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To cite this article: Natasha Bergmann, Søren Ballegaard, Jesper Krogh, Per Bech, Åke Hjalmarson, Finn Gyntelberg & Jens Faber (2017): Chronic psychological stress seems associated with elements of the metabolic syndrome in patients with ischaemic heart disease, Scandinavian Journal of Clinical and Laboratory Investigation, DOI: 10.1080/00365513.2017.1354254

To link to this article: http://dx.doi.org/10.1080/00365513.2017.1354254

Published online: 20 Jul 2017.
Chronic psychological stress seems associated with elements of the metabolic syndrome in patients with ischaemic heart disease

Natasha Bergmann, Søren Ballegaard, Jesper Krogh, Per Bech, Åke Hjalmars, Finn Glyntelberg and Jens Faber

Background and objectives: Chronic psychological stress, the metabolic syndrome (MS) and ischaemic heart disease (IHD) seem closely connected. In this study, we evaluate the association between chronic stress and elements of MS in patients with stable IHD.

Design: Cross-sectional cohort study.

Methods: Three hundred and fifty patients with stable IHD were included. Chronic stress was evaluated by the two questionnaires, Major Depression Inventory (MDI) and the psychological wellbeing index WHO-5, as well as by Pressure Pain Sensitivity (PPS), a physiological measure of hyperalgesia at the sternum known to be associated to elements of the chronic stress syndrome. Elements of MS were evaluated by dual-energy X-ray absorptiometry, body weight, HOMA-IR and blood lipids.

Results: Depressive symptoms were associated with a high percentage of body fat ($\beta = 0.179$, $p = 0.001$), and high level of triglycerides ($\beta = 0.150$, $p = 0.007$). Low psychological wellbeing was associated with a high percentage of body fat ($\beta = -0.165$, $p = 0.002$) and low level of HDL cholesterol ($\beta = 0.128$, $p = 0.024$). Chronic stress measured by PPS was associated with a high percentage body fat ($\beta = 0.327$, $p < 0.001$), low body weight ($\beta = -0.218$, $p < 0.001$) and low HDL-cholesterol ($\beta = -0.137$, $p = 0.013$). Adjusting for several life style factors did not change these results.

Conclusions: In patients with stable IHD, different measures of chronic psychological stress seem associated with a high percentage of body fat and adverse blood lipids independent of several lifestyle factors.

Introduction

The metabolic syndrome (MS) (consisting of the four individual elements adiposity, dyslipidaemia, reduced glucose tolerance and hypertension) is closely linked to the development of ischaemic heart disease (IHD) and has in meta-analyses been found to increase the risk of morbidity and mortality from IHD by two-fold [1,2]. Another risk factor for IHD is chronic stress. The stress concept is usually divided into stressors (strain), stress (bodily reaction to stressors) and distress (the psychological consequences) [3]. If stress persists, a state designated allostatic load or chronic stress persists, a state designated allostatic load or chronic stress is reached [4]. Chronic stress is typically measured by questionnaires evaluating stressful life events, perceived stress, depression, anxiety, wellbeing or quality of life (QOL) [5].

Also chronic stress and MS seem closely connected. Thus, in healthy subjects, two prospective cohort studies have demonstrated that a high score of chronic stress doubles the risk of developing MS during 6 and 15 years of follow-up, respectively [9,10]. The impact of chronic stress on the individual elements of MS has also been widely studied in healthy subjects although with less consistent results [11]. Despite the close connection between chronic stress, MS, and IHD, the association between stress and MS in patients with IHD has not been thoroughly evaluated. One study by Cohen et al. found that depressive symptoms, anger, hostility and pessimism were associated with a higher prevalence of MS in patients with IHD [12]. The association was however lost after adjusting for life style factors [12]. Conversely, regarding the individual elements of MS, several studies have indicated a connection independent of lifestyle factors. E.g. a review of 16 longitudinal studies concluded that depression led to weight gain independent of medical therapy, baseline body mass index (BMI), education, exercise and other lifestyle factors [13].
Chronic stress, and especially the elements depression, anxiety, and reduced wellbeing have recently been shown to be associated with hyperalgesia at certain points of the body [14–18]. Accordingly, a new approach has been developed where chronic stress is evaluated by the physiological measure of hyperalgesia, designated Pressure Pain sensitivity (PPS) [14,15]. The PPS measure is thought to be based on the plasticity of the diffuse noxious inhibitory system of pain [17]. The changes in this afferent/efferent nervous system seem to occur when people are exposed to chronic stress [17,18], and seems to result in a change in pain sensation which can be measured as PPS [14]. PPS has previously been validated and we have shown that PPS is associated with measures of chronic stress such as depressive symptoms, reduced wellbeing and reduced QOL both in healthy individuals and in individuals with stable IHD [15,19]. Thus, PPS appears to combine the different components of the chronic stress-concept normally measured by different questionnaires.

