Perceived stress and hepatic parameters

Francesco Tomei1
Serafino Ricci2
Pier Agostino Gioffrè3
Carmina Sacco3
Luigi Antetomaso3
Franco Pagliara3
Alessandra Di Marzio3
Angela Sancini1
Pasquale Ricci3
Teodorico Casale1
Vincenza Anzelmo4
Maria Valeria Rosati3
Gianfranco Tomei5

1 Spin off of “Sapienza” University of Rome, Italy
2 Department of Anatomy, Histology, Legal Medicine and Orthopaedics, “Sapienza” University of Rome, Italy
3 Department of Anatomy, Histology, Medical-Legal and the Orthopedics, Unit of Occupational Medicine, “Sapienza” University of Rome, Italy
4 Institute of Public Health, Unit of Occupational Medicine, “Cattolica del Sacro Cuore” University of Rome, Italy
5 Department of Psychiatric and Psychological Science, “Sapienza” University of Rome, Italy

Corresponding author:
Francesco Tomei
Spin off of “Sapienza” University of Rome,
Viale Regina Elena 336
00161 Rome, Italy
E-mail: francesco.tomei@uniroma1.it

Abstract

Introduction: the aim of the study is to evaluate work-related subjective stress in a group of employees, of both sexes, operating in the healthcare and welfare, through the administration of a questionnaire (HSE “Indicator Tool”), specifically developed and officially validated, and to analyze any possible correlations between stress levels taken from the questionnaire scores and the concentrations of three main hepatic parameters (GOT, GPT, GGT).

Materials and methods: we studied a final sample of 232 subjects (143 males and 89 females) operating in the health and welfare sector. For research purposes during the medical examination each subject underwent the HSE indicator tool, a collection of information about relevant clinical and medical history and a venous blood sample for the assay of GOT, GPT and GGT.

All questionnaires were analyzed using special software provided by the HSE. The results obtained from the questionnaires were statistically compared with the blood concentrations of hepatic parameters.

Results: the dimensions found to be critical, associated with a stressful condition (yellow area) or a highly stressful condition (red area), are: managers support, colleagues support, quality of relationships and changes. The Pearson’s correlation showed a statistically significant negative correlation (p <0.05) between the mean values of all the critical dimensions and the concentrations of the hepatic parameters, both on the total sample and after subdivision by gender. These results were confirmed in the multiple linear regression analysis, which indicated that the critical dimensions are the main significant variables contributing to the liver parameters alterations.

Discussion: preliminary results indicate that a critical perception of stress at work can be statistically associated with increases in mean concentrations of GOT, GPT and GGT in a working asymptomatic population. These results provide a starting point for future studies on this topic, to a greater definition of the link between stress and liver injury, to confirm the effects on the parameters of liver injury (GOT, GPT, GGT) and to investigate possible correlations with the cholestasis parameters (bilirubin, alkaline phosphatase) and serum albumin.

KEY WORDS: HSE questionnaire, liver injury, stress work-related, workers.

Introduction

In October 2004 the European social partners signed a framework agreement about stress in the workplace, with the aim to provide employers and workers with a reference guide designed to identify, prevent or manage problems of work related stress. According to the agreement the stress is defined as: “a condition accompanied by physical, mental, psychological or social pain or dysfunction, which results from the individual feeling of not being able to respond to requests or of not living up to expectations”. In addition, “stress is not a disease but a prolonged exposure to it may reduce effectiveness at work and may cause disease”.

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The concept of work-related stress is included in a book of Kahn et al. (1) who first examined its features. Work-related stress can be considered as the product of the dynamic interaction between the person and the social and organizational contexts in which he works, constituting the result of (unequal) relation between the stresses imposed by the tasks/roles and the worker’s ability to cope with them (2-5). According Sonnentag and Mills (6, 7), in modern industrial systems work-related stress is a source of problems both for the health of workers and for the companies because of the cost it causes. In a study conducted in the USA on a sample of 96,000 workers, Goetzel et al. (8) showed that the costs for the health were higher than 46% in those who had high levels of stress, and in these costs were not considered those indirectly due to the absence from the work. Other European and American studies have shown that an alarming percentage of days of absence from work was due to reasons of occupational stress. According to Eurofound the work-related stress is an international problem that is very expensive, both for the society as for the companies, estimated about hundreds of billions of dollars a year worldwide (9).

