classification Criteria [5] attending to our rheumatology out-patient clinic, and 65 (43 female, 22 male) healthy subjects, age and gender matched with SS group without any liver disease, were included in the study. Serum paraoxonase (PON) 1 activity, stimulated paraoxonase (SPON), PON 1 phenotypes that represent polymorphism (Q192R; QQ, QR, RR), arylesterase (ARE), total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stres index (OSI), advanced oxidative protein products (AOPP), total thioles (TTL) (Serum TTL representing sulfhydryl groups have antioxidant properties), ischemia modified albumin (IMA) were measured in all study participants. The study protocol was approved by local ethics committee and was in accordance with Helsinki decleration 2008. Informed consent was taken from all participitants.

Blood samples from patients with SS and the control group were taken, and were immediately placed on ice 4 ℃. Plasma was separated from the cells by centrifugation (Hettich Lab Technology, Tuttlingen, Germany) at 25 °C.for 10 min and stored at -80 ℃ until analysis.

The TOS of serum was determined using an automated measurement method developed by Erel [6]. Oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ion generates a coloured complex with Xylenol Orange in an acidic medium. Colour 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 expressed in terms of micro-molar hydrogen peroxide equivalents per liter (mmol H2O2 equiv./L).

Serum TAS was determined using an automated measurement method [6]. Hydroxyl radical, the most potent biological radical, is produced in this method. Ferrous ion solution, present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. Sequentially-produced radicals like the brown-colored dianisidinyl radical cation, produced by the hydroxyl radical, also are 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.

The OSI is defined as the ratio of the TOS to TAS level, expressed as a percentage. For the calculation, TAS units were changed to mmol/L, and the OSI value calculated according to the following formula (4): OSI (arbitrary units) = TOS (μmol H_2O_2 equivalents/L)/ TAS (mmol Trolox equivalents/L)x10^{-1}.PON1 polymorphism and ARE activities studied by previously determined methods [7–9].

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distributions of continuous variables were normal or not was determined by Shapiro Wilk test. Levene test was used for the evaluation of homogeneity of variances. Data are shown as mean ± standard deviation or median (IQR), where applicable. While the mean differences between groups (case vs control or QQ vs QR + RR) were compared by Bonferroni Adjusted Student's t test, otherwise, Bonferroni Adjusted Mann Whitney U test was used for comparisons of the median values. All possible multiple comparisons, the Bonferroni Correction was applied for controlling Type I error. Thus, $p < 0.025$ was considered statistically significant.

Results

When the age, gender and laboratory parameters of the patient and healthy control groups were compared, both groups were similar, except that the female ratio was higher in healthy control than the patient group. Among the SS patients included in our study, there was no patient with organ involvement and on severe immunosuppressive therapy. There were mostly sicca symptoms, arthralgia, and arthritis. (▶ **Table 1**)

Of the SS patients, 39 (45.8 %) had QQ phenotype, 38 (44.7 %) had QR and 8 (9.4 %) had RR. Of healthy controls, 30 (46.2 %) had QQ, 31 (47.7 %) had QR and 4 (6.2 %) had RR phenotype (▶ **Table 2**).

The mean level of TAC was 3.48 ± 0.48 μmol Trolox eqv./l in controls and 2.72 ± 0.63 μmol Trolox eqv./l in SS patients according to QQ. The mean level of TAC was 3.43 ± 0.40 μmol Trolox eqv./l in controls and 2.60 ± 0.59 in SS patients according to QR + RR. The median level of TOS was 1.90 (1.55) μmol H2O2 eqv./l in controls

▶ **Table 1** Patient characteristics and laboratory parameters of the study population.

	Sjögren Syndrome patients, n = 85	Control patients, n = 65	p
Age, years, mean ± SD	55.1 ± 11.3	53.5 ± 11.2	0.538
Female, n (%)	76 (89.4)	43 (66.2)	**< 0.0001**
Disease duration, years, median (min-max)	7.8 (0.3–20)	NA	
Hb g/dl, mean ± SD	13.3 ± 1.2	13.1 ± 1.2	0.422
White blood cell count (10^9/L), mean ± SD	6895 ± 2313	6826 ± 2067	0.849
Trombosit ,mean ± SD	256 ± 61	265 ± 58	0.334
Erythrocyte sedimentation rate (mm/h), median (min-max)	14 (5–48)	12 (4–44)	0.623
C-reactive protein (mg/dL), median (min-max)	3.0 (1.0–13.2)	3.2 (1.0–7.1)	0.187
Creatinine mg/dL, mean ± SD	0.75 ± 0.19	0.71 ± 0.16	0.247
AST (IU), mean ± SD	22.6 ± 5.7	21.8 ± 5.4	0.422
ALT (IU), mean ± SD	21.5 ± 7.4	21.0 ± 7.1	0.834
Sicca symptom, n (%)	83 (97.6)		
Schirmer test positivity (< 5 mm/5 min), n (%)	61 (71.8)		
Anti SSA/Ro antibody positivity, n (%)	35 (41.2)		
Anti SSB/La antibody positivity, n (%)	21 (24.7)		
ANA positivity, n (%)	69 (81.2)		
Minor salivary gland biopsy positivity, n (%)	48/66 (72.7)		
Arthritis, n (%)	47 (55.3)		
Hydroxychloroquine, n (%)	85 (100)		
Steroid, n (%)	38 (44.7)		
DMARDs, n (%)	32 (37.6)		

