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Reduced ubiquinone plasma levels and oxidative stress in ankylosing spondylitis and rheumatoid arthritis

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Abstract

65 RA-patients, 29 AS-patients and 21 healthy persons (controls) were investigated to obtain information about the serum concentration of the radical scavenger ubiquinone (coenzyme Q_{10}) in patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS). Measured parameters: Ubiquinone, total antioxidant status (TAS), oxidized LDL antibodies (oxLDL-AB), copper zinc superoxide dismutase (Cu/ZnSOD), rheumatoid factor, anti-citrullinated protein antibodies (ACPA) and anti-RA33 antibodies. Ubiquinone was significantly decreased in patients with RA ($p<0.03$) and AS ($p<0.01$) compared to healthy controls; and oxLDL-AB were significantly increased ($p<0.001$ and $p<0.05$). No significant differences were found concerning TAS and Cu/ZnSOD. However, a positive correlation was seen between ubiquinone and TAS ($p<0.01$) in AS. We conclude that in chronic inflammatory diseases such as RA and AS, ubiquinone is decreased leading to oxidative imbalance with raised oxLDL which may further enhance inflammation, tissue damage, and cardiovascular risk.

Keywords

Ubiquinone Coenzyme Q10, Rheumatoid Arthritis, Ankylosing Spondylitis, Oxidative Stress

1. Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are characterized by chronic activation of proinflammatory mechanisms. Oxidative stress is known to be increased in both diseases [1, 2].

The coenzyme Q10 molecule (ubiquinone, CoQ10) acts as a radical scavenger. Bauerová et al. found a reduction of oxidative stress after the treatment with coenzyme Q10 (daily oral dose of 20 mg/kg) in an animal model with adjuvant arthritis [3]. Another study demonstrated the

antinociceptive effect of coenzyme Q10 in an osteoarthritis rat model. Coenzyme Q10 has a therapeutic effect on pain suppression and cartilage degeneration by inhibiting inflammatory mediators in osteoarthritis [4].

Ubiquinone levels decrease with age and may be disturbed in various diseases [5]. Reduced endogenous production, lacking supply by food, and increased consumption caused by enhanced oxidative stress are discussed as potential reasons. Hence, the question arises whether levels of coenzyme Q10 are altered in RA and AS because of chronically activated inflammatory mechanisms and the increased oxidative stress which may lead to increased consumption of this radical scavenger.

2. Methods

94 patients were included: 65 RA patients (ACR-criteria; 16% male, 84% female), age 56.3 ± 15.4 years; 29 AS patients (New York criteria; 93% male, 7% female), age 39.3 ± 10.7 years; 21 healthy controls (HC) (35% male, 65% female), age 49.4 ± 12.9 years. Basing on pilot measurements of coenzyme Q10 a sample size of n=60 RA patients (α-error 0.5, power 0.90) was calculated. For patients with AS a sample size of 26 patients was ascertained by a power of 0.95. The patients were recruited multicentrically in 6 Austrian hospitals resp. rehabilitation centres with focus on rheumatology. The patient inclusion period was defined to last 1 year by the ethical review committee. Main target parameter was the Ubiquinone plasma level.

Ubiquinone was measured in EDTA plasma by HPLC methods (Ubiquinone / Coenzyme Q10, HPLC-Assay, Immundiagnostik Germany). Total antioxidant status (TAS/TAC) was determined using the photometric test system ImAnOx (Immundiagnostik, Germany). ELISAs were used for quantitation of Cu/ZnSOD (eBioscience, Austria) and antibodies against oxidized low densitiy lipoproteins (oxLDL-Ab; IMTEC/Human GmbH, Germany). CRP was measured in clinical routine. Additional determinations in RA samples: IL-6, TNF-α, rheumatoid factor (RF; nephelometry), antibodies to citrullinated proteins (Anti-CCP; Phadia, Sweden), and anti-RA33 antibodies (according to Schett et al. [6]).

The statistical data were evaluated with Sigma Plot Vs 11.0 and Systat 12 (Systat Software Inc.) comprising descriptive statistic, Mann-Whitney test, Spearman correlation analysis. A p value of < 0.05 was considered to be statistically significant (two-sided).

3. Results

Compared to healthy controls, the radical scavenger ubiquinone was significantly decreased in by approximately 15% in RA patients ($p<0.03$) and 25% in AS patients ($p<0.01$) (figure 1). Furthermore, antibodies against oxLDL were increased in RA ($p<0.001$) and AS ($p<0.03$) (table 1).

