Musculoskeletal Pain in Melancholic and Atypical Depression

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Funding sources: The study was supported by the Central Finland Health Care District and Jyrjö Jahnsson Foundation.

Disclosure and conflicts of interest: The authors declare that they have no conflicts of interest related to this study.

Abstract

Objective. Pain and depressive disorders often present together, but little is known about the prevalence of pain in depression subgroups. The objective of this study was to examine the possible differences in the prevalence of musculoskeletal pain between participants in melancholic and atypical depression subgroups.

Design. Cross-sectional study.

Setting. Depression nurse case managers where depression patients receive treatment in primary health care.

Subjects. Participants included 413 depression patients and 401 controls.

Methods. Depressive symptoms were determined with the Beck Depression Inventory (BDI-21), and diagnosis of depression was confirmed with the Mini-International Neuropsychiatric Interview (MINI). The participants were dichotomized into subgroups with melancholic depression (n = 269), atypical depression (n = 144), and controls (n = 401). Musculoskeletal pain was identified during last four weeks. Participants were enrolled in the study between 2008 and 2009.

Results. The prevalence of pain was 37% in controls, 57% in atypical depression, and 71% in melancholic depression (P < 0.001, after adjusting for sex and age). A logistic regression model showed that the odds ratio of pain after adjusting for confounding factors was 2.35 (1.56 to 3.56) with atypical depression compared with controls (P < 0.001) and 4.38 (3.03 to 6.33) with melancholic depression compared with atypical depression (P = 0.006). BDI scores were higher for those with melancholic depression than for those with atypical depression (P < 0.001).

Conclusions. Melancholic depression showed to be associated with a higher prevalence of musculoskeletal pain in comparison with atypical depression. This finding highlights the need for further studies about the mechanisms behind the association, particularly in melancholic depression.

Key Words. Depression Characteristics; Depressive Disorder; Musculoskeletal Pain

Introduction

Pain and depressive disorders often present together. On average, 65% of patients with depression are identified as simultaneously having pain, and the prevalence
of pain symptoms is as high as 69% in primary care patients with depression [1]. In addition, about half of pain patients fulfill the criteria for depression [2]. Comorbidity of chronic pain and depression has been consistently associated with a poorer prognosis and greater disability in patients when compared with those suffering from each illness alone [3]. Moreover, evidence from epidemiologic studies confirms this comorbidity. A large population-based survey conducted by the World Health Organization reported twice as high a prevalence of pain among those with depression and, further, that pain was more frequent in more severely depressed patients [4].

Pain symptoms present in depression cannot be explained by organic illness in all cases. There are multiple and complex neurobiological mechanisms that might explain the relationship. Dysfunction in neurotransmitter systems during depression may increase the perceived intensity of pain and the unpleasant emotional experience caused by pain [5]. Especially, lower concentrations of serotonin and noradrenaline during depression are involved in controlling pain processing as well, as they weaken the ability of descending inhibitory pathways to regulate experience of pain, resulting in a lowered threshold of pain and leading to perceived pain that is otherwise ignored [6,7]. Moreover, neuroendocrine abnormalities, such as an overactive hypothalamic-pituitary-adrenal (HPA) axis, have also been recognized in both depression and chronic pain disorders [7]. Hyperactivity of the HPA axis results in sympathetic overactivity, which in turn contributes to immune activation and a release of pro-inflammatory cytokines shown to be associated with both depression and pain [7].

Depression can be dichotomized into subgroups with mainly melancholic and atypical depression, and there may be differences in the biological correlations of these subtypes [8]. Melancholic depression is considered to be a more multifaceted biological condition with dysfunction involving the HPA axis, and, further, it is thought to be genetically predisposed [9,10]. Atypical depression, in turn, is characterized by increased inflammation levels and metabolic abnormalities such as higher levels of body mass index (BMI), waist circumference and triglycerides, and lower high-density lipid cholesterol [11,12]. Moreover, the prevalence of cardiometabolic risk cluster metabolic syndrome has shown to be higher in subjects with atypical depressive symptoms [12]. Especially elevated fasting glucose and triglyceride levels and high waist circumference, out of the components of the metabolic syndrome, have shown to be associated with atypical depression [12]. Additionally, it has been shown that there are differences and changes in sympathetic nervous system regulation between the subgroups [13]. Different depression subtypes may have different clinical symptoms, as melancholia is typified by features of psychomotor slowing, anxiety, appetite loss, and insomnia, whereas atypical depression is associated with increased appetite and hypersomnia [9].

