Stress biomarkers' associations to pain in the neck, shoulder and back in healthy media workers: 12-month prospective follow-up

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Received: 17 December 2006 / Revised: 6 August 2007 / Accepted: 4 November 2007 / Published online: 13 December 2007
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Abstract Physiological and psychological mechanisms have been proposed to link stress and musculoskeletal pain (MSP), and a number of stress biomarkers in patients with chronic pain have shown to be associated with stress-related disorders as well as health and recovery. The aim was to study if similar results might be found in a working population, in stress and computer intensive occupations with mild/moderate pain in neck, shoulder and back. The questions were if there are: (1) associations between self rated neck, shoulder and back pain (VAS) on one hand and stress-related (catabolic), recovery related (anabolic) variables, cardiovascular/lifestyle factors and immune markers on the other hand. (2) associations between long term changes in pain and stress marker

values (6 month period). (3) predictive values in stress biomarkers for pain (12 month period) A study group with 121 media workers, 67 males (average 45 years) and 53 females (average 43 years), at three news departments of a media company was recruited. Pain occurrence and pain level in neck, shoulder, upper and low back were self-rated at three times with a 6-month interval towards the last month. Stress biomarker sampling was performed, at the same intervals. An additional similar questionnaire with momentary ratings focusing on “at present” i.e. within the same hour as stress biomarker sampling was performed. There were no changes in medicine intake or computer working hours during the 12 month study period. The total pain level and prevalence of pain decreased between baseline and 12 months follow-up. The rate of participation was 95%. Cross-sectional analyses on differences in stress biomarkers in groups of “no pain” and “pain” showed less beneficial stress biomarker levels ($P < 0.05$) in the “pain” group after age and gender adjustments in: S-DHEA-S and P-endothelin, S-insulin and P-fibrinogen. Analyses of each gender separately, adjusted for age, revealed in males differences in S-insulin, saliva cortisol 3, and P-endothelin. Furthermore, tendencies were seen in BMI, P-fibrinogen, and S-testosterone. In the female “pain” group a less beneficial P-BNP level was found. Longitudinal analysis of changes in pain levels and stress biomarkers within an interval of 6 months showed beneficial changes in the following stress markers: P-NPY, S-albumin, S-growth hormone and S-HDL when pain decreased, and vice versa when pain increased. Linear regression analyses showed statistically significant predicting values at the initial test instance for pain 12 months later in lower S-DHEA-S and S-albumin and higher B-HbA1c and P-fibrinogen. In stepwise regression and after age and gender adjustments, the

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associations with S-DHEA-S remained statistically significant. The present study shows that individuals in working life with a high level of regenerative/anabolic activity have less pain than other subjects, and that decreased regenerative/anabolic activity is associated with increasing pain. The levels of NPY, albumin, GH and HDL increased when pain decreased and vice versa. Low DHEA-S predicted pain 12 months later. These findings might contribute to increased knowledge about strategies to prevent further progression of neck/shoulder/back pain in persons who are “not yet in chronic pain”.

Keywords Stress biomarkers · Neck- shoulder- and back pain · Work stress

Introduction

The relationship between work-related stress and pain in the locomotor system has been investigated from several perspectives [4, 7, 17, 20, 27]. However, to our knowledge, there are only few studies on the associations between stress biomarkers and musculoskeletal pain (MSP) in a working population.

In patient groups with MSP associations between pain and biological stress markers have been described. For instance, Hasselhorn et al. [12] found that endocrine and immunologic variables, i.e. low MHPG (methyl 5hydroxy phenylethylene glycol = reflecting sympathoadrenomedullary activity), low DHEA-S, and low β -endorphin predicted a 6 month prognosis of low back and neck/shoulder pain in a female patient group. Tritilanunt et al. [29] found pain-related changes in serum HDL in a patient sample with chronic low back pain. A dysregulation of the hypothalamic- pituitary-adrenal- axis (HPA-axis) in patients with fibromyalgia syndrome and in patients with low back pain was found by Griep et al. [10].

In groups of workers with shoulder pain and physically demanding occupations, Lundberg et al. [21] found a rise in catecholamines and blood pressure. Kaergard et al. [14] found associations between neck and shoulder disorders and low levels of testosterone in female workers. Also Wiholm et al. [30] found a relationship between testosterone levels and upper extremity pain in knowledge workers.

In other words, most previous studies on the relationship between stress biomarkers and pain in the locomotor system have been performed on patient samples with chronic pain. It is, however, unclear whether similar associations between stress biomarkers and pain can be found in a healthy working sample with none or mild/moderate MSP, and whether stress biomarkers can predict self-reported pain occurrence and intensity.

Aim of the study

The overall purpose of this 12-month prospective study was to identify possible relationships between stress biomarkers and pain in a healthy working population with stress and computer intensive occupations, and whether stress biomarkers can predict pain. In particular the aims were to analyze whether there are any associations between pain in the neck, shoulders, upper and low back on one hand and stress biomarkers on the other hand, and whether there is an association between changes in pain intensity and changes in stress biomarker values.

The specific goals were therefore to evaluate:

- (1) associations between self reported neck, shoulder and back pain (VAS) on one hand and stress-related (catabolic), recovery related (anabolic) variables, cardiovascular/lifestyle factors and immune markers on the other hand.
- (2) associations between long term changes in pain and stress marker values (6 months time frame).
- (3) stress biomarkers with predictive value for pain (12 months time frame).

Materials and methods

Participants in the study

The study group were media workers at news departments. Both oral and written information was given to all participants. The participation flow throughout the study is shown in Fig. 1

The study was performed in collaboration with the personnel managers at three news departments at the Swedish Broadcasting Companies for public service radio and television. One of these departments was situated in a medium-sized town, and the other two in the national capital. One hundred and twenty seven persons were asked to participate and 121 (95%) took part, mean age 45 years, 68 males and 53 females.