▶ **Table 2** Distribution of groups according to paraoxonase pheontypes.

	Control	SjS Group	Total
QQ	30 (20.0%)	39 (26.0%)	69 (46.0%)
QR	31 (20.7%)	38 (25.3)	69 (46.0%)
RR	4 (2.7%)	8 (5.3%)	12 (8.0%)
Total	65 (43.3%)	85 (56.7%)	150 (100%)

* RR phenotype was not found to be enough in SjS and in control groups, the QR and the RR phenotype groups were unified for statistical analysis.

and 2.96 (3.88) µmol H2O2 eqv./l in SS patients according to QQ. The median level of TOS was 1.51 (1.50) µmol H2O2 eqv./l in controls and 2.51 (2.02) µmol H2O2 eqv./l in SS patients according to QR + RR. There were statistically significant differences between QQ and QR + RR phenotype for TAC, and TOS ($p < 0.001$) between controls and SS patients. The median level of TTL of control group was 284.50 (57.75) µmol/L according to QQ . The median level of TTL of SS patients was 207.81 (41.07) µmol/L according to QQ. There were statistically significant differences between the groups ($p < 0.001$). The median level of TTL of control group was 296.00 (63.00) µmol/L according to QR + RR. The median level of TTL of SS patients was 202.62 (64.96) µmol/L according to QR + RR. There were statistically significant differences between the groups ($p < 0.001$). There was no statistically significant difference between the patients and the controls for the other parameters according to QQ and QR + RR (▶ **Table 3**).

Discussion

In the present study, the SS patients with QQ and QR + RR phenotype of PON 1 enzyme had lower TTL levels than controls. Serum TOS levels were higher in SS patients than in controls. On the other hand, serum TAC levels were higher in controls than in SS patients. The other parameters including ARE were not significantly different .

Similar to our study, Szanto et al studied human PON1 activity and phenotype distributionin patients with Sjögren's ayndrome by dual-substrate method [10]. It was found that phenotype distribution cause decrease in PON activity in patients with SS.

Both plasma and tissue TAC, TOS and OSI levels had been previously studied in cardiovascular diseases [11]. Plasma and tissue oxidant stress and antioxidant parameters were not different than patients with rheumatic and degenerative heart valve disease [12]. Harma et al suggested that measuring TAC, TOS, and OSI during pregnancy may help us for determining oxidative damage on plasental tissue in preeclampsia which is another vasculoendothelial disease [11]. Sarban et al studied plasma TAC levels, lipid peroxidation, erythrocyte antioxidant enzyme activities in patiets with rheumatoid arthritis (RA) and osteoarthritis (OA) [13]. They suggested

that TAC measurement may be useful for evaluating the plasma antioxidant status of RA patients. Also, they found antioxidant defense system doesn't work properly in RA patients. Decreased levels of TAC, antioxidant enzymes (GSH-Px, CAT) and increased MDA concentrations may be seen in RA patients in contrast to OA [13]. In another study, serum PON1, ARE activity and PON1 phenotype distribution were evaluated in chronic liver disease [14]. It was suggested that serum PON1 and ARE activities were reduced in patients with chronic liver damage and these could be promising biomarkers to evaluate of the presence and severity of chronic liver damage [14].

PON and ARE activity were studied in some other rheumatic diseases. There was no significant difference in ankylosing spondylitis and control group, and no relation with disease activity [15]. In rheumatoid arthritis, their levels had significantly decreased [16, 17]. In psoriasis, there was no relation with percentage of lesions [18]. In systemic lupus erythematosus, decreased levels of them were related with hyperlipidemia and atherosclerosis [19, 20]. In attack free patients with familial Mediterranean fever, their levels were normal [21]and in active Behçet's disease their levels were decreased [22].