This heterogeneity of biological correlations between melancholic and atypical depression may also affect the experience of pain to some extent. Although extensive research has been carried out on the relationship between depression and pain, studies about the prevalence of pain in depression subgroups are sparse or nonexistent. Thus, the aim of this study was to analyze the possible differences in the prevalence of pain between participants in melancholic and atypical depression subgroups and, further, to explore the occurrence of metabolic abnormalities in these subtypes of depression.

**Methods**

**Data Source and Study Population**

The study participants of this cross-sectional Finnish Depression and Metabolic Syndrome in Adults study (FDMSA) were patients older than age 35 years with depressive symptoms and scoring 10 or higher in the 21-item Beck Depression Inventory (BDI-21) (n = 706). They were enrolled within the area of the Hospital District of Central Finland when referred by themselves or by general practitioners to depression nurse case managers in 2008 and 2009. After exclusion of patients who did not receive depression diagnosis, there were 413 participants. Random sampling was used to form a control group of 401 middle-aged (≥35 years) residents in the participating municipalities with a BDI score of less than 10 who participated in the same health evaluation. All the participants signed an informed consent form. Ethical permission for the study was granted by the Hospital District of Central Finland Ethics Committee.

**Measurement of Demographic and Clinical Data**

In a health examination, all the participants completed a standard questionnaire including questions about years of education, use of medications including antidepressants, current smoking, and alcohol use (number of drinks per week). Leisure-time physical activity was assessed by asking: “How often do you do physical activity at least for half an hour so that you get out of breath and sweating?” Answers were classified as follows: low (twice per month or less), moderate (once or twice per week), or high (three times per week or more). To determine lipid and glucose levels, fasting blood samples were drawn after 12 hours of fasting, followed by a two-hour oral glucose tolerance test (OGTT). In a physical examination, waist circumference was measured midway between the lower rib margin and the iliac crest. To calculate BMI, height was measured to the nearest 0.1 cm and weight was measured in light clothing. Blood pressure was measured with a mercury sphygmomanometer twice in a sitting position after a minimum of 15 minutes of acclimatization.

**Pain Variables**

Musculoskeletal pain was captured by asking “Do you have pain?” with response categories: 1) not at all; 2)
I have pain rarely or temporarily; and 3) I have pain frequently or continuously in the joints, back, neck, or multisite. The prevalence of pain was based on the answer category 3 (frequent or continuous pain in the joints, back, neck, or multisite). Severity of pain was formed based on the three pain-related questions. Participants were asked if they had 1) pain or stiffness in joints; 2) neck pain; or 3) back pain during the last four weeks. Answers (0, have not had; 1, have had mild; 2, have had difficult; 3, have had severe) were summed in a total score (scale ranging between 0 and 9), which accounted for severity of pain.

**Mental Health Variables**

The severity of depressive symptoms was assessed with the BDI, where the items are summed into a total score that ranges from 0 to 63; higher numbers indicate greater depressive symptoms [14]. Depression diagnoses were confirmed from all those participants with a BDI score of 10 or higher, and subgroups of melancholic and atypical depression were determined with a diagnostic interview—the Mini-International Neuropsychiatric Interview (MINI)—out of those with depression diagnosis [15]. A melancholic and atypical status was defined according to DSM-IV criteria from the MINI.

**Statistical Analysis**

The data are presented as means with standard deviations (SDs) or as counts with percentages. The most important outcomes are given with 95% confidence intervals (CIs). Statistical comparisons were made by using the chi-square test in categorical variables, analysis of variance (ANOVA), or bootstrap-type analysis of variance (5,000 replications) in continuous variables. The bootstrap method is significantly helpful when the theoretical distribution of the test statistic is unknown or in the case of a violation of the assumptions (e.g., non-normality) [16]. When adjusting for confounding factors, analysis of covariance or a logistic regression model was applied. Logistic regression models were used to analyze the age-adjusted percentage of subjects with prevalence of pain in depression subgroups according to gender and, further, to analyze the relative odds ratios (ORs) for having pain with depression subgroups, age, gender, education, living alone, LTPA, smoking, alcohol use, and BMI as independent variables.