Questionnaire

A questionnaire was compiled and included the following items:

- Age, gender, occupation, and number of computer working hours per week.
- Self-rated pain during the last month on a visual analogue scale (VAS 0-10), end-points “no pain” and “strong pain” (neck, shoulder, upper back and low back).

Fig. 1 The study participation in each stage of the study during 12 months with description of exclusion criteria and reasons for drop-out

- Consumption of medicine due to (a) pain, (b) stress/depression (answer alternatives yes/no) during the last month.

This questionnaire was distributed by mail three times with 6-month intervals. Furthermore, the study group answered an additional similar questionnaire with momentary ratings focusing on “at present” i.e. within the same hour as stress biomarker sampling was performed. These momentary ratings were coded as “h6” and “h12”, where h symbolizes measurement within the same hour as stress biomarker sampling.

The reliability of the questionnaire was assessed. A four-week test re-test procedure on 30 randomly selected participants was performed. Twenty-four (80%) participated. There were significant correlations between the two response occasions on self rated pain and computer working hours ranging from $r = 0.694$ – 1.000 (Spearman’s, $P < 0.001$) and on responses for medicine intake (Chi Square, $P = 0.011$ – 0.021).

Stress biomarkers in the study group

At the same intervals as the questionnaires were distributed, the following tests were performed: blood sampling, blood pressure and body mass index (BMI). Saliva cortisol was also tested at four occasions during 12 h (upon waking, lunch, dinner, and bed time). For further details see Hasson et al. [13]. All these tests are labelled “stress biomarkers” in the current study (Table 1).

Blood samples were collected 7.00–11.30 am. The exact time for blood sampling was recorded for each participant at all three occasions so that the blood could be collected at the

Table 1 Stress biomarkers: blood sampling and physiological measures

Categories	Stress biomarkers
Cardiovascular system and lifestyle	Blood pressure, body mass index (BMI), P-BNP (brain natriuretic peptide), P-PAI-1 (plasminogen activator inhibitor 1), S-insulin, B-HbA1C (glycosylated hemoglobin), S-triglycerides, S-cholesterol, S-HDL (high density lipoproteins), S-LDL (low density lipoproteins)
Stress-related hypothalamic - pituitary adrenal (HPA) -axis, (catabolic)	S-prolactin, P-ACTH (adreno corticotrophic hormone), S-cortisol, S-TSH (thyroid stimulating hormone), S-T3 (tri-iodothyronine), S-T4 free (thyroxine/tetra-iodothyronine), S-urate, S-CK (creatininkinase), S-LD (lactate dehydrogenase), saliva cortisol (x4), S-albumin, P-fibrinogen
Recovery-related (anabolic)	S-GH (growth hormone), S-IGF-1 (insulin like groth factor), S-DHEAS-S (dehydroepiandrosterone sulphate), S-estradiol, S-testosterone, S-SHBG (sexual hormone binding globulin), S-gastrin
Immune markers and neuropeptides	S-IL-1beta (interleukin 1 beta) S-TNF α (tumour necrosis factor alpha), S-CRP, high sensitive (c-reactive protein), P-substance P, P-endothelin, P-NPY (neuropeptide Y)

same time (± 15 min). Participants were instructed not to eat, drink (except water), nor use nicotinic substances at least 10 h before blood sampling. The blood samples were analyzed by the Karolinska University Hospital laboratory which has been approved by Swedish Board for Accreditation and Conformity Assessment (SWEDAC), which accredits laboratories in the medical sector according to the standard ISO/IEC 17025 (Intra-assay and inter-assay coefficients of variation can be obtained from the laboratory peter.matha@karolinska.se or by e-mailing the first author).

Statistical analyses

Chi Square analyses were conducted to test medicine intake recorded as “yes” or “no” between the response occasions; months 0–6, 0–12, and 6–12.

Initially the variables of pain in neck, shoulder, upper back and low back (VAS 0–10) were summed as the variable “total sum of pain” (score 0–40). The “total sum of pain” variable did not contradict normal distribution, Appendix 1. Parametric analyses were considered acceptable for these variables. This is in accordance with the central limit theorem (CLT), which cited from Wayne et al. [6] “allows us to sample from not normally distributed populations with a guarantee of approximately the same results as would be obtained if the populations were normally distributed, provided that we take a large sample” and is described by Altman [1]. Testing according to Kolmogorov–Smirnov did not change this. The sample sizes for this variable were between $n = 119$ and 35 with the gender separated analyses included.

All further analyses described below are based on parametric tests, namely students *t*-test, one way ANOVA, and univariate and multivariate linear regression.

Independent students *t*-test was performed to compare possible gender-related difference within the group.

“The total sum of pain” at “h12” (h = pain ratings within the same hour as the stress biomarker sampling) was tested for possible gender differences with students *t*-test. To compare “total sum of pain” between “h6” and “h12”, the paired *t*-test was performed.

The stress biomarkers, Appendix 2, were tested for normal distribution as above. They were considered normally distributed except for saliva cortisol 4, S-TNF alfa, S-gastrin, S-SHBG, S-testosterone, S-estradiol, S-ACTH, S-prolactin, S-insulin, P-PAI-1 and P-BNP. For these variables logarithmically transformed values were used, which rendered a less skewed distribution. The stress biomarkers that exhibited statistically significant gender differences at baseline are presented separately, Appendix 2.

Cross-sectional analyses were performed with independent student’s *t*-tests between groups with “no pain” and

“pain”, (VAS ≥ 1 in the neck, shoulder, upper and low back) and the stress biomarkers. These cross-sectional analyses were performed on the pain ratings at “h12” (h12 = pain ratings within the same hour as the stress biomarker sampling month 12) in the total study group and for each gender. The results were adjusted for age and gender. Gender separated analysis were adjusted for age.

