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Relationship between oxidative and occupational stress and aging in nurses of an intensive care unit

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Abstract Stressful conditions lead to formation of excessive reactive oxygen species (ROS) and cause oxidative stress and aging. The aim of this study was to determine superoxide dismutase (SOD) and catalase (CAT) activity, and malondialdehyde (MDA) levels in nurses of a hospital intensive care unit according to demographic and occupational parameters, and to analyse the relationship with aging. Thirty-two nurses working in an intensive care unit and 35 aged-matched healthy individuals of both sexes as a control group were surveyed. No significant variations with respect to sex were detected in SOD, CAT, MDA and burnout levels. MDA levels increased with age in both the control group and the nurses, and we observed significant differences in MDA levels between the control group and nurses for all age groups. Significant variations in MDA levels were detected between single (286.12±8.41) and married (318.82±6.02), people, between those who frequently practice some kind of sport (281.41±7.32) and those who never participate in sport (298.24±8.11) ,and between those who frequently eat fruit and greens (289.75±8.41) and those who never eat them (315.12± 7.21). Significant differences were detected between smokers and nonsmokers in SOD, CAT and MDA, but not for alcohol, coffee, tea or cola consumption. Higher SOD activity and MDA levels were detected in nurses on evening and night shifts ($P<0.01$); these nurses also scored significantly higher on burnout subscales. These results suggest that: (1) occupational stress increases oxidative stress levels as a response to elevated ROS generation; (2) occupational stress increases MDA levels as a response to an elevation in free radical generation and can lead to aging; (3) working evening and night shifts increases oxidative and burnout levels. It is evident that preventive changes in job conditions and lifestyle are necessary to improve the quality of life of nurses who work in intensive care units.

Keywords Aging · Antioxidant enzymes · Burnout · Lipid peroxidation · Malondialdehyde · Oxidative stress · Occupational stress

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Introduction

Reactive oxygen species (ROS) are formed in the human body in the cytosol, mitochondria, lysosomes, peroxisomes and plasma membranes under both

physiological and pathological conditions (Hemnani and Parihar 1998); their levels can be increased by stress situations such as occupational stress (Casado et al. 2005, 2006). Such ROS are extremely reactive and unstable chemical species, and can react with proteins, lipids, carbohydrates and nucleic acids in the body (Sevanian and Hochstein 1985). The reactions of ROS with macromolecules can lead to DNA mutations, changes in the structure and function of proteins, and peroxidative damage to cell membrane lipids (Halliwell and Gutteridge 1985). Lipid peroxidation is one of the major outcomes of free radical-mediated injury that directly damages membranes and generates a number of secondary products including aldehydes, such as malondialdehyde (MDA), and 4-hydroxy-2-nonenal, ketones, etc. (Slater 1984). MDA is the most abundant individual aldehyde resulting from lipid peroxidation; consequently, this aldehyde can be considered as a marker for lipid peroxidation (Draper et al. 1988). In this way, elevated levels of MDA are indicative of high oxidative stress (Ambrosio and Flaherty 1991) and aging (Gil et al. 2002).

The biological effects of these highly reactive compounds are controlled in vivo by a wide spectrum of antioxidative defence mechanisms such as vitamins E and C, carotenoids, metabolites such as uric acid or glutathione, and antioxidant enzymes. Cells have developed an enzymatic antioxidant pathway against the free radicals and ROS that are generated during oxidative metabolism: firstly, superoxide dismutase (SOD) catalyses the formation of hydrogen peroxide from superoxide radicals. Hydrogen peroxide can generate toxic hydroxyl radicals, but it is removed by a reaction catalysed by catalase (CAT) and glutathione peroxidase (GPx) (Michel et al. 1994). Glutathione reductase is a flavoprotein catalysing the NADPH-dependent reduction of glutathione disulfide (GSSG) to glutathione (GSH), which is essential for the maintenance of glutathione levels. Any increase in SOD catalytic activity produces an excess of hydrogen peroxide that must be efficiently neutralised by CAT or GPx. The activity of first and second step antioxidant enzymes must, therefore, be balanced to prevent oxidative damage to cells, which may contribute to various pathological processes (Sun and Chen 1985).

Stress has been a focus of science, research and practical medicine for many decades (Esch 2002; Selye 1950, 1973). Stress is an adaptive response that prepares an organism for a threatening situation. It induces strain upon both emotional and physical endurance, and has been considered a basic factor in the aetiology of a number of diseases (Jezova et al. 2003; Holmes et al. 2003; Black 2003). Stress as a concept describes the effects of psychosocial, occupational work and environmental factors on physical or mental well-being.