Stress-related syndromes are now explicitly considered in the legislature of many European countries. In Italy, with the Decreto Ministeriale 27 April 2004, the phenomenon of stress and biological damage arising from it is officially recognized. Also in the current legislation for the protection of health and safety in the workplace (Legislative Decree no. 81/2008, as amended), the stress was specifically introduced as an element to be included in the risk assessment in all areas of employment, although to date there is no established method to quantify this risk (10, 11).

In this context, several strategies have been used to assess employees’ subjective experience of work-related stress (12, 13), mainly through questionnaires: the Occupational Stress Indicator (14), the Pressure Management Indicator (15), the Job Content Questionnaire (16), the Health and Safety Executive’s Management Standards (17). The latter appears, in recent literature, one of the most complete and was officially validated, in the United Kingdom and in the Irish Republic, on more than 26,000 workers and in Italy, through a process promoted by ISPESL (INAIL, 2011) (18), on more than 75 companies covering different industries and more than 6,300 workers.

The HSE questionnaire appears also compatible with the guidelines for the evaluation of work-related stress present in Communication of the Ministry of Labour and Social Policy of 18/11/2010 (referred to Legislative Decree no. 81/2008), as it provides results relating to groups of workers and not only to single individuals and can be used both in the preliminary stage of analysis, to get directions on some factors of content (e.g. physical environment) and context (e.g. role in the organization, control, etc.), and in the in-depth evaluation of the subjective perception of the workers of the stress related factors.

The psychometric properties of this questionnaire were analyzed in many studies (19, 20), which confirmed the factorial structure and showed the presence of significant associations with other indicators related to job stress such as anxiety, depression, work, satisfaction with the work and the frequency of sick leave.

From the results of this research, the HSE questionnaire is considered one of the most valid and reliable instrument for the assessment of work-related stress.

**Stress and stress related diseases**

Working under some pressure can improve performance and give satisfaction when challenging goals are reached, but when the demands and pressure become excessive they are always cause of stress. In the medical field if the cause of stress is not eliminated the reaction to it turns chronic and can become an important pathogenic cofactor and source of various psychic and somatic syndromes including anxiety, insomnia, anorexia, panic attacks, irritability, difficulty concentrating and decision (21-23), hypertension, tachycardia (24-26), gastro-intestinal disorders (27, 28), immune system reduction (29-33) and cognitive and emotional diseases (21-23, 34-35).

The literature has repeatedly shown that exposure to acute and chronic stress is able to alter specific hormonal responses involving, in addition to the autonomic nervous system, the neuroendocrine circuits (36, 37), the pituitary axes and the organs related to them (38, 39).

Among these, in recent literature the role played by stress in gastrointestinal and hepatic inflammation is attracting particular interest. These preliminary studies, pointed out how under conditions of increased stress a physiological alteration of liver functions can be observed (40) and current scientific evidence confirms that psychosocial stress may both induce primitive liver injury and induce worsening of a pre-existing liver disease (41). The understanding of the effects of stress on the onset and progression of acute and chronic liver diseases has assumed considerable importance (42) and recent studies on animals and clinical evidences in humans are trying to clarify this complex relationship (43-45).

These studies were carried out in a national and international context (40, 41, 43-45) but the hepatic effects of specific exposures such as those related to chronic work stress were evaluated in very few epidemiological studies (46) and the bibliographic database on the topic is seriously incomplete. In literature the priority was given, above all in clinical trials to the effects of stress in patients already suffering from pre-existing liver disease for which the stress acted as an aggravating factor. Hardly ever research (46) concern working asymptomatic populations, for whom prevention is still possible.

This research represents the first evaluation, in Italian literature, concerning the analysis of exposure to work-related stress in workers occupationally exposed and its effects at the level of the liver.

**Aim of the study**

The purpose of our study was to determine and eval-
quate alterations of the subjective perception of work-related stress in a group of employees of both sexes who work in the medical and health care settings. We used the Italian version of the HSE questionnaire ("indicator tool") and analyzed the possible correlations between the stress levels taken from questionnaire scores, in the 7 dimensions it is composed of, and the concentrations of the 3 main parameters of liver injury (GOT, GPT, GGT).

Materials and Methods

Study population
The research was conducted in the period between January and December 2014, from an initial working population of n. 316 subjects, both males and females, belonging to a large Italian association working in the healthcare and welfare field. All the subjects were health professionals and their tasks were divided as follows: doctors, nurses, biologists, technicians and laboratory workers, medical social workers, drivers and operators who assist disabled people.