The adverse effect of chronic stress on the risk of developing IHD might be due to both a direct effect but also due to chronic stress induced worsening of elements of the MS, which in turn act as risk factors for IHD. Thus, the objective of this study was to examine the cross-sectional association between different aspects of chronic stress and measures of elements of the MS in patients with IHD. We used validated questionnaires and deliberately chose questionnaires covering different aspects of chronic stress, including measures of depression and anxiety (the major depressive inventory scale (MDI)), as well as the general psychological wellbeing questionnaire WHO-5 [3]. This was done knowing that depressive symptoms as well as anxiety for future life aspects in people suffering from IHD are highly prevalent [20], and further depression as well as depressive mood is associated with increased risk of developing IHD [21]. We also included PPS as a chronic stress measure. Extensive adjustments for demographic variables including life style factors were performed.

Methods

The study was designed as a cross-sectional cohort study. We have previously published parts of the protocol as well as the association between the PPS and the questionnaires used in this manuscript [15].

Participants

Patients with established and stable IHD were recruited from a database at two departments of Cardiology in Denmark (HjerteRask). Inclusion criteria were: (1) documented IHD defined as having had a myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery, (2) completed cardiac rehabilitation more than 6 month prior to inclusion, (3) age 75 years or younger at inclusion. Exclusion criteria were: (1) previous hospitalization due to psychiatric disease, (2) scheduled cardiac surgery, (3) changes in heart medication within the last month prior to inclusion, (4) a chronic competing disorder clearly impairing the patients QOL (such as severe lung disease or cancer in progress) and (5) suffering from chronic pain syndromes as e.g. fibromyalgia or arthritis.

A letter of invitation was sent to 1129 patients with IHD and 386 accepted to participate. Twenty-five participants were excluded due to lack of complete data. Additionally, three participants were excluded from this sub-study because of use of fibrates (drugs used to lower levels of circulating triglycerides), and eight patients were excluded because of treatment with insulin, affecting the insulin level used in the multivariate regression analyses. Thus, 350 participants were evaluated.

In order to test whether the participants were representative for the whole population, we have previously made comparison-analyses between participants (responders) and patients not accepting participation (non-responders), based on data from the registry of the Danish National Board of Health. In this analysis, we found no significant differences between the two groups regarding number of heart-related hospitalizations or number of coronary artery bypass or percutaneous cardiac interventions [16].

Written and oral informed consent was obtained from all participants and the study was carried out in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the local ethical committee (www.regionh.dk/vek, ID: H-4-2010-135 and amendment 31962) and by the Danish Data Protection Agency (ID: 2011-41-7022), and was registered on www.clinicaltrials.gov (reg. no. NCT01513824).

Assessment of psychological factors by questionnaires

A website was established for the study (www.songheart.org). On the website, participants answered questionnaires with a personal login, which was first opened after the study ended. The questionnaires included a demographic questionnaire with information on IHD history, co-morbidity, medical treatment, socio-economic status, alcohol, physical activity and smoking [15,16], the Major Depression Inventory (MDI) assessing depressive symptoms on a score from 0 to 50, with a high score reflecting high number of depressive symptoms [22], and WHO-5’s Wellbeing Index assessing psychological wellbeing in general, with a high score reflecting high psychological wellbeing [23].