Longitudinal analysis between months 6 and 12 (h6–h12) was conducted with a one-way ANOVA. Groups with categorized differences of pain coded as “better”, “unchanged” and “worse” during the period were compiled. The analysis was conducted on differences of mean values’ heterogeneity, in stress biomarkers in the groups coded as “better”, “unchanged” and “worse” with respect to “total sum of pain”. A difference was considered when any pain change occurred on the scale 0–40.

Linear regression analyses were conducted to test if any stress biomarkers at baseline predict pain 12 months later. Both the dependent variable “total sum of pain” and the independent variables, namely stress biomarkers, were expressed as continuous variables. Competing factors at month 0, before the linear regression analyses were initially determined by Pearson’s correlation test and *r*-values and *P*-values, were found. Univariate linear regression analyses were conducted on the statistically significant factors with explicable direction and the regression coefficients (*B*) and *P*-values were given. Furthermore a forward stepwise multiple linear regression was conducted on competing factors, aiming to study if any of the variables was contributing to explain the variation of “total sum of pain” at “h12” and at month 12 (the last month) respectively. Adjustments for age and genders were performed.

The confidence interval 95% was used and *P*-value ≤ 0.05 (two-tailed) was considered significant [1]. When presenting and discussing the results of predictors also tendencies are given ($P < 0.10$) as well as when discussing cross-sectional results.

Results

At baseline, questionnaire responses were recorded for 119/121 (98%). The rate varied during the 12 months study period (95–98%) as depicted in Fig. 1.

At baseline the participation rate for stress biomarkers was 121/121 (100%). Missing values occurred sporadically at all biological test occasion (Fig. 1). However for saliva cortisol missing values were more frequent.

The questionnaire response rate within the same hour as stress biomarker sampling at “h12” (month 12) was 107/127 (84%). At “h6” (month 6) the response rate was 79/127 (62%)—the lower rate due to a technical failure. At one test occasion the nurse who sampled the blood tests by

mistake let the test persons leave before answering the questionnaire. Altogether 72 individuals had complete records, at the two occasions.

Questionnaire in study group

The study group's gender, age, occupation, hours at computer work, and permanent employment is depicted in Table 2. There were no significant changes over time.

Consumption of medicine due to pain and stress

The medicine intake rate, due to pain, and due to stress (recorded as “yes” or “no”) at baseline was 9.5 and 4.3% respectively (Table 2). There were no significant changes over time.

Total sum of pain

The occurrence of “pain” stated for the last month (VAS ≥ 1 in the neck, shoulder, upper and low back) at month 0, 6 and 12 was: 83, 85 and 82% without significant differences.

The occurrence of “pain” according to statements within the same hour as stress biomarker sampling at “h6” was 79% ($n = 79$) and at “h12” 67% ($n = 107$), without significant changes differences.

Table 2 Description of the study group

Basic facts	Study group $n = 121$
Male/female (n/n) (%)	68/53 (56/44%)
Mean age male and female, years (SD)	45 (10.84)
Mean age male, years (SD)	43 (10.04)
Mean age female, years (SD)	47 (11.88)
Reporters, program leaders, editors, and project leaders n (%)	81 (67)
Executives and group leaders n (%)	16 (13)
Technicians, translators, meteorologists n (%)	17 (14)
Administrators n (%)	7 (6)
Hours of computer work per week, mean (SD)	28 (8.70)
Permanent employment, yes (%)	(93)
Medicine intake due to pain, yes (%)	9.5
Medicine intake due to stress, yes (%)	4.3

There were no significant differences over time in any variable

The mean values of “total sum of pain” stated for the last month (score 0–40, VAS 0–10 in the neck, shoulder, upper and low back) in the total study group at baseline, month 6 and 12 are given in Fig. 2, and Appendix 1.

The mean values of “total sum of pain” stated within the same hour as stress biomarker sampling in the study group at “h6” and “h12” are given in Fig. 2 and Appendix 1.

There was a significant difference in pain levels between months 0 and 12 ($P < 0.05$). No other differences over time, between months 0–6 and 6–12, nor between h6 and h12 were found (Fig. 2). The mean values and SD in total group, genders and anatomical body regions are given in Appendix 1.

The females recorded a higher pain level than males. The differences in “total sum of pain” was statistically significant between genders at month 6 ($P = 0.008$). At month 12 a tendency was seen ($P = 0.060$), but none at month 0. No differences between the genders were found at “h6” and “h12”.

Stress biomarkers

The stress biomarkers' mean values in the study group were mostly within reference intervals according to Karolinska University Hospital Laboratory [24] (see Appendix 2 including gender differences).

Cross-sectional comparison between pain ratings and stress biomarkers

The cross-sectional test was conducted on data from “h12” (pain ratings within the same hour as stress biomarkers were sampled at month 12).

Fig. 2 Distribution of mean values and SEM for “total sum of pain” (score 0–40) ($n = 115$). A Study group at month 0, 6 and 12. Significant difference between month 0 and 12 ($P < 0.05$). B Study group at “h6” and “h12” (pain rating the same hour as the stress biomarker sampling), ns. C Gender separated values at “h12”, ns

In groups of “no pain” and “pain” ($VAS \geq 1$ in the neck, shoulder, upper and low back) statistically significant differences were found in stress biomarkers. Before age and gender adjustments the statistically significant differences between the groups were found with higher levels in the “pain” group in P-BNP, S-insulin, P-fibrinogen, and S-CRP, and lower levels in S-DHEAS, P-endothelin, and S-testosterone. In males a higher BMI was found in the “pain” group and in females a higher P-BNP in the “pain” group (Table 3).

After adjustment for age and gender, significant differences between “no pain” and “pain” were found in higher P-insulin, P-fibrinogen, and lower S-DHEA-S, and P-endothelin in the “pain” group. Additionally, in males significantly higher saliva cortisol 3 and in females higher P-BNP were found (Table 3).