Occupational burnout is a complex phenomenon that has gathered significant attention among researchers over the last decade. Gillespie (1991) defines burnout as a reaction to chronic, job-related stress, characterised by physical, emotional, and defensive coping. Maslach and Jackson (1996) contend that human service workers who have considerable interaction with patient problems (psychological, social, and/or physical) are potentially more subject to chronic stress, which can be emotionally draining and lead to burnout. Maslach and Jackson (1996) provide a multifaceted conception of burnout, consisting of three sequential components that result from chronic stress. The first stage is emotional exhaustion, where individuals feel emotionally overwhelmed by the demands of others. The second stage, depersonalisation, occurs by inappropriately attempting to cope with exhaustion, and is characterised by feelings of detachment and dehumanisation. The final stage is an increased sense of inadequacy, personal failure, and feelings of poor professional self-esteem.

Occupational stress is prevalent in work areas in which there is much contact with distressed or dependent members of the public and in people who work in intensive care and emergency departments. Health professionals at risk include physicians, nurses, social workers, dentists, care providers in oncology, emergency service staff members, and mental health workers, among others (McGrath et al. 2003; Duane et al. 2002; Casado et al. 2005, 2006).

For this reason, we tested the hypothesis that a direct relationship exists between oxidative stress (as determined by antioxidant enzyme activities), occupational stress (estimated by elements of the Maslach Burnout Inventory) and aging (evaluated by MDA levels) in nurses working in intensive care units.

Materials and methods

Human subjects

This study was reviewed and approved by the Superior Council of Scientific Investigations and by

the Ethical Committee of Clinical Investigation of Gregorio Marañón Hospital, and performed in accordance with the Ethical Standards outlined in the 1975 Declaration of Helsinki, as revised in 1983 and 1996.

The study sample consisted of 32 nurses of both sexes (7 men and 25 women) working in the intensive care unit of a Public Hospital in Madrid (Spain). We also analysed 35 age-matched healthy individuals of both sexes (12 men and 23 women) as a control group. All sample and control subjects were resident in the same geographic area at the time of the study. All subjects were in good health and none of the subjects was taking any product potentially interfering with antioxidant status (vitamins or minerals). Each participant gave their informed consent prior to their inclusion in the study.

Subjects were given a questionnaire to obtain the following information:

- Sociodemographic parameters: sex, age, place of birth, residence, marital status, number of children.
- Lifestyle: balanced and healthy diet, exercise, smoking, consumption of alcohol, coffee, tea or Coke.
- Occupational factors: qualifications and assigned task, length of professional experience, work shifts (morning, evening, night), professional category, working conditions, relationship with other members of the staff, workload.

The total number of questionnaires returned including the parameters mentioned above was 32 (100%) and every subject completed the burnout test.

Blood sampling

Blood samples were taken from the cubital vein. Fresh blood (5 ml) was collected into vacutainer tubes containing lithium heparinate and stored at 0–4°C. All assays were carried out within 24 h of sampling.

Superoxide dismutase activity determination

SOD activity was measured in red blood cells. Blood (0.1 ml) was hemolysed by 0.9 ml ice-cold water (0–4°C). Haemoglobin was removed by adding 0.25 ml chloroform and 0.5 ml ethanol followed by vigorous mixing. The mixture was centrifuged at 18,000 *g* for 60 min. The clear supernant was used for the SOD assay. The assay was performed using the method of Minami and Yoshikawa (1979), which is based on the inhibition by SOD of the nitro blue tetrazolium (NBT) produced by superoxide radicals generated by autoxidation of pyrogallol. The rate of inhibition of the SOD reaction by SOD was calculated according to the definition of McCord and Fridovich (1969).

Catalase activity determination

CAT activity was measured in haemolysates by the method of Aebi (1974). The haemoglobin solution was obtained from fresh red blood cells. Heparinised blood samples were centrifuged at 2,500 *g* for 10 min, and the plasma was then removed as completely as possible. The red cells were washed three times with 0.9% NaCl solution and subsequently haemolysed by the addition of distilled water. Decomposition of the substrate, H_2O_2, was measured using a spectrophotometer (UVIKON 810, Kontron, Zurich) at 240 nm. The activity was expressed as K—rate constant of the first order reaction as defined by Aebi—per gram haemoglobin.

Malondialdehyde determination

MDA levels were measured in erythrocytes according to the method of Bull and Marnett (1985). Blood was centrifuged at 2,500 *g* for 10 min, and the plasma was then removed as completely as possible. Erythrocytes were washed three times with 0.9% NaCl solution and subsequently haemolysed by addition of distilled water. The supernatant solution was diluted by addition of acetonitrile (v/v) followed by vigorous mixing. The mixture was centrifuged at 3,000 *g* for 5 min. The supernatant solution was filtered (0.2 μm pore diameter membrane).