Assessment of PPS

The PPS measurement device is a hand-held algometer by which a gradually increasing pressure is applied to the skin of the sternum on a 1 cm² area. The pressure is ended when the participant (after instructions prior to the test), signals that the pain threshold has been reached. The PPS algometer transforms the pain threshold into a logarithmic scale (30–100 PPS units). The PPS measurement procedure, the theory behind, and choice of point for measurement on the body, as well as validation studies have previously been described in detail [14,15,19]. In short, the participants were
placed in a supine position and were accustomed to the feeling of pressure from the PPS algometer by measurements on the tibia bone. After 10 minutes of rest, the most sensitive area on the sternum at the level of intercostal spaces 3–5 was identified and the most sensitive point selected for PPS measurements. A gradually increasing pressure per unit of area on the sternum at the level of intercostal spaces on the tibia bone. After 10 minutes of rest, the most sensitive of pressure from the PPS algometer by measurements placed in a supine position and were accustomed to the feeling approximately 50% applied to the sternum changes approximately in the following way: A doubling in PPS (i.e. from 30 to 60 units) equals as reduction of the pressure applied at the sternum of approximately 50%, from 4 to 2 kg/cm².

**Laboratory assessments**

The patients were studied between 8 and 10 a.m. after an overnight fast. Lipids were assayed immediately by enzymatic technique (Vitros 5.1 FS, Ortho-Clinical Diagnostics, Raritan, NJ), inter-assay CV was 11%, 5% and 2%, respectively. Similarly, glycated hemoglobin (HbA1c) was measured immediately by high performance liquid chromatography (Variant II TURBO, Bio-RAD, Hercules, CA), inter-assay CV was 5%. Plasma insulin levels were analysed on frozen serum samples kept at −80°C using a sandwich chemiluminescence immunoassay (ADVIA Centaur Xp®, Siemens, Germany). The intra- and inter-assay CV was <7%. Insulin resistance was calculated by the homeostasis model assessment index (HOMA-IR): ((Fasting plasma glucose, mmol/l) × (fasting plasma insulin, μU/ml)/22.5).

**Body composition measurements**

The percentage of body fat and visceral adipose tissue (VAT) (g) was measured by dual-energy X-ray absorptiometry (DXA) according to the manufacturer’s instructions (Hologic Discovery A, Bedford, MA). DXA was used instead of traditional anthropometric measures as it has been found to be a better predictor for IHD and diabetes risk factors as compared to e.g. BMI [24]. The VAT region covers the fat inside the abdominal cavity. The Hologic Discovery software with additional software (APEX 4.0, Hologic, Bedford, MA) automatically estimates VAT as total abdominal adipose tissue minus the subcutaneous adipose tissue (SAT). The total abdominal adipose tissue was measured on a 5 cm transverse slice at the L4/L5 level between the borders of the inner abdominal muscle. The SAT was estimated from measuring the subcutaneous fat between the skin line and outer abdominal wall on both flanks.

**Statistical analysis**

Tests for collinearity were performed in two analyses including the following parameters respectively: (1) body weight, percentage body fat, VAT, HDL and triglycerides. (2) Smoking status, alcohol consumption, physical activity, marital status and highest finished education level. After collinearity was ruled out multiple linear regressions with backward elimination were conducted using MDI, WHO-5 and PPS, as dependent variables. Due to the many participants, we only applied one statistical model including all potential independent variables. Thus we included: age, gender, total body weight (kg), percentage body fat, VAT (g), HOMA-IR, HDL, triglycerides, LDL, mean arterial pressure (MAP), the following life style factors: smoking status (current smoker 1: Yes, daily; 2: Yes, once in a while; 3: No), alcohol consumption (units per week), physical activity (light physical activity <4 hours per week; light physical activity >4 hours per week or moderate physical activity <4 hours per week; moderate activity >4 hours per week or vigorous activity every week), marital status (married or cohabitant yes/no), highest finished education level (elementary school/high school/university education <3 years/university education 3–4 years/university education ≥5 years) and use of statins (yes/no). We did include LDL and MAP in the model although patients with IHD are commonly treated with anti-hypertensive medication and statins, affecting blood pressure and mainly LDL cholesterol. Omitting LDL and MAP from