Longitudinal comparisons between changes in pain intensity and changes in stress biomarkers during 6 months

A longitudinal comparison between the changes in pain intensity and changes in stress biomarkers between “6” and “h12” was performed. On these occasions the questionnaire responses were captured at the same hour as the stress biomarker sampling.

The changes in stress biomarkers differences were compared with the changes of “sum of pain”. The changes of “sum of pain” were coded as “better”, “unchanged” or “worse”.

Statistically significant heterogeneity between the three groups was found in P-NPY, S-albumin, S-GH and S-HDL. The mean differences of these stress biomarkers were increased when pain decreased and the opposite when pain increased (Fig. 3; Table 4).

Table 3 Comparison in the study group between mean levels of stress biomarkers in the groups “no pain” and “pain” at “h12” as well as for each gender (pain ratings within the same hour as stress biomarkers were sampled at month 12)

Variables with statistically significant values before and after age and gender adjustments are shown. Statistically significant *P*-values are marked bold

		Pain No/yes n	No pain mean (SD)	Pain mean (SD) age and gender	<i>P</i> -value	<i>P</i> -value after adjustment for
Total group (<i>n</i> = 105)						
P-endothelin	pmol/l	34/71	2.00 (0.61)	1.65 (0.73)	0.018	0.008
S-insulin	MeI/l	34/71	4.89 (2.45)	6.62 (4.34)	0.032	0.042
S-DHEA-S	μmole/l	34/71	7.19 (3.08)	5.22 (2.93)	0.002	0.045
P-fibrinogen	g/l	34/71	2.82 (0.43)	3.11 (0.60)	0.014	0.046
P-BNP	ng/l	19/46	12.68 (9.91)	26.61 (15.30)	0.022	0.068
S-testosterone	mol/l	34/71	15.24 (10.44)	10.86 (10.39)	0.043	0.065
S-CRP (high sense)	mg/l	34/71	0.94 (1.16)	2.11 (3.24)	0.045	0.078
Males (<i>n</i> = 61)						
P-endothelin	pmol/l	23/38	1.99 (0.60)	1.59 (0.67)	0.024	0.015
P-insulin	mEl/l	23/38	4.95 (2.22)	7.60 (4.77)	0.018	0.033
Saliva cortisol 3	pmol/l	11/21	2.90 (1.25)	4.26 (3.11)	0.177	0.020
P-fibrinogen	g/l	23/38	2.71 (0.47)	2.99 (0.48)	0.024	0.060
BMI	kg/m ²	22/33	23.42 (2.18)	25.70 (4.16)	0.022	0.090
S-DHEA-S	μmole/l	23/38	8.30 (2.74)	6.61 (3.01)	0.031	0.095
Females (<i>n</i> = 35)						
P-BNP	ng/l	9/27	8.66 (4.30)	25.89 (15.13)	<0.001	<0.001

Decreased pain “better” “h6-h12”	P-NPY ↑	S-albumin ↑	S-GH ↑	S-HDL ↑
Increased pain “worse” “h6-h12”	P-NPY ↓	S-albumin ↓	S-GH ↓	S-HDL ↓

Fig. 3 Directions ($\pm$) of mean differences in stress biomarkers in groups of pain intensity coded as “better” and “worse” with respect to “total sum of pain” within a time frame of 6 months (“h6”–“h12” i.e. pain ratings the same hour as the stress biomarker sampling)

Table 4 Mean differences of changes in the stress biomarkers in groups of pain intensity coded as “better”, “unchanged” and “worse” according to “total sum of pain” during a time frame of 6 months (“h6” to “h12” i.e. pain ratings the same hour as the stress biomarker sampling)

	Decreased pain “better”		“Unchanged” pain		Increased pain “worse”		<i>P</i> -value (ANOVA)
	<i>n</i>	Mean diff (SD)	<i>n</i>	Mean diff (SD)	<i>n</i>	Mean diff (SD)	
P-NPY	17/65	0.06 (9.01)	13/65	4.00 (8.93)	35/65	−3.97 (8.23)	0.016
S-albumin	18/71	0.44 (2.62)	14/71	−2.79 (4.02)	39/71	−0.87 (2.89)	0.017
S-GH	18/71	1.05 (2.65)	14/71	−0.32 (1.23)	39/71	−0.63 (1.85)	0.016
S-HDL	18/7	1 0.06 (0.24)	14/71	−0.10 (0.17)	39/71	−0.07 (0.19)	0.039

Statistically significant heterogeneity in stress biomarkers between groups is shown. Significant *P*-values are marked bold

Predicting factors of stress biomarkers at month 0 for pain intensity at month 12

Predicting factors of stress biomarkers at study baseline (month 0) for pain intensity expressed as “total sum of pain” 12 months later “at present” (“h12”) and during the last month were analyzed.

Low S-DHEAS ($P = 0.007$), showed a statistically significant relation to “total sum of pain” at “h12”, so did a high P-fibrinogen ($P = 0.033$) and a high B-HbA1c ($P = 0.052$). A similar tendency was seen for a low S-testosterone ($P = 0.060$).

After age and gender adjustments the S-DHEA-S relationship was statistically significant ($P = 0.035$) in relation to “h12” and a tendency was seen for B-HbA1c ($P = 0.066$) and P-fibrinogen ($P = 0.084$).

After the first step of a forward stepwise multiple linear regression analysis on the statistically significant factors, only S-DHEA-S showed a significant relation to “h12” ($P = 0.040$). No contribution in reducing the variance in relation to “h12” could be seen in the next step with the two factors B-HbA1c and P-fibrinogen, when S-DHEA-S was already in the equation. S-testosterone was not included in the stepwise linear regression (Table 5).

Lower S-DHEA-S ($P = 0.026$) also showed a statistically significant relation to “total sum of pain” at month 12. This was also found for lower S-albumin ($P = 0.050$).