High-pressure liquid chromatography (HPLC) was performed in a high-pressure liquid chromatograph (Pharmacia LKB Bromma model 2151 Sweden) equipped with an LKB Bromma 2151 model diode array UV detector and ChromJet integrator Spectra-Physics data processor (PEMED; Denver, CO), which enabled the peak purity to be analysed. An ODS Hypersil column (25 cm×4,6 mm, 5 μm) (Shandon Scientific, Runcorn, UK) was the stationary phase. The chromatographic conditions employed were: mobile phase PO_4HNa_2 and myristyltrimethylammonium bromide buffer (pH 7.4)/acetonitrile; flow rate, 0.4 ml/min; UV detection, 268 nm; chart speed was 0.5 cm/min; attenuation 6; temperature, ambient; and injection volume, 10 μl.

The column was equilibrated at the beginning of each daily series of measurements with at least 50 ml of the eluant. The MDA peak in the chromatogram was identified by comparison with a reference chromatogram of freshly prepared free MDA. The concentration of MDA was calculated from the area, based on a calibration chromatogram performed with a standard solution of MDA prepared by acid hydrolysis as described by Esterbauer et al. (1984).

Burnout determination

To measure burnout, a Spanish version of the Maslach Burnout Inventory (MBI) adapted for hospital staff was used (Maslach and Jackson 1996; Oliver 1993). This is a 22-question instrument designed by Maslach and Jackson (1996). Each question consists of a sentence with four alternative answers, of which only one should be chosen. A different score from 1 to 4 is assigned to each of the four possible answers. The final score is obtained by adding up the results of all the questions. This score is used to measure the three stages of burnout. The first stage, emotional exhaustion, consisted of nine questions (1,2,3,6,8,13,14,16,20). The second stage, depersonalisation, was assessed by five questions (5,10,11,15,22). The final stage, personal accomplishment, was measured by eight questions (4,7,9,12,17,18,19,21). The scores for each of the three stages of burnout were the total summation of the scores for the questions related to each area. A high score for emotional exhaustion or depersonalisation indicated high levels for those stages of burnout. For the third stage, personal accomplishment, low scores demonstrated a low level of personal accomplishment, thus indicating high levels of this type of burnout.

Statistical analysis

Data were processed using standard statistical software such as SPSS 10.2 (SPSS, Chicago, IL). Results are expressed as mean ± standard deviation. The distribution of the groups was analysed using the Kolmogorov-Smirnov test. As both groups showed a normal distribution, parametric statistical methods were used. For comparison of the groups, Student's "t" test and analysis of variance (ANOVA) were performed. To asses significant *F*-ratios obtained via analysis of variance, the Bonferroni post-hoc test was used. Differences were considered significant for $P<0.05$.

Results

Sociodemographic parameters

No significant variations in SOD activity with respect to sex were detected (4.30±0.07 males vs 4.31±0.20 females). These results agree with those obtained in the Spanish population (De la Torre et al. 1990). Table 1 shows the SOD activity results, expressed as mean ± standard deviation, obtained from nurses working in an intensive care unit and controls. Significant differences were observed between the group of nurses and the control group for ages from 30 to 39 years, but not for other age groups (nurses and controls).

No significant variations with respect to sex were detected in CAT activity expressed as mean ± standard deviation (239.22±3.21 males vs 235.15±4.97 females). These results agree with those obtained in the Spanish population (Casado and López-Fernández 2003). No significant differences were observed between the control group and the group of nurses.

No significant variations with respect to sex were detected in MDA levels (331.39±31.99 males vs 335.86± 30.33 females). These results agree with those obtained in the Spanish population (Gil et al. 2002). As can be seen in Table 2, MDA levels increase with age in both the control group and in intensive care unit nurses. However, significant differences were found between the control group and the nurses group at all ages.

With regard to marital status (Table 3), significant variations in MDA levels were detected between single (286.12±8.41) and married (318.82±6.02) workers but not with respect to divorces (287.07). No significant differences in SOD and CAT activities and MDA levels were observed (Table 3) between having children or not, or the number of children they had.