| Table 1. Demographic characteristics of included subjects (N = 350). |
|-----------------|-----------------|
| Age in years, mean (range) | 63 (33–75) |
| Male, n (%) | 278 (79) |
| Cardiac variables | | |
| Self-reported time (years) since first diagnosis of ischaemic heart disease (mean, SD) | 7.7 (5.6) |
| Treated with percutaneous coronary intervention (n, %) | 236 (67) |
| Treated with coronary artery bypass grafting (n, %) | 96 (27) |
| Self-reported heart medication, n (%) | | |
| Beta-blockers | 210 (60) |
| Anticoagulants or thrombocyte function affecting drugs | 338 (96) |
| Cholesterol-lowering medication (excl. fibrates) | 311 (89) |
| Calcium-antagonists | 83 (24) |
| Angiotensin II-antagonists and/or Angiotensin converting enzyme inhibitors | 201 (57) |
| Psychometrics, mean (SD) | | |
| Major Depression Inventory | 8.2 (7.1) |
| WHO-5 Wellbeing Index | 66 (18) |
| Pressure Pain Sensitivity | 65 (20) |
| Metabolic variables, mean (SD) | | |
| Body weight (kg) | 85 (17) |
| Percentage body fat (%) | 27 (5.5) |
| Visceral adipose tissue (kg) | 6.3 (2.9) |
| Triglycerides (mmol/l) | 1.4 (0.9) |
| HDL (mmol/l) | 1.3 (0.3) |
| LDL (mmol/l) | 2.4 (0.8) |
| Systolic blood pressure (mmHg) | 137 (18) |
| Mean artery pressure | 100 (11) |
| HOMA-IR (units) | 4.0 (9.3) |
| HbA1c (%) | 5.6 (1.7) |
Table 2. Multiple linear regression analyses with Major Depression Inventory (MDI), WHO-5 Wellbeing Index (WHO-5) and Pressure Pain Sensitivity (PPS), respectively, as dependent variables.6

<table>
<thead>
<tr>
<th>MDI as dependent variable Predictors</th>
<th>β</th>
<th>p Value</th>
<th>WHO-5 as dependent variable Predictors</th>
<th>β</th>
<th>p Value</th>
<th>PPS as dependent variable Predictors</th>
<th>β</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage body fat</td>
<td>0.17</td>
<td>.001</td>
<td>Percentage body fat</td>
<td>-0.17</td>
<td>.001</td>
<td>Percentage body fat</td>
<td>0.31</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.15</td>
<td>.005</td>
<td>Age</td>
<td>0.22</td>
<td>&lt;.001</td>
<td>Body weight</td>
<td>-0.17</td>
<td>.002</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.12</td>
<td>.029</td>
<td>HDL cholesterol</td>
<td>0.15</td>
<td>.013</td>
<td>HDL cholesterol</td>
<td>-0.12</td>
<td>.028</td>
</tr>
<tr>
<td>Smoking status</td>
<td>-0.16</td>
<td>.002</td>
<td>Body weight</td>
<td>0.13</td>
<td>.021</td>
<td>MAP</td>
<td>-0.17</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking status</td>
<td>0.14</td>
<td>.100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Independent variables included: age, gender, body weight, percentage body fat, VAT: visceral adipose tissue, HOMA-IR, HDL cholesterol, LDL cholesterol, triglycerides, MAP: mean arterial pressure, smoking status (current smoker: 1: Yes, daily; 2: Yes, once in a while; 3: No), alcohol consumption, physical activity, marital status and highest finished education level.

the analysis did not change results. VAT was included in the regression analysis since regional fat mass and especially VAT seem strongly associated with cardiovascular risk factors [25]. SPSS version 24 was used for all analyses (SPSS Inc., Chicago, IL).

Results

Three hundred and fifty patients with stable IHD were included in the analyses. For demographic characteristics, see Table 1. Test for collinearity between body weight, percentage body fat, VAT, HDL and triglyceride using each parameter as dependent factor, showed a low and non-relevant collinearity ($R^2$: 0.18–0.46). With regard to the lifestyle factors, the $R^2$ for collinearity was even lower ($R^2$: < 0.1).