They had been examined by doctors during the morning shift (between 08:00 and 14:00), in a business day between January and December 2014. For every worker information regarding work history, medical history, physiological anamnesis (including information about cigarette smoking and the consumption of alcoholic beverages), pathological anamnesis and pharmacological anamnesis were collected.

During the medical anamnesis collection, following the World Health Organization (WHO) recommendations, we classified as smokers all subjects: 1) who reported having smoked at least 100 cigarettes in their lives and being a smoker; 2) who had stopped smoking less than six months before (47).

For the evaluation of the alcohol consumption each worker underwent the AUDIT test, developed by the WHO as a screening tool.

Questionnaire
For evaluating the work-related stress perception in the working environment, a dimensional assessment of the subjective components of the stress was conducted through the use of a standardized and validated questionnaire, developed by the Health and Safety Executive (HSE), British regulation organism responsible for health and safety at work.

The questionnaire is easy to administer, it guarantees anonymity and can be used in all companies with more than 10 workers. It’s also compatible with the guidelines for the evaluation of work-related stress according to European standards and contained in the circular of 18/11/2010 of Ministry of Labour and Social Policy (referred to the Legislative Decree no. 81/2008).

To facilitate its understanding we used the recently validated Italian version easy to be administered (48). The HSE questionnaire includes 35 questions each of which provides one single response, based on a 5-point Likert scale with 23 items measuring the frequency (answers from never to ever) and 12 items which measure the degree of agreement (from strongly agree to totally disagree). The questions identifies 7 organizational dimensions:

1-request: including aspects such as workload, work organization and work environment;
2-control: the autonomy of the workers on how to carry out their professional activity;
3-4 support: divided into two subscales: “support from managers” and “support among colleagues”; dealing with the encouragement, support and resources provided by the company, by the employer and by colleagues;
5-relations: promotion of a positive working, to avoid conflict and deal with unacceptable behaviors;
6-role: awareness of the worker as to the position he covers in the organization;
7-change: evaluation of how the organizational changes, of any size, are managed and communicated within the company.

The questionnaires were examined to verify the correct and full implementation: in particular if there were multiple answers or non-answers. All answers were then checked by a software, provided by the HSE which produces an average stress score (49-52).

Measurement of liver parameters
In the same day of the administration of the HSE questionnaire, a venous blood sample of 10 ml was taken from each worker for the analysis of liver parameters. Blood samples were stored at work in blood collection tubes contained within a refrigerator at +4°C, until the moment in which they are transferred (in a special container and the same temperature) in the laboratory, where they were centrifuged and subsequently stored at -20°C until they were analyzed (within 3 days). The laboratory performed the dosage of GOT, GPT and GGT through spectrophotometric method. Normal levels of the parameters analyzed were those used routinely by the laboratory for clinical analysis: GOT: 10-35 IU/L; GPT: 10-45 IU/L; GGT: 7-55 IU/L.

Factors of exclusion and description of the final sample
To avoid the influence of the major confounding factors, from the initial working population, made up of 316 workers, we excluded all workers who reported exposure to potentially hepatotoxic substances (e.g. Solvents, paints and pesticides) (n.=5) (53), all workers with a seniority of less than one year (n.=16), all workers with a history of hepatitis (n.=10), all workers who were heavy smokers (daily consumption> 20 cigarettes/day (47) and/or drinkers (AUDIT test> 8) (n.=12) and those who reported making use of potentially hepatotoxic drugs (n.=18). All employees who had not completed the questionnaire HSE in its every section were also excluded (n.=23). The final sample was thus composed of 232 workers of which: 143 male subjects, aged between 28 and 67 years (mean:...
48.3; DS: ± 7.55) and 89 females, aged between 27 and 65 years (mean: 48.5, SD: ± 7.60). The characteristics of the studied working population are reported in Table 1.

All workers included in the study decided to make available their personal information after being aware that such data would be classified as “sensitive information”. They also agreed that they would be treated anonymously and collectively, and examined with scientific methods and analyzed for scientific purposes in accordance with the principles of the Declaration of Helsinki.

**Statistical analysis**

**Analysis of the questionnaire via software HSE**

The data obtained from the questionnaires were analyzed using a specific software, provided by the HSE, which allows a comparison with the reference population (49), by comparing the results obtained with conditions that were considered to be ideal.