After age and gender adjustments the S-DHEA-S relationship was statistically significant ($P = 0.043$) and a tendency was still seen for S-albumin ($P = 0.062$).

In the first step of a forward stepwise linear regression analysis no contribution in reducing the variance at month 12 was seen. However S-DHEA-S showed a tendency ($P = 0.082$).

Discussion

The aim of this prospective study over 12 months on healthy workers was to determine whether associations

could be found between stress biomarkers and self rated pain in a normal “white collar” working population with stress and computer intensive work.

Previous studies on this issue are rare. Our findings are based on analyses cross-sectionally at one occasion and longitudinally within a 6 month time frame, and furthermore with regard to stress biomarkers’ predictive value for pain also in a 12 months time frame. Associations between stress biomarkers and self rated pain were found at all three test instances.

Stress biomarkers versus pain

The results show that individuals in working life with a higher level of regenerative/anabolic activity are less likely to have pain than other subjects, and that decreasing such activity is associated with more pain. Accordingly, the concentration of DHEA-S and endothelin was higher among those without pain than those with pain. Analogously those with decreasing NPY, growth hormone, albumin and HDL concentrations had more pain at follow-up. That NPY is a pain-protective factor, that the general albumin concentration level reflects the general anabolic level, that growth hormone is one of the main anabolic factors and finally that HDL is a factor that protects the vessels against atherosclerosis, agrees with these prospective findings. The predicting power for pain in low levels of DHEA-S, and S-albumin, and in high levels of P-fibrinogen and HbA1c, and with a tendency in the same direction in low S-testosterone values also agrees with the notion that decreasing regenerative/anabolic activity is associated with increasing pain.

It may be surprising that it is not the same factors that appear in the cross-sectional and prospective analyses. However, we have examined a number of factors with differing characteristics, for instance with regard to breakdown and duration. Cross-sectional and prospective analyses are therefore likely to provide different correlates between pain and changes in pain.

Table 5 Stress biomarkers at baseline predicting “total sum of pain” at “h12” and month 12. Pearson’s correlation coefficient (*r*) and univariate linear regression analysis with regression coefficients (Beta) for statistically significant factors are given

P-values from age and gender adjustments are shown as well as from stepwise linear regression. Significant *P*-values are marked bold

Factor	<i>r</i> Pearson’s	Beta univariate linear regress	<i>P</i> -value univariate linear regress	<i>P</i> -value after adj age/gender	<i>P</i> -value stepwise linear regress
Competing factors month 0 to pain “h12”					
S-DHEA-S μmole/l	−0.264	−0.584	0.007	0.035	0.040
B-HbA1c%	0.190	4.219	0.052	0.066	0.268
P-fibrinogen g/l	0.209	1.912	0.033	0.084	0.222
S-testosterone mol/l	−0.184	−0.111	0.060	0.344	×
Competing factors month 0 to pain month 12					
S-DHEA-S μmole/l	−0.212	0.245	0.026	0.043	0.082
S-albumin g/l	−0.187	0.199	0.050	0.062	0.183

The fact that predictive stress biomarkers could be identified in spite of low mean pain levels, and that significant differences in stress biomarkers between “no pain” and “pain” groups were shown, supports the hypothesis that pain- and stress-related catabolic/anabolic activities exist before the pain becomes chronic and limits the daily functions.

Representativeness of the study group

Hormonal variations for women were not considered. This is not intended to distort the results on group level. Gender dependent markers were presented separately for males and females if significant differences at baseline were found. Age and gender adjustments were performed. For the predictive analyses the tests were made at the same time of the year to avoid season dependent hormonal variations shown by Myrianthefs P et al. [22].

Pain, stress and biomarkers

In spite of the fact that very few studies have been published on the relationship between stress biomarkers and moderate pain in working populations, some support for the present results can be found in the literature. Most of the results in previous literature, however, pertain to chronic pain.

Cardiovascular system markers

BNP has been described by Struthers et al. [25] to be “a simple new test to identify coronary artery disease”. Their findings were made on males. In the present study, the females showed a strongly significant difference between pain and no pain groups in BNP levels with higher BNP in the pain group. A similar difference was not seen in males. According to our knowledge associations between MSP and BNP have not been documented in earlier literature.

Increased BMI values, moderate though in the present study, in the “pain” group in males is in accordance with Kaila-Kangas [15] and Evers Larsson [8] who found a relationship between MSP and high BMI. Also Han et al. [11] found that women with overweight or a high waist-hip ratio have increased likelihood of low back pain. Toda et al. [28] showed that obesity may be a risk factor for chronic low back pain in women. Even a slight increase in BMI might be associated with increased pain prevalence, as seen in the present study.

Stress-related (hypothalamic-pituitary-adrenocortical) HPA-axis, catabolic biomarkers

Lower albumin values are seen in inflammatory and catabolic conditions [9]. The present study showed decreased albumin values at “pain”. During the time frame between months 6 and 12 (h6–h12) albumin also increased when pain decreased and vice versa. This finding agrees with decreased albumin values in inflammatory and catabolic conditions. Pain might be considered an inflammation equivalent. Furthermore albumin concentration level is known as a reflector of general anabolic level, which is in accordance with lower DHEA-S, growth hormone, and higher insulin in the “pain” group in the present study.

A well documented and sensitive marker of inflammation and/or any tissue injury is CRP. Sturmer et al. [26] found that intensity of pain during the previous 24 h as assessed by VAS was independently associated with high levels of CRP in patients with acute sciatic pain but not in those with chronic low back pain. CRP was significantly higher in the “pain” group before age and gender adjustments in the current study. This is a finding in accordance with Sturmer et al. Fibrinogen is a sensitive indicator of inflammation, an acute phase protein [9], which can be a complement to CRP. Fibrinogen level was significantly higher in the “pain” group in the present study.