Table 1 Superoxide dismutase (SOD) activity (U/ml blood) in nurses of an intensive care unit and controls

	Nurses in intensive care units		Controls	
Age	*n*	$\bar{x}$ ± SD	*n*	$\bar{x}$ ± SD
< 20 years	10	4.39±0.74	10	4.30±0.10
20–29 years	17	4.36±0.21	20	4.29±0.18
30–39 years	5	4.40±0.33*	5	4.09±0.19*

Values are mean ± standard deviation (SD)

*$P<0.05$

Table 2 Malondialdehyde (MDA) levels (nm/mg haemoglobin) in nurses of an intensive care unit and controls

	Nurses in intensive care units		Controls	
Age	*n*	$\bar{x}$ ± SD	*n*	$\bar{x}$ ± SD
< 20 years	10	282.60±3.14*	10	267.23±8.72*
20–29 years	17	342.28±7.36*	20	285.26±9.15*
30–39 years	5	376.63±5.24*	5	329.14±10.38*

Values are mean ± SD

*$P<0.05$

Neither was a difference in SOD and CAT activities and MDA levels observed according to place of birth.

Lifestyle parameters

Significant differences were detected in SOD and CAT activities and MDA levels between smokers and non-smokers, but not for alcohol consumption, or coffee, tea and cola consumption (Table 3).

Significant differences were obtained in MDA levels between those who frequently practice some kind of sport (281.41±7.32) and those who never practice sport (295.24±8.11) (Table 3).

With regard to consumption of fruit and greens, significant differences in SOD activity ($P<0.03$) and MDA levels ($P<0.01$) were obtained between those who frequently eat fruits and greens and those who never eat them (Table 3).

Occupational factors

Higher SOD activity and MDA levels were detected in nurses working night and evening shifts ($P<0.01$), and we also observed that qualification had a strong relationship with antioxidant enzyme activity and MDA levels. Likewise, length of intensive care unit professional experience showed a relationship with respect to MDA levels and SOD activity. In general, nurses with more years of professional experience showed higher levels of these two oxidative stress parameters.

As far as factors that produce professional uneasiness were concerned, no significant differences in oxidative stress parameters were observed in intensive care unit nurses. These factors have been classified into: uneasiness produced by work conditions (lack of staff and resources), and institutional uneasiness caused by lack of promotion and training.

No significant variations in levels of burnout were detected with respect to age, sex or marital status. We

Table 3 SOD (U/ml blood) and catalase (CAT; k/g haemoglobin) activity and MDA (nm/mg haemoglobin) levels according to sociodemographic and lifestyle parameters

	Parameters	*n*	SOD ($\bar{x}$ ± SD)	CAT ($\bar{x}$ ± SD)	MDA ($\bar{x}$ ± SD)	*P* value
Marital status	Single	11	4.35±0.51	236.15±4.89	286.12±8.41*	$P<0.05$
	Married	20	4.36±0.48	240.11±5.22	318.82±6.02*	
	Divorced	1	4.37	238.16	287.07	
Children	No children	17	4.36±0.68	233.89±6.07	287.53±9.31	NS
	With children	15	4.37±0.71	238.01±5.63	296.12±8.74	
Tobacco	Smoker	6	4.38±0.20*	234.50±3.93*	321.43±6,09*	$P<0.05$
	Non smoker	26	4.21±0.13*	228.72±3.26*	286.12±5.71*	
Alcohol	Sometimes	7	4.34±0.47	238.18±5.09	283.15±7.21	NS
	Never	25	4.35±0.39	239.87±4.31	287.23±8.17	
Coffee, tea, cola	From time-to-time	6	4.33±0.23	237.16±4.33	285.11±6.42	NS
	Habitually	26	4.35±0.31	239.53±5.46	289.36±9.31	
Sport	Frequently	10	4.31±0.14	230.41±6.80	281.41±7.32*	$P<0.05$
	Sometimes	16	4.32±0.19	233.22±4.57	287.73±6.25	
	Never	6	4.35±0.15	238.91±5.32	298.24±8.11*	
Fruit, greens	Frequently	12	4.32±0.23*	235.26±5.89	289.75±8.41*	$P<0.05$
	Sometimes	15	4.34±0.31	237.46±6.12	297.51±7.85	
	Never	5	4.38±0.42*	239.18±5.62	315.12±7.21*	

Values are mean ± SD

*$P<0.05$, NS not significant

detected higher burnout scores in workers on night and evening shifts. These workers also obtained significantly higher scores in burnout subscales (Table 4).

Discussion

We observed no significant variations with respect to sex in SOD and CAT activities and MDA levels in nurses of an intensive care unit. These results agree with those obtained in the Spanish population at large (De la Torre et al. 1990; Casado and López-Fernández 2003; Gil et al. 2002) and in the emergency services (Casado et al. 2005, 2006).