After the analysis, the software provides a score for each of the 7 dimensions. Each score is also characterized by a “color code”.

The red color, which indicates a serious situation requiring immediate corrective action, includes the results below the 20th percentile (20% of the lower reference values). The yellow color indicates a clear need for corrective action, and includes the results that are below the average (<50%) but above the 20th percentile. In the case of values that fall in the blue area, the level of performance is good, it however requires interventions, due to values above the average (>50%) but below the 80th percentile. The green area indicates a good level of performance with fulfillment of Management Standards, the level must be maintained over time, the values are above the 80th percentile (20% of the higher reference values).

The color code is the basis of the interpretation of the results derived from the analysis of the questionnaire through the software HSE (54). The correlation between numerical score and color varies in 7 different dimensional scales and for each question. The analysis of data based on HSE-software, statistically validated, ensures that the changes in color code, in the 7 dimensions analyzed, is not a result of chance (54).

**Table 1 - Features of the studied sample.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>Total n. 232</td>
</tr>
<tr>
<td>Gender</td>
<td>Males n.(%) 143 (61.8)</td>
</tr>
<tr>
<td></td>
<td>Females n.(%) 89 (38.2)</td>
</tr>
<tr>
<td>Cigarette smoking habit</td>
<td>Yes n.( %) 45 (19.5)</td>
</tr>
<tr>
<td></td>
<td>No n.( %) 187 (80.5)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Score Test AUDIT</td>
</tr>
<tr>
<td></td>
<td>Score 0 n.(%) 44 (19,07)</td>
</tr>
<tr>
<td></td>
<td>Score 1 n.(%) 39 (17.01)</td>
</tr>
<tr>
<td></td>
<td>Score 2 n.(%) 53 (22.68)</td>
</tr>
<tr>
<td></td>
<td>Score 3 n.(%) 49 (20.61)</td>
</tr>
<tr>
<td></td>
<td>Score 4 n.(%) 47 (20.10)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean (SD) 48.73 (7.60)</td>
</tr>
<tr>
<td></td>
<td>Min-Max 27-67</td>
</tr>
<tr>
<td></td>
<td>Median 49</td>
</tr>
<tr>
<td>Length of service (years)</td>
<td>Mean (SD) 17.95 (9.46)</td>
</tr>
<tr>
<td></td>
<td>Min-Max 0-42</td>
</tr>
<tr>
<td></td>
<td>Median 15</td>
</tr>
<tr>
<td>GOT (AST)</td>
<td>Mean(SD) 18.92 (5.17)</td>
</tr>
<tr>
<td>Range: 10-35 UI/L</td>
<td>Min-Max 10-41</td>
</tr>
<tr>
<td></td>
<td>Median 18</td>
</tr>
<tr>
<td>GPT (ALT)</td>
<td>Mean (SD) 22.46 (13.02)</td>
</tr>
<tr>
<td>Range: 10-45 UI/L</td>
<td>Min-Max 7-84</td>
</tr>
<tr>
<td></td>
<td>Median 18</td>
</tr>
<tr>
<td>GGT</td>
<td>Mean (SD) 25.50 (22.79)</td>
</tr>
<tr>
<td>Range: 7-55 UI/L</td>
<td>Min-Max 5-129</td>
</tr>
<tr>
<td></td>
<td>Median 18</td>
</tr>
</tbody>
</table>

SD = Standard Deviation
Results of the HSE questionnaire and liver parameters

The normal distribution of haematological variables was assessed using the Kolmogorov-Smirnov, which was statistically significant for GOT, GPT and GGT. These parameters were then converted to logarithmic form for the Pearson’s correlation and multiple linear regression analysis.

The results for the values of all liver studied parameters for the questionnaire score and all confounding factors were expressed in terms of frequency (%), mean, standard deviation (SD), median, range (min - max) and confidence interval (Tables 1, 2).

In order to assess the degree of correlation, for each worker, between stress levels (scores obtained from HSE software, for each of the 7 dimensions) and liver parameters we used the Pearson’s correlation coefficient, with two tails p.

To exclude the influence of the major confounding factors it was finally carried out the multiple linear regression analysis, that was performed considering GOT, GPT and GGT as dependent variables and the ques-

Table 2 - Results HSE questionnaire.