ACTH and cortisol levels are inter-dependent. They respond to stress [9] and vary throughout the day. The

ACTH is normally highest in the early morning, though it can vary rapidly within a few minutes, and it is at its lowest level in the evening. Cortisol excretion is normally high in the morning and increases during the early morning period, and is reduced in the afternoon and the evening. Only Saliva cortisol 3 concentration in males in the “pain” group was significantly higher than in the “no pain” group. Statistically non-significant associations between “pain” and “no pain” groups in ACTH and serum-cortisol in the current study may be explained by low mean pain levels.

Regenerative, anabolic stress biomarkers

It is known from previous studies [9, 13] that sex hormones might be sensitive to stress exposure. DHEA-S is found to be related to stress and psychiatric disorders, insulin sensitivity, immunological and cardiovascular disorders according to Kroboth et al. [18]. Hasson et al. [13] found a possible association between the effects of a web based stress intervention and DHEA-S. In the current study DHEA-S was significantly lower in the “pain” group, and occurred as a predictor of pain at a 12 month follow-up. In the cross-sectional analysis the “pain” group as compared to the “no pain” group showed a significantly lower testosterone level before age and gender adjustments and a tendency after adjustments, whereas no difference was found in estradiol levels. These results are in accordance with Kaergard et al. [14] and Wiholm et al. [30] who found indications of relations between testosterone level and MSP. They are also in accordance with Hasselhorn and Theorell [12] who showed that in women with acute onset low back pain a low DHEA-S predicted long-lasting disability due to pain. The findings in DHEA-S and testosterone fit well with the notion that decreasing regenerative/anabolic activity is associated with increasing pain.

A higher insulin level in the “pain” group as compared to “no pain” was found. This finding has to our knowledge not been confirmed in earlier literature. It might be related to the changes in GH showing a lower level when the pain increased and vice versa in the current study. GH has a circadian variation which increases the risk of random results. The excretion increases in recovery and relaxation processes, and decreases with lack of recovery [9]. Leal-Cerro et al. [19] found that patients with fibromyalgia exhibited a marked decrease in spontaneous secretion of GH and IGF-I. Bennett et al. [5] found lower GH in patients with chronic inflammation in patients with rheumatoid arthritis. The relation to lower DHEA-S in the “pain” group might also be a contributing factor. Our findings support the hypothesis that increasing pain is negatively associated to recovery/anabolic activity and vice versa.

Immune markers and neuropeptides

NPY has been shown to promote sleep and inhibit ACTH and cortisol release in young men, HPA-axis activity, according to Antonijevic et al. [3]. Anderberg [2] found increased NPY levels in patients with fibromyalgia and long lasting pain. She concluded that long lasting pain may activate NPY anxiolytic and sedative effects. NPY is clearly a marker that can be influenced in both directions by pain. In the longitudinal analyses, the current study shows a higher NPY level when the pain decreased and vice versa indicating reaction in the NPY system as well in persons with moderate pain levels.

Endothelin is known as one of the most powerful vasoconstrictor substances. In mice with neuropathic pain after chronic constriction injury of the sciatic nerve Klass et al. [16] found that endothelin was a mediator of pain in general. They suggest that their results motivate studies of endothelin as a potential novel therapy for neuropathic pain. Nattero et al. 1996 [23] showed that plasma endothelin-1 concentrations decreased during migraine attacks. Endothelin was found to be associated with pain in the present study, as there were lower endothelin levels in the “pain” group as compared to “no pain”. Study results on relations between low endothelin and MSP in healthy working subjects with mild/moderate pain have not been found in the literature.

Methodological considerations

As many analyses were performed, the risk of mass-significance can neither be avoided nor ignored. Adjustments for mass significance effects, such as using $P = 0.010$ or Bonferroni corrections [1] are not necessarily good solutions of the problem that several tests may arise randomly, when a large number of statistical analyses are performed. It is not possible to use such corrections in each individual test. An exclusion of findings with P between 0.05 and 0.01, for instance, could mean possible exclusion of true associations, and an acceptance of a finding with p equal to 0.01 could still be accepting a random finding. Therefore we chose to present all findings with $P \leq 0.05$.

Surprisingly in the cross-sectional analysis fewer statistically significant differences in stress biomarkers between groups of “no pain” and “pain” were found in females in spite of a higher intensity of pain among them. A possible reason is the smaller size of this subgroup.

Future implications

The finding in the present study, i.e. that the biomarker hormone DHEA-S, as well as HbA1c, albumin and

fibrinogen, predict pain in a working population in spite of only mild/moderate pain, is new. This might in a longer perspective, provided that more studies make the same findings, be a step towards future use of stress biomarker measures, particularly in non specific pain patients, in pain management.

Another new finding is the increased BNP concentrations association to pain, particularly in women, as well as the fact that lower endothelin concentration was associated to pain, which is of interest for future studies.

The causality in our findings—i.e. whether the pain causes deteriorated levels in stress biomarkers or vice versa, and if pain- and stress-related anabolic/catabolic activities exist before the pain becomes long lasting, intense and limits the daily functions—need further investigations.

The current study results might contribute to increased knowledge about strategies to prevent further progression of neck/shoulder/back pain in persons who are “not yet in chronic pain”.

Conclusion

The present study shows that individuals in working life with a high level of regenerative/anabolic activity are less

likely to have pain than other subjects, and that decreased regenerative/anabolic activity is associated with increasing pain. The levels of NPY, albumin, GH and HDL increased when pain decreased and vice versa. Low DHEA-S predicted pain 12 months later. These results might contribute to increased knowledge about strategies to prevent further progression of neck/shoulder/back pain in persons who are “not yet in chronic pain”.