Chronic lymphocytic infiltration of glands, and imbalance of antioxidant/oxidant status could be responsible in the pathogenesis of SS. Excess expression of proinflammatory cytokines may increase oxidative stress with reactive oxygen species produced by activated granulocytes. In some studies, excess levels of oxidative stress markers in saliva, decreased expression of antioxidant activities in cojunctival epithelial cells and parotid gland tissue were reported in SS' patients [23].Also, mitochondrial dysfunction was reported in SS pathogenesis [24]. It was postulated that oxidative modifications of inflammation of proteins contributes to the development of autoantibodies of SS and systemic lupus erythematosus by inactivating T cells through nitration, epigenetically altering gene expression in a subset of CD4 + T cells [25].

We didn't evaluated the relationship antioxidant and oxidant parameters according to the SS disease activity which is limitation of the study In the present study, we studied serum PON1 and ARE activities, PON1 phenotype distributions and correlation between these and TAC, TOS, OSI and other parameters. We commended that antioxidant parameters were lower in SS patients compared with healthy controls, and inversely oxidants were higher. Further studies are necessary for determining and evaluating for relationship oxidative stress and chronic inflammation of the salivary and lacrimal glands, and other tissues such as vascular system in SS.

▶ **Table 3** Distribution of measurements according to groups and PON 1 phenotypes.

	Control	SS Patients	p-value[a]
TAC (µmol Trolox eqv./l)			
QQ	3.48 ± 0.48	2.72 ± 0.63	<0.001
QR + RR	3.43 ± 0.40	2.60 ± 0.59	<0.001
p-value [b]	0.659	0.382	
TOS (µmol H2O2 eqv./l)			
QQ	1.90 (1.55)	2.96 (3.88)	<0.001
QR + RR	1.51 (1.50)	2.51 (2.02)	<0.001
p-value [b]	0.385	0.160	
PON (U/L)			
QQ	94.18 (31.21)	110.36 (30.53)	0.015
QR + RR	282.08 (122.19)	308.28 (132.41)	0.139
p-value [b]	<0.001	<0.001	
SPON (U/L)			
QQ	279.35 (101.65)	216.68 (62.00)	<0.001
QR + RR	678.00 (259.00)	601.19 (220.96)	0.079
p-value [b]	<0.001	<0.001	
TTL (µmol/L)			
QQ	284.50 (57.75)	207.81 (41.07)	<0.001
QR + RR	296.00 (63.00)	202.62 (64.96)	<0.001
p-value [b]	0.155	0.640	

▶ **Table 3** Continued.

	Control	SS Patients	p-value [a]
ARES (U/L)			
QQ	201.93 ± 66.83	214.82 ± 61.94	0.410
QR + RR	215.26 ± 62.95	223.84 ± 64.03	0.549
p-value [b]	0.411	0.513	
OSI (AU; arbitrary unit)			
QQ	0.08 (0.16)	0.07 (0.06)	0.140
QR + RR	0.07 (0.07)	0.06 (0.07)	0.075
p-value [b]	0.385	0.350	
AOPP (mmol/L)			
QQ	21.26 (21.17)	14.19 (8.38)	0.095
QR + RR	17.79 (15.06)	17.19 (13.10)	0.819
p-value [b]	0.407	0.130	
IMA (U/mL)			
QQ	6415.00 (4850.62)	5075.00 (2980.00)	0.345
QR + RR	61.05.00 (3697.50)	5280.00 (3223.75)	0.399
p-value [b]	0.854	0.788	
SPONAR (U/mL)			
QQ	1.50 (0.40)	1.02 (0.28)	< 0.001
QR + RR	3.20 (0.79)	2.60 (0.79)	< 0.001
p-value [b]	< 0.001	< 0.001	
PONAR (U/mL)			
QQ	0.47 (0.13)	0.50 (0.16)	0.116
QR + RR	1.32 (0.40)	1.38 (0.45)	0.947
p-value [b]	< 0.001	< 0.001	

a = Comparisons between Control and SS groups according to PON 1 phenotypes. Bonferroni Correction was applied for controlling Type I error. $p < 0.025$ was considered statistically significant, b = Comparisons of groups in their own right accordinrg to PON 1 phenotypes. Bonferroni Correction was applied for controlling Type I error. $p < 0.025$ was considered statistically significant. RR phenotype was not found to be enough in SS groups and in control groups, the QR and the RR phenotype groups were unified for statistical analysis.

Competing interest

The authors declare that they have no conflicts of interest.

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