<table>
<thead>
<tr>
<th>Dimensions investigated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demands</td>
<td>Mean (DS) 3.73* (0.48)</td>
</tr>
<tr>
<td>Control</td>
<td>Mean (DS) 3.49** (0.87)</td>
</tr>
<tr>
<td>Management Support</td>
<td>Mean (DS) 3.39*** (0.89)</td>
</tr>
<tr>
<td>Peer Support</td>
<td>Mean (DS) 3.77*** (0.76)</td>
</tr>
<tr>
<td>Relationships</td>
<td>Mean (DS) 3.51**** (0.92)</td>
</tr>
<tr>
<td>Role</td>
<td>Mean (DS) 4.52* (0.58)</td>
</tr>
<tr>
<td>Change</td>
<td>Mean (DS) 2.69**** (1.13)</td>
</tr>
</tbody>
</table>

The result is included in the green area of the HSE questionnaire (data set: Organizational Averages)

** The result is included in the blue area of the HSE questionnaire (data set: Organizational Averages)

*** The result is included in the yellow area of the HSE questionnaire (data set: Organizational Averages)

**** The result is included in the red area of the HSE questionnaire (data set: Organizational Averages)
tionnaire HSE scores (divided into the 7 dimensions), age, sex, length of service, and the alcohol consumption (results AUDIT test) and cigarette smoking habits as independent variables. The independent variables that were statistically significant were studied individually by layering and comparing the subgroups. The results were considered significant when p values were lower than 0.05. The statistical analysis described above was performed using SPSS® Advanced Statistical TM 21.0.

Results

Analysis of the questionnaire software via HSE
The results obtained from the analysis of the questionnaire by software HSE in each of the 7 dimensions investigated, are reported in Table 2. The analysis of the questionnaire by the HSE software showed that the dimensions with the lowest average score, to which workers have more frequently associated stressful condition (code yellow color, 50° -20° percentile) or highly stressful condition (code red color, <20th percentile) are “manager support”, “colleagues support”, “quality of relationships” and “changes” (Table 2). The dimension to which the employees have more frequently attributed a low stressful condition (color code blue, between 50th and 80th percentile) is “control” (decision-making autonomy). The dimensions where they reached the required standards or ideal conditions (no stressful condition, green area, > 80th percentile) are “load (demand of work)”, and “defining the role.” The results obtained from the questionnaire through software HSE did not change after splitting the sample on the basis of sex, smoking habit and consumption of alcoholic beverages.

Analysis of liver parameters and correlation with the results of the questionnaire HSE
The values of average concentrations of GOT, GPT and GGT in the studied population were expressed as mean, standard deviation (SD), median and range (min-max) and are shown in Table 1. In the Pearson correlation analysis, in the total sample, the average scores obtained from the HSE questionnaire, in all critical dimensions (yellow or red areas), were negatively correlated, in a statistically significant way (p two-tailed), with GOT (log), GPT (log) and GGT (log) values (Table 3). After the splitting on the basis of sex, smoking habits and alcohol consumption the results remained unchanged and statistically significant. The multiple linear regression analysis confirmed the significance of the negative correlation between the scores of the questionnaire HSE and the values of GOT (log), GPT (log) and GGT (log), even with respect to the main confounding factors (age, sex, seniority, smoking cigarette habit to drink alcohol) (Table 4). These results show that a part from stress, the confounding factors analyzed in the study, did not influence significantly the values of liver parameters. The frequency of values outside of the normal range suggested by our laboratory was comparable with that of the general asymptomatic population.

Discussion
The current regulatory plan for the protection of health and safety at work, that is the Legislative Decree 81/2008, identifies “work-related stress” as a risk to be evaluated and managed. It is evident the relevance of the scientific research in providing rigorous contributions on this specific subject for the development of reliable and useful tools for the assessment and risk management of work-related stress. In this context, the methodological approach based on Model Management Standards prepared by the Health and Safety Executive (HSE) is one of the most valid and reliable tools. The psychometric properties of the HSE questionnaire were analyzed, in literature in numerous studies which

Table 3 - Analysis of the Pearson correlation coefficient (R), two tails, between GOT (log), GPT (log), GGT (log) and the results of the HSE questionnaire dimensions on the studied population.