Ethical considerations

The study was approved by the Ethical Committee at Karolinska Institutet (Dnr 01-355) and at the Ethical Committee at Uppsala University (Dnr 01-188). All participants signed an informed consent to their participation in the study.

Acknowledgments We thank the administration staff at the Swedish Broadcasting Company for Radio and Television for their collaboration. We also thank Bo Nilsson for contribution and assistance in the statistical analyses. No financial interests were involved.

Appendix 1

Table 6.

Table 6 The mean values and SD of total sum of pain (score 0–40, VAS 0–10 for the locations neck, shoulder, upper and low back) and at each body localization (VAS 0–10) recorded at all different time periods

	Neck mean (SD)	Shoulder mean (SD)	Upper back mean (SD)	Low back mean (SD)	Total sum of pain each gender mean (SD)	Total sum of pain both gender mean (SD)
Study males						
Month 0	2.02 (2.53)	2.65 (3.01)	1.56 (2.37)	3.05 (3.21)	9.27 (848)	×
Month 6	1.82 (2.45)	2.25 (2.58)	1.42 (1.96)	2.17 (2.87)	7.65 (7.67)	×
Month 12	1.41 (2.08)	1.94 (2.34)	1.06 (1.48)	2.25 (2.88)	6.37(6.47)	×
Month 6 (h6)	×	×	×	×	6.14 (6.79)	×
Month 12 (h12)	×	×	×	×	4.64 (5.48)	×
Study group females						
Month 0	2.77 (3.07)	3.32 (2.89)	2.12 (2.83)	2.79 (3.04)	10.94 (8.68)	×
Month 6	3.44 (3.04)	3.72 (3.12)	2.56 (2.98)	2.26 (2.26)	11.98 (9.21)	×
Month 12	2.48 (2.56)	3.00 (2.45)	1.58 (2.19)	2.06 (2.32)	9.72 (7.53)	×
Month 6 (h2)	×	×	×	×	10.11 (8.02)	×
Month 12 (h3)	×	×	×	×	6.59 (6.82)	×
Total study group						
Month 0	×	×	×	×	×	9.99 (8.54)
Month 6	×	×	×	×	×	9.68 (8.64)
Month 12	×	×	×	×	×	7.66 (7.08)
Month 6 h (n = 79)	×	×	×	×	×	8.00 (7.61)
Month 12 h (n = 105)	×	×	×	×	×	5.40 (6.11)
Month 6 h (n = 72)	×	×	×	×	×	6.86 (7.68)
Month 12 h (n = 72)	×	×	×	×	×	5.21 (6.37)

Each gender in study and reference group, are presented

Appendix 2

Table 7.

Table 7 Mean values and SD of biological stress markers in the study group ($n = 105$) at month 0, 6 and 12^a

Variable		Month 0 mean (SD)	Month 6 mean (SD)	Month 12 mean (SD)	Reference interval
Cardiovascular system and lifestyle					
Diastolic blood pressure	mmH	77.82 (11.10)	77.77(11.00)	77.09 (10.90)	<90
Systolic blood pressure	mmHg	126.06 (19.60)	127.18 (18.00)	126.78 (16.20)	<140
BMI M/F	kg/m ²	27.00 (3.69)	24.50 (3.90)	24.63 (4.11)	20/19–25/24
P-BNP	ng/l	10.58 (12.10)	11.598 (12.00)	19 (14.20)	<22
P-BNP M	ng/l	7.18 (9.81)	9.27 (11.75)	15.194 (12.78)	<22
P-BNP F	ng/l	14.8 (13.31)	14.61 (12.66)	22.03 (14.77)	<22
P-PAI I	klE/l	10.93 (15.60)	9.65 (13.00)	10.67 (13.00)	<15
P-PAI I M	klE/l	12.71(16.80)	9.69(11.68)	12.26(14.08)	<15
P-PAI I F	klE/l	8.73 (13.92)	9.60(14.34)	8.51(11.24)	<15
S-insulin	mEl/l	6.65 (3.53)	8.50 (7.50)	6.10 (3.80)	<20
B-HbA ₁ C	%	4.62 (0.60)	4.63 (0.30)	4.34 (0.38)	<5.2
f S-triglycerides	m mmol/l	1.37(0.72)	1.27 (0.70)	1.29 (0.71)	<2
S-triglycerides M	mmol/l	1.53 (0.84)	1.38 (0.74)	1.41 (0.80)	<2
S-triglycerides F	mmol/l	1.18 (0.48)	1.12 (0.47)	1.12 (0.52)	<2
S-Cholesterol	mmol/l	5.34 (1.04)	5.46 (1.00)	5.18 (0.89)	<5
S-HDL	mmol/l	1.50 (0.42)	1.49 (0.40)	1.46 (0.37)	>1
S-HDL M	mmol/l	1.35(0.35)	1.34 (0.31)	1.30 (0.27)	>1
S-HDL F	mmol/l	1.69 (0.43)	1.69 (0.40)	1.66 (0.39)	>1
S-LDL	mmol/l	3.22 (0.90)	3.38 (0.90)	3.17 (0.79)	<3
Stress-related (hypothalamic-pituitary -adrenocortical) HPA-axis (catabolic)					
S-prolactin	µg/l	6.11(3.70)	8.86 (19.00)	8.19 (17.90)	x
S-prolactin M	µg/l	3.13 (2.30)	4.96 (2.27)	4.65 (2.06)	<10
S-prolactin F	µg/l	7.34 (4.65)	14.05 (28.74)	12.97 (26.73)	<20
P-ACTH	pmol/l	5.25 (4.47)	5.37(3.00)	5.76 (4.269)	2–10
P-ACTH M	pmol/l	6.52 (5.53)	6.25 (3.52)	6.76 (5.13)	2–10
P-ACTH F	pmol/l	3.67 (1.60)	4.19 (1.55)	4.41 (2.04)	2–10
S-cortisol	nmol/l	399.97 (131)	358.75 (134)	355.43 (121)	200–700
S-TSH	mE/l	1.7 (1.15)	1.77 (1.00)	1.86 (1.13)	0.2–4.0
S-T3	nmol l	1.84 (0.31)	1.84 (0.30)	1.75 (0.23)	1.1–2.5
S-T4 (free)	pmol/l	12.96 (1.62)	13.38 (1.80)	13.12 (1.72)	10–20
S-urate	µmol/l	287.26 (73.6)	278.25 (68)	281.0 (70.20)	x
S-urate M	µmol/l	323.1 (58.08)	306.87 (52.82)	312.0 (55.99)	200–450
S-urate F	µmol/L	242.8 (66.42)	240.10 (66.80)	238.0 (65.64)	<50/>50 years 150–340/180–340
S-LD	µkat/l	5.98 (0.85)	5.81 (0.90)	6.04 (1.02)	<8
S-CK M/F	µkat/l	2.02(2.13)	1.78(1.25)	1.95(1.60)	<3.3/<2.5
P-fibrinogen	g/l	2.99 (0.67)	3.24 (0.70)	3.03 (0.56)	2.0–4.2
S-albumin	g/l	42.12(3,27)	42.48 (3.8)	41.89 (3.11)	35–48
Saliva cortisol					
Wake up time	pmol/l	12.70(9.58)	11.94 (6.50)	13.20 (7.54)	6.2–38.1
Male	pmol/l	12.28 (10.16)	12.13(7.18)	13.44(6.85)	6.2–38.1
Female	pmol/l	13.08(9.12)	11.76(5.80)	12.92(8.39)	6.2–38.1