We found higher SOD and CAT activities in nurses than in the control group, but significant differences were obtained in SOD activity only between the group of nurses and the control group for ages from 30 to 39 years. Our results agree with those obtained by Türkan et al. (2005), who observed a significant increase in plasma and erythrocyte SOD activity in workers in intensive care units compared to personnel exposed to the effects of volatile anesthetics. Malekirad et al. (2005a) found significantly a higher concentration of total antioxidant capacity (TAC) in radiology staff; however, these authors observed that TAC was lower in operating room personnel (Malekirad et al. 2005b).

MDA levels increase with age, supporting the premise that MDA levels are a valid marker for oxidative stress and aging, as it is known that cell membrane structures are subjected to increased oxidative stress as a consequence of age and occupational stress. Inal et al. (2001) also observed significantly higher MDA levels in healthy individuals with respect to age. Staruchova et al. (2008) found an increase in MDA levels in workers of a mineral wool factory in Slovakia, and similar results were obtained in a group of radiology unit employees and in operating room personnel (Malekirad et al. 2005a, b).

Marital status has an influence on oxidative stress levels because married nurses showed higher MDA levels than single or divorced nurses, but no significant differences were observed with regard to having children or to the number of children. These results agree with those obtained in emergency workers (Casado et al. 2006). De la Torre et al. (1990) have observed significant differences according to place of birth (urban or rural), but no such difference was apparent in this study because all subjects had been living in a big city for many years.

With respect to the effects of cigarette smoking, we found that SOD and CAT activities and MDA levels were higher in the erythrocytes of smokers than in those of non-smokers with statistical significance ($P< 0.05$). Similar results were obtained by Bolzan et al. (1997), Karabulut et al. (2002) and Cigremis et al. (2002). Tobacco smoke contains numerous compounds, many of which are oxidants and prooxidants, capable of producing free radical and enhancing oxidative stress “in vivo” (Preston 1991).

No significant differences in MDA levels were correlated to consumption of alcohol, coffee, tea or cola, and no significant differences in antioxidant enzyme activities could be demonstrated. These results agree with those obtained by Casado et al. (2005, 2006) in the emergency services. Nielsen et al. (1997) found a positive correlation between plasma MDA and weekly alcohol consumption; however, in our study the alcohol consumption of the participants analysed included only small quantities drunk during meals. This practice has certain proven beneficial effects in humans and epidemiological evidence indicates that moderate alcohol consumption reduces

Table 4 Burnout levels and work shifts in intensive care unit nurses

Shift	Morning ($\bar{x}$ ± DS)	Evening ($\bar{x}$ ± DS)	Night ($\bar{x}$ ± DS)
n	9	12	11
Burnout	42.67±4.59*	52.08±7.00**	43.00±5.46**
EE	16.68±1.37	18.78±4.31	15.91±2.74
DP	7.33±0.82*	9.67±2.06**	6.37±1.42**
RPA	18.68±4.50*	23.67±2.50*	20.36±3.80

Values are mean ± SD. *EE* Emotional exhaustion, *DP* depersonalization, *RPA* reduced personal accomplishment

* Significant differences between evening and morning shift

**Significant differences between evening and night shift

the incidence of heart disease (Eidelman et al. 2002; Abou-Agap et al. 2005).

No significant variations in burnout levels were obtained with respect to age, sex or marital status, and our findings partially agree with those obtained by Smith et al. (2000), who observed no significant difference between men and women in occupational stress, and that single and married workers reported very similar stress levels. We did, however, detect higher oxidative stress in married workers than in single or divorced workers, and similar results were obtained with emergency workers (Casado et al. 2006). The results obtained by Geetika (2004) revealed that male nurses experience significantly higher stress levels as compared to females.

We found that burnout is higher in workers on evening and night shifts. These workers also obtained higher scores in burnout subscales with statistical significance. Purvi et al. (2004) also reported that the shift work that is highly prevalent among nurses is a significant source of stress. The results obtained in this work showed that SOD activity and MDA levels are higher in workers on night and evening shifts ($P<0.01$). Similar results were obtained in a study on the emergency services (Casado et al. 2005, 2006). Sharifian et al. (2005) evaluated the effect of night-shift-working and their results confirm that shift work can act as an oxidative stressor.

Conclusions

In conclusion, our findings suggest that oxidative stress, occupational stress and burnout levels are similar in men and women. Occupational stress increases oxidative stress levels as a response to elevate ROS generation. Occupational stress increases MDA levels as a response to an elevation in free radical generation and can lead to aging. Working in evening and night shifts increased oxidative and burnout levels. It is evident that preventive changes in job conditions and lifestyle are necessary to improve the quality of life in nurses who work in intensive care units.

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