<table>
<thead>
<tr>
<th>HSE Dimensions</th>
<th>Demands</th>
<th>Control</th>
<th>Management Support</th>
<th>Peer Support</th>
<th>Relationships</th>
<th>Role</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOT (log) R Pearson</td>
<td>-0.109</td>
<td>-0.291</td>
<td>-0.525</td>
<td>-0.363</td>
<td>-0.439</td>
<td>-0.124</td>
<td>-412</td>
</tr>
<tr>
<td>P (2 tails)</td>
<td>0.193</td>
<td>0.061</td>
<td>0.002*</td>
<td>0.005*</td>
<td>0.011*</td>
<td>0.163</td>
<td>0.000*</td>
</tr>
<tr>
<td>GPT (log) R Pearson</td>
<td>-0.380</td>
<td>-0.223</td>
<td>-0.472</td>
<td>-0.318</td>
<td>-0.423</td>
<td>-0.356</td>
<td>-0.477</td>
</tr>
<tr>
<td>P (2 tails)</td>
<td>0.244</td>
<td>0.072</td>
<td>0.002*</td>
<td>0.001*</td>
<td>0.002*</td>
<td>0.221</td>
<td>0.001*</td>
</tr>
<tr>
<td>GGT (log) R Pearson</td>
<td>-0.092</td>
<td>-0.393</td>
<td>-0.506</td>
<td>-0.456</td>
<td>-0.563</td>
<td>-0.101</td>
<td>-0.504</td>
</tr>
<tr>
<td>P (2 tails)</td>
<td>0.152</td>
<td>0.076</td>
<td>0.015*</td>
<td>0.003*</td>
<td>0.000*</td>
<td>0.143</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

* statistically significant (p<0.05)
confirmed the factorial structure and showed significant associations with other indicators linked to work-related stress such as anxiety, depression, job satisfaction and frequency of sick leave (19, 20). On the base of the results of these studies, the HSE questionnaire is considered a valid and reliable tool for the assessment of work-related stress. In particular it allows to easily obtain an assessment of the different dimensions of the organization so to identify the way to reduce the risk of work-related stress.

The questionnaire is compatible with the guidelines for the evaluation of work-related stress in the European legislation, inasmuch it provides results for groups of workers, not only for individual workers. Furthermore, it appears to be an useful tool because it can be used both in a preliminary stage of analysis, to get directions on some content factors (e.g. physical environment) and context (e.g. role in the organization, control, etc.), and in a phase of deeper evaluation of the subjective perception the workers have of factors related to stress.

The current study was carried out on a sample of healthcare operators that work in a wide range of different types of employments. The administration of the HSE questionnaire allowed to analyze individual responses to stressful events in a simple and quick way. Data showed that the dimensions with the highest average score, in which workers have associated a high stressful condition (yellow or red codes), are “Support...
for Managers”, “Support of Colleagues”, “Relations” and “Changes” (Table 2). For all other dimensions the employees of each group attributed a low or no stressful condition (blue or green codes). These results were unchanged also after the division of the sample on the basis of sex, smoking habit and alcoholic beverage. Research on this topic showed that nurses tend to find the solution of their working problems through a close collaboration with their superiors. Nurses work together with managers and doctors that make up the hospital staff and when they finish their shifts, a new shift starts, so workload and responsibilities are shared (55, 56). According to Gibb et al., the best and most common coping technique adopted by health care personnel to deal with their work problems is the collaboration between colleagues and the support of their superiors (57).

Data also showed that the dimensions “Managers support”, “Colleagues Support” and “Relations” are in a yellow area, and then to an almost critical level. Based on this result, the most common health care personnel coping technique is altered and perceived in a negative way and therefore requires targeted interventions. The reason of the results can be provided investigating the dimension of “Change”. The subjects of the sample work in a Company which is going through a delicate moment because passing from public to private property with consequent state of insecurity and potential economic and social consequences for the employees under contract. In addition to the potential changes in the economic sector, the workers had gone through changes of workplace and task. It’s been widely shown in the literature that these organizational changes have an impact on the psychological well-being of employees (58-61).

The type of reaction to these events depends on the assessment of the organizational change that employees perceive (59). The result infact showed that the workers associated a high stressful condition to the items the dimension of “Changes” (red area). For the same reasons and in consequence to the organizational change of the Company also the questions about the dimensions “Support of Managers”, “Support of Colleagues” and “Relationship” are associated with a stressful condition (yellow area).