Table 7 continued

Variable		Month 0 mean (SD)	Month 6 mean (SD)	Month 12 mean (SD)	Reference interval
Lunch time	nmol/l	6.32 (5.27)	7.20 (5.00)	5.55 (3.00)	x
Male	nmol/l	6.01(3.84)	7.25(4.52)	5.99 (4.14)	x
Female	nmol/l	6.59 (6.29)	7.15(5.45)	5.05(3.84)	x
Dinner time	nmol/l	4.90 (3.82)	4.76 (3.50)	3.40 (2.42)	x
Male	nmol/l	4.40(2.83)	4.59(3.61)	3.76(2.64)	x
Female	nmol/l	5.33(4.49)	4.92(3.38)	2.92(2.06)	x
Recovery-related (anabolic)					
S-SHBG M/F	nmol/l	53.44 (37.75)	59.05 (74.73)	56.53 (68.35)	<40/>40 years 0–50/2
S-IFG- 1 (age and gender dependent)	mikrog/l	147.64 (46.40)	143.24 (48)	135.09 (43.30)	0–370 33/56 years
	mikrog/l				40–370/100–260 38/63 years
	mikrog/l				30–340/90–240
S-DHEA-S (age dependent)	μmol/l	6.03 (2.74)	6.20 (3.10)	5.94 (3.14)	0.5–15
S-DHEA-S M (age dependent)	μmol/l	7.55 (3.02)	3.93 (1.98)	3.93 (1.98)	39 years 4.1–15
	μmol/l				0–49 years 2.7–11
	μmol/l				0–59 years 1.6–8.2
	μmol/l				60 years 0.8–5.4
S-DHEA-S F (age dependent)	μmol/l	4.30 (1.78)	4.39 (2.07)	5.94 (3.14)	0.5–15
	μmol/l				29 years 2.7–14
	μmol/l				30–39 years 1.6–9.5
	μmol/l				40–49 years 1.1–6.8
S-estradiol	pmol/l	171.04 (244.92)	144.17(202.0)	117.57(106.0)	110–1470
S-estradiol M	pmol/l	105.30(21.9)	92.06 (22.75)	91.58 (21.33)	<130
S-estradiol F	pmol/l	252.61(350.68)	218.00(299.30)	154.30 (156.27)	110–1470 50–70 years < 400
S-testosterone	nmol/l	11.08 (10.10)	11.64 (10.00)	12.20 (10.40)	0.3–30
S-testosterone M	nmol/l	19.01 (6.03)	19.17 (5.99)	19.84 (6.50)	10–30
S-testosterone F	nmol/l	1.25 (2.71)	1.60 (2.88)	1.87 (3.28)	0.3–3.0
fP-gastrin	pmol/l	25.30 (17.80)	32.99 (38.00)	30.84 (38.5)	<60
fP-gastrin M	pmol/l	27.46(22.51)	31.59(25.72)	29.45(27.96)	<60
fP-gastrin F	pmol/l	22.57(8.13)	34.86(50.50)	32.72(49.59)	<60
S-GH	μg/l	0.90 (2.01)	1.00 (1.84)	1.00 (2.40)	<15
S-GH M	μg/l	0.20(0.42)	0.47(1.14)	0.26 (0.65)	<15
S-GH F	μg/l	1.77(2.75)	1.70(3.32)	2.01 (3.38)	<15
Immune markers and neuropeptides					
S-TNF alpha	ng/l	3.97(3.12)	3.37 (5.50)	2.12 (4.19)	<8
S-CRP, high sensitive	mg/l	1.42 (2.00)	1.64 (2.10)	1.69 (2.70)	<2
P-NPY	pmol/l	17.28 (7.02)	15.16 (7.99)	13.18 (3.67)	<50
P-endothelin	pmol/l	missing	2.76 (1.22)	1.76 (0.70)	<8
P-substance P	pmol/l	5.00 (0)	5.00 (0)	5.00 (0)	<16
P-SI - I beta	ng/l = pg/ml	1.00 (0)	1.01 (0)	1.01 (0.09)	<5

^a Gender description in study group is presented for values with significant difference between genders at baseline ($P < 0.05$). Values outside the normal reference interval [25] are marked bold, M = males, F = females

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