Multiple linear regression analyses with MDI as dependent: Depressive symptoms were positively associated with higher percentage body fat, higher triglyceride levels and being a current smoker (Table 2).

Multiple linear regression analyses with WHO-5 as dependent: A low psychological wellbeing was associated with a higher percentage of body fat, lower HDL-cholesterol levels, and being a current smoker (Table 2).

Multiple linear regression analyses with PPS as dependent: A higher PPS level, i.e. a higher stress-level, was independently associated with a higher percentage body fat, a lower body weight, and lower HDL-cholesterol level (Table 2).

Discussion

In the present study, we found in patients with stable IHD that different aspects of chronic stress as measured by different questionnaires and PPS were associated with measures of elements of the MS. Thus, increasing depressive symptoms were associated with increased percentage body fat and triglyceride levels, reduced psychological wellbeing was associated with increased percentage body fat and decreased HDL-cholesterol, whereas increasing levels of PPS indicating an increased stress level were associated with increased percentage body fat, and decreased body weight and HDL-cholesterol levels. These changes, indicating an unhealthy metabolic phenotype in patients with IHD, were independent of the evaluated life-style factors of which only smoking was independently associated with increased depression score, and low psychological wellbeing.

Among patients with IHD, Cohen et al. previously found an association between chronic stress and MS, however this association was confounded by socioeconomic status and health behaviours [12]. In the present study, we controlled for socioeconomic status and a battery of lifestyle factors and found that the chronic stress associated parameters evaluated were independently associated to the elements of MS evaluated. This difference between our finding and the findings by Cohen et al. could be due to differences in measurement of psychological factors as Cohen et al. measured depressive symptoms, hostility, anxiety, anger and optimism/pessimism, whereas we focused on depressive symptoms, psychological wellbeing in general and level of chronic stress. Another difference was the evaluation of MS, since Cohen et al. evaluated the association between MS as such, whereas we evaluated components of the syndrome. We did not register the number of metabolic elements or MS in total since one of the key elements is hypertension, which could not be evaluated due to patients with IHD receiving antihypertensive medication on other indications, i.e. IHD as such.

Regarding dyslipidaemia, a recent study in patients with IHD, found a week association between dyslipidaemia, chronic stress (anxiety, depression, and loss of emotional control) and poor physical QOL [26]. Though the study differed from our study in the design and aim, the results are in line with our findings regarding an association between chronic stress and dyslipidaemia among patients with IHD.

Regarding body composition, we found depressive symptoms and reduced psychological wellbeing to be associated with a high percentage body fat but not with the amount of VAT. One could have thought that increased depressive symptoms and reduced wellbeing would be associated with a higher amount of visceral fat, as chronic stress previously has been associated with central adiposity [27]. However, our results are in accordance with a meta-analysis of longitudinal studies on stress and adiposity, concluding that central adiposity (measured as waist circumference) is no more sensitive to chronic stress than general adiposity (measured as BMI) [28]. In line with this, our findings also support that chronic stress in patients with IHD is closer associated with the total amount of body fat than with the distribution of body fat. We used percentage fat instead of absolute amounts of fat as we included body weight in the multiple regression analyses.
Depression, chronic stress and chronic pain seem to induce a widespread increased pain sensitization, which has been hypothesized to be due to a defect in the diffuse noxious inhibitory control system (DNIC) [29,30]. PPS records this altered pain sensation, and as such might be regarded as a new concept for evaluating chronic stress. In the present cohort, PPS has previously been found associated with depressive symptoms, reduced psychological wellbeing, reduced QOL and perceived stress, all elements of the chronic stress syndrome [15]. In the present study, an increased PPS was found to be associated with an increased percentage body fat, and reduced level of HDL-cholesterol, associations not previously reported in the literature. PPS was also associated with reduced body weight which was somewhat counterintuitive and must be validated in a new study.

Considering healthy individuals, several studies have examined the association between psychological stress and MS as well as individual elements of MS. Concerning the association between psychological stress and weight gain in healthy individuals, no clear tendency seems present as evaluated in a meta-analysis on prospective studies [28]. None of the included studies measured body composition. Our cross-sectional data also found diverging support for an association between stress and a high body weight.