Comparing the results of the questionnaire HSE and liver parameters

Even if the alanine amino transaminase (ALT), aspartate amino transaminase (AST) and gamma glutamyl transferase (GGT) are intracellular enzymes present in different tissues throughout the body, an increase in their plasma concentration is frequently cause of suffering and/or liver damage, even in asymptomatic patients (62). As a marker of liver damage, an increase in plasma levels of ALT, AST and GGT typically reflects the presence of a hepatocellular disease (63, 64). Close interaction between psychosocial stress and the development of liver disease has been suggested in the literature in studies using experimental methods with animal models (65). The results of these studies showed that the experimental exposure of guinea pigs to psychological stress had a negative impact on the liver and the effect was even more pronounced in animals with pre-existing liver or cardiovascular diseases. Sanchez et al. in 2007 described the development, in lab male mice, of an increase in plasma concentrations of ALT and AST after three hours of exposure to severe psychological stress and the occurrence of necrotic lesions of the parenchyma with damages of liver hepatocytes after 8 hours of exposure (66). Similar results were obtained by other Authors, such as Salas et al. who described through electron microscopy the development of liver autophagic reactions compatible with liver injury in guinea pigs after 2 days of acute exposure to different varieties of psychological stressor (67). Adachi et al., via the same animal models, documented the development of oxidative damages to the DNA of hepatocytes after a period of 4 days of exposure (68).

With regard to human studies, the understanding of the role played by stress on the onset and progression of acute and chronic liver diseases has assumed considerable importance in the current literature (42). In a recent review concerning the main scientific investigations carried out on the subject, Chida et al. concluded that psychological stress promotes the development of a liver inflammatory response that can contribute (as a cause or contributory cause) to the risk of developing and/or worsening the course of various liver diseases (41).

Providing their scientific contribution on this topic, Hirose et al. showed that emotional stress, such as that induced by hypnotic suggestion of “fear” and “anxiety”, causes a significant reduction in hepatic blood flow (69) and Fukudo et al. showed a positive correlation between the intensity of exposure to psychosocial stress and aggravation of inflammatory changes in the liver of patients with alcoholic liver disease (70). A statistically significant positive correlation between the levels of transaminases and the degree of depression (measured by the short form of the “Beck Depression Inventory”) was demonstrated in several studies, even in patients with either chronic B and C hepatitis, even after adjustment of results for key factors such as age, sex, level of education, smoking, alcohol, and length of disease (71-73).

Most of recent studies on the topic concerns the effects of psychological stress in patients with pre-existing liver diseases, on which the stressors would act as an aggravating factor. Very few research (46), no one produced in Italy, concern epidemiological studies carried out on working asymptomatic populations, on which prevention activities could be carried out.

Considering our preliminary results we believe that work-related stress can cause alterations of liver in occupationally exposed workers. These data are confirmed, in the studied subjects, by the statistically significant negative correlation between the mean values derived from the HSE questionnaire score, in all critical dimensions (red or yellow area) (Table 2), and the mean plasma values of GOT, GPT and GGT (Table 3).
The results were also confirmed by the multiple linear regression analysis (Table 4) which showed that the main studied confounding factors (age, sex, length of employment, habit to cigarette smoking and alcohol drinking) did not significantly contribute to influence the results of the correlation. The most stressful dimensions of the HSE questionnaire (yellow and red area) were then as the only significant variables that could influence the plasma GOT, GPT and GGT values.

The pathophysiological mechanisms underlying these stress-induced changes have been the subject of scientific analysis by different Authors in literature. Some studies showed that stress causes induction of oxidation and reduction of the protective function of antioxidant molecules (43). However other systems would be involved in the liver damage related to psychological stress, and recent studies in animal models and clinical evidence in humans have tried to clarify this complex relationship.

Involvement of the hypothalamic-pituitary-adrenal (HPA)
In bodies exposed to stressors we witness the activation of two main systems: the hypothalamic-pituitary-adrenal axis (HPA) and the autonomic nervous system (SNA).

The activation of the HPA axis usually causes an inhibition of the inflammatory response and immune system, since virtually all of the components of the immune response are inhibited by the glucocorticoids produced by the adrenal cortex (74). In the liver, however, the glucocorticoids seem to have different effects and scientific research on this topic are controversial.

It has been recently suggested that glucocorticoids have an inhibitory role on the inflammatory response at pharmacological doses, while at physiological basal levels or stress-induced levels they promote the intrahepatic production of IL-6 and TNF-alpha, thus implying a direct link between psychological stress and liver inflammation (41, 75).