Table 1. *Parameters of oxidative balance and inflammation in RA, AS and HC. x = mean, s = standard deviation, p = significance compared to HC.*

		RA		AS		HC
		x ± s	p	x ± s	p	x ± s
Cu/ZnSOD	ng/ml	42.53 ± 29.31	ns	31.07 ± 19.61	ns	39.28 ± 33.3
TAS	mmol/l	326.53 ± 48.64	ns	336.24 ± 44.80	ns	340.76 ± 40.36
oxLDL-AB	U/ml	50.42 ± 61.40	<0.001	31.08 ± 19.00	<0.05	20.8 ± 7.21
CRP	mg/dl	0.98 ± 1.52	<0.01	1.20 ± 1.91	<0.03	0.27 ± 0.27

Although we could not find a significant difference between rheumatic diseases and controls for TAS and Cu/ZnSOD, we noticed positive correlations between ubiquinone and TAC ($r = 0.55$; $p<0.01$) as well as Cu/ZnSOD ($r = 0.46$; $p < 0.02$) in AS in which Cu/ZnSOD also correlated weakly with TAS. Remarkably, such correlations were not seen in RA.

Additionally, in RA samples none of the RA-specific measured autoantibodies RF, ACPA and anti-RA33 correlated with ubiquinone.

During further investigations on patients with AS, we determined increased visfatin levels while sRAGE (receptor for advanced glycation endproducts) did not differ significantly [7].

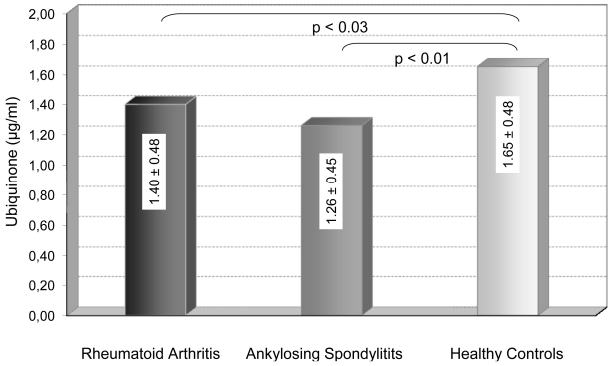

Figure 1*. Significantly decreased ubiquinone levels in rheumatoid arthritis and ankylosing spondylitis compared to healthy controls. Mean ± standard deviation, p = significance compared to healthy controls*

4. Discussion

Ubiquinone was shown to exhibit dose-dependent anti-inflammatory activity [8]. We detected ubiquinone to be significantly decreased in RA and AS compared to healthy controls (HC) (figure 1). A decrease of CoQ10 as a consequence of increased oxidative stress due to the enhanced inflammatory activity could be a possible implication of these preliminary results. Furthermore, although the clinical relevance of low ubiquinone levels is currently rather unknown, this has been suggested as a possible cause of myopathy, rhabdomyolysis and fatigue associated with statin use [9]. Circulating oxLDL, an oxidative stress marker is consistently associated with proinflammatory markers [10]. We found high levels of oxLDL-antibodies particularly in the circulation of RA

patients which correlated with Cu/ZnSOD and anti-RA33 antibodies but not with RF or ACPA.

Supplementation of coenzyme Q10 in adjuvant arthritis showed protective effects on the level of mitochondrial energetic and antioxidant disbalance. A possible breakdown of mitochondrial structure and function by increased oxidative stress in RA with potential counteraction of CoQ10 as an effective radical scavenger is subject of discussion [11]. The combination of coenzyme Q10 with MTX showed better effects on the proinflammatory cytokine IL-1 with suppressed arthritic progression and enhanced antioxidant effects [12]. In the presence of higher amounts of ubiquinone an inflammatory TNF response could be significantly reduced via NF B dependent gene expression [13]. Ubiquinone administration diminished increased levels of CRP in obese rats with increased oxidative stress and inflammation [14]. These findings suggest that the antioxidative properties of ubiquinone can be effective for reducing the cardiovascular risk and inflammatory mechanisms.

5. Conclusions

- Ubiquinone in serum is reduced in patients with AS and RA
- Oxidative stress due to the inflammatory mechanisms in AS and RA induces enhances oxLDL-Ab
- OxLDL-Ab correlate with ubiquinone

Our preliminary results on decreased ubiquinone levels in RA and AS compared to literature suggest that supplementation of CoQ10 might be considered patients with inflammatory rheumatic diseases and decreased ubiquinone levels.

Consent

The study was performed according to the principles of the World Medical Association Declaration of Helsinki and approved by the local Ethics Committee. All patients gave their written informed consent to the laboratory investigations.

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