Concerning the association between percentage of body fat, fat distribution and stress, our results are in line with previous studies on patients without IHD [31,32]. Thus, a study on 50 obese individuals with MS found no correlation between depressive symptoms and BMI, WC or waist-to-hip ratio, while they did find a correlation between depression and anxiety symptoms and a higher percentage body fat measured by DXA [31]. A study on 979 randomly-selected women found that a history of depressive disorder was associated with a 7.4% increased body fat mass and a 4.3% higher body fat percentage [32].

**Limitations**

This study suffers from the limitation of being a cross-sectional study. As such we cannot conclude on the causality between stress and the development of elements of the MS, and cannot definitively say which of the two that is the primary event. However, since both the questionnaires and the PPS measurement used for characterizing the chronic stress syndrome were associated with plasma levels of HDL and triglycerides, if anything chronic stress seems to be the primary event. Our hypothesis is that chronic stress causes the development of the MS, and secondary to this the development of IHD. In order to elucidate this, prospective studies using stress intervention modalities with elements of the MS as outcome are needed. With regard to healthy subjects, we performed a small scale randomized clinical trial on office workers with elevated PPS as a sign of increased chronic stress level [33]. In this study, stress intervention was performed by a stress management program which was guided by repeated self-measurement of PPS in the active treatment group in order to improve empowerment. During 3 months of intervention, the active group as compared to controls demonstrated both a reduction in PPS, as well as an approximately 10% reduction in total- and LDL-cholesterol, blood pressure and heart rate, and the reduction in PPS correlated with reductions in heart rate, BMI and visceral fat. With regard to the effects of psychological interventions in patients with IHD, one meta-analysis published in 2005 found relaxation therapies to increase HDL-cholesterol, and decrease the frequency of cardiac events and deaths [34]. A more recent meta-analysis from 2009 found that psychological interventions seemed effective in reducing total cholesterol [35]. However, a Cochrane review from 2014 concluded that psychological treatments did not reduce total deaths, risk of revascularization or non-fatal infarction, although psychological treatment did result in small effects on cardiac mortality [36]. Overall these studies support our finding of a relationship between chronic stress and the development of elements of MS. Essential for understanding our results is the low intern collinearity found between the fat parameters as well as the life style parameters. This justifies the use of our statistical model using multiple linear regression analysis with backward elimination.

We were not able to adjust for the confounding factor of differences in food intake, and we might have overlooked other confounders. Nevertheless, we believe that the most important factors have been adjusted for, as extensive questionnaires were used to measure variables known to influence stress as well as metabolic factors. The different psychological measures correlated internally as previously reported [15] which may also be seen as a limitation to the study. We however believe that each of the questionnaires covers a separate angle of the chronic stress concept and thereby contributes to the overall understanding of the connection between chronic stress and elements of the MS in patient with IHD.

**Conclusions**

This study supports depressive symptoms, low psychological wellbeing, and chronic stress measured as PPS to be associated with elements of the MS, including a high percentage body fat and dyslipidaemia among patients with IHD. Moreover, the study finds the associations to be persistent after extensive adjustments for demographic variables including life style factors, of which only current smoking was independently associated with increased depression score and low psychological wellbeing.

**Acknowledgements**

We thank the staff at Department of Cardiology, Gentofte Hospital, Denmark for providing us with their database on patients with cardiovascular disease that had been appointed to rehabilitation. We are thankful to the staff of the Metabolic Ward, Herlev Hospital, Denmark, for their contribution concerning practical issues.

**Disclosure statement**

SB invented the instrument used to measure PPS (Ullmeter, patent numbers: PA 2004-00349; PA 2004-00550) and is a shareholder of the
firm that owns the PPS instrument (Ullcare A/S). To avoid bias, he was not involved in patient contact, the collection of data or the statistical analysis. NB, JK, PB, AH, FG and FJ declare no conflicts of interest.

Funding
This work was supported by the Johan Schroder’s Family and Business Foundation, the Lundbeck Foundation, Else and Mogens Wedell-Wedellborg’s Foundation and Carpenter Sophus Jacobsen and Wife Astrid Jacobson’s Foundation.

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