Although the effects of the HPA axis on the liver have not yet been adequately studied, it is reported in the literature the activation of this system in the presence of acute liver failure, liver disease and inflammatory liver disease (45), together with an increase of local expression of cytokines.

Effect of glucocorticoids on natural killer T cells in the liver
T cells play a key role in the induction and maintenance of a chronic inflammatory state in the liver and glucocorticoids have important effects on the function of T cells. Recently, Chida et al. showed that the increase of stress-induced glucocorticoids in guinea pigs is able to cause an activation of hepatocytes apoptosis (76). The increase in glucocorticoids induced by stress seems to promote apoptosis through the liver natural killer T cells ratio and intrahepatic hyper-expression of Fas antigen (40-42).

Tamada et al. (77) showed that in vivo administration of dexamethasone, an exogenous glucocorticoid, boosted the number of NKT cells in the liver of lab animals. In the same study they documented that NKT cells were more resistant to apoptosis than conventional T cells, due to a high level of intracellular expression of the anti-apoptotic protein Bcl-2. Shimizu et al. (78) obtained similar results demonstrating that psychological stress is able to increase the concentration of NKT cells in the liver of guinea pigs through the production of endogenous glucocorticoids. Based on these studies, and given the evidence regarding the role of NKT cells play in the apoptosis of the hepatocytes (79-81) we can assume that an increase in glucocorticoids, including the increase induced by psychological stress, may be able to cause an expansion of the number of NKT cells liver, favoring an alteration of physiological liver function and, in some cases, worsening the state of some liver diseases.

Effect of glucocorticoid on the expression of membrane antigen Fas in hepatocytes
The Fas antigen (named CD45) is a membrane protein implicated in the apoptotic process triggered by receptor (programmed cell death). Inflammatory cells, like T, B and NK cells, which express "Fas bind", bind this membrane protein and trigger apoptosis of the cell. The Fas antigen is then able to stimulate cell apoptosis by binding with inflammatory cells; this effect has been analyzed in several studies of literature concerning the pathogenesis of the liver damage induced by drugs, toxins, viral infections, autoimmune liver disease, liver ischemia, and liver rejection and sepsis (82-87). Some researches based on in vivo experiments, showed that glucocorticoids are able to induce a hyper-expression of the membrane Fas on hepatocytes in a way to further promote the apoptosis mediated by NKT cells (88).

Involvement of the autonomic nervous system (SNA): reduction of hepatic blood flow
The autonomic nervous system connects the liver organ with the brain via the sympathetic system (efferent) and the parasympathetic system (afferent and efferent) (89).

Both axes are susceptible to stressful stimuli: the sympathetic system is indeed quickly activated, while the parasympathetic system is inhibited: thus promoting further adrenergic activation of the sympathetic system.

The activation of the sympathetic system, through the release of catecholamines, is able to induce vasospasm and, ultimately, center-lobular liver hypoxia, with consequent liver damage. Hirose et al., in 1961, showed that emotional stress can significantly decrease the liver blood flow, which was measured by the Authors through a radiometric method (AU198 colloidal) (69). These findings were regained by other Authors (45) and suggest that the SNA, and the release of catecholamines, may be involved in the impaired intrahepatic blood flow induced by stress.
Also the catecholamines would have a role in the modulation of the inflammatory and immune response (45); their action seems to involve the production of TNF-alpha and IL-6, in the Kupffer cells and in hepatocytes respectively, although the link between the catecholamines and the pro-inflammatory effect is not yet completely understood (41). Finally we must consider that the SNA, in addition to the catecholamines, is involved in the release of a wide variety of neuropeptides (CRH, somatostatin, ATP, nitric oxide) and mediators that may be involved in liver stress-related disease (41).

In recent years psychosocial stress has been identified as an important factor that can affect the progression and severity of various liver diseases. The relationship between psychosocial stress and liver disease largely depends mainly on the activation of the HPA axis and of the SNA, although the effects on the pathogenesis of liver injury mediated by psychological stress is not yet fully understood.

Our preliminary results indicate that a critical perception of workplace stress can be statistically associated with increases in average concentrations of GOT, GPT and GGT in a working asymptomatic population. Further studies are necessary to better define the link between stress and liver damage, to confirm the effects on the parameters of liver injury (GOT, GPT, GGT) and to investigate possible correlations with the parameters of cholestasis (bilirubin, alkaline phosphatase) and albumin, which are hardly investigated.

References

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Perceived stress and hepatic parameters