**Results**

The proportion of participants with musculoskeletal pain was 37% (n = 148) in the controls, 57% (n = 82) in atypical depression, and 71% (n = 189) in melancholic depression (P < 0.001, P < 0.001 after adjustment for sex and age). There were several statistically significant differences in the descriptive and clinical characteristics between controls and depression subgroups (Table 1). Controls had lower BMI and triglyceride values and, further, waist circumference among females compared with those participants in depression subgroups. However, there were no statistically significant differences between the depression subgroups, except that the BDI score was higher among those in the melancholic depression group than among those in the control and atypical depression groups (P < 0.001), and the use of antidepressive medication was more common in both depression subgroups and especially in the melancholic subgroup (P < 0.001).

A statistically significant difference in pain prevalence was found between controls, participants with atypical and with melancholic depression (Figure 1). A similar difference was found also in the severity of pain in depression subgroups compared with controls (P < 0.001). Adjusted proportion was estimated using the logistic regression model.

Logistic regression models showed that the odds ratio of the pain experience was 2.49 (1.67 to 3.72) for those with atypical depression when compared with those without depression (P < 0.001), and 4.63 (3.27 to 6.56) for those with melancholic depression when compared with those with atypical depression (P = 0.005) (Table 2). After adjusting for gender, age, education, living alone, LTPA, smoking, alcohol use, and BMI, the odds ratios of pain with atypical (2.35 [1.56 to 3.56]) and melancholic depression (4.38 [3.04 to 6.33]) still remained.

**Discussion**

This study demonstrated clinical and biochemical differences and divergent musculoskeletal pain associations between subtypes of depression and controls. The novel finding of our population-based, geographically defined study was the highest prevalence of pain in melancholic depression, and to the best of our knowledge this is the first study in which the difference in prevalence of pain in subgroups of depression has been studied. The results of this study indicate that patients with melancholic depression had a higher prevalence of pain and also higher severity of pain than did those with atypical depression. In addition, odds for pain remained strong after adjusting for several potential mediators.

**Pain and Depression**

Slightly over one-third of those without depression had musculoskeletal pain, while the amount was twice as high among those with melancholic depression. In turn, more than half of the participants with atypical depression had musculoskeletal pain. The prevalence of pain in nondepressed participants seems to be consistent with previous studies. Demyttenaere et al. (2006) showed pain prevalence to be 29% in nondepressed and 50% in depressed participants. Some of the differences in socio-demographic factors found in this study might explain part of this divergence. The finding of a higher proportion of females among the depressed participants in this study—which has been clearly revealed...
in earlier literature as well [17]—might be one of the explaining factors, as females generally have more pain symptoms than males [18,19]. It is well known that higher age is a strong predictor of pain [20,21]. However, in our study, the mean age of both depression subgroups was lower than that of the controls. Additionally, the lower educational level related to melancholic depression in our study has been shown to increase the likelihood of the existence of pain [17,22].

Cardiometabolic Risk Factors in Depression and Pain

In accordance with previous studies [8], the present results demonstrated higher BMI and triglyceride values among the depressed participants than among the controls. This finding might be somewhat related to the finding of deleterious life habits among those with depression, as a sedentary lifestyle can lead to obesity. But, on the other hand, weight gain can be a consequence of inactivity due to pain, as well, as evidence suggests that chronic pain is associated with several cardiometabolic risk factors like dyslipidemia, high BMI, and greater waist circumference [23,24]. However, the logistic regression models in this study showed that depression—in particular melancholic depression—is associated with musculoskeletal pain even after adjusting for socio-demographic factors, lifestyle, and BMI. Thus, other explanatory factors have to be highlighted.

Melancholic and Atypical Depression: Mechanisms Behind

The novel finding of the observed association between melancholic depression and high prevalence of musculoskeletal pain may to some extent reveal the

### Table 1

Demographic and clinical data according to melancholic and atypical depression subgroups

<table>
<thead>
<tr>
<th></th>
<th>Control N = 401</th>
<th>Atypical depression N = 144</th>
<th>Melancholic depression N = 269</th>
<th>P values [contrast]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>238 (59)</td>
<td>101 (70)</td>
<td>194 (72)</td>
<td>&lt;0.001 [c/a, c/m]</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>53 (10)</td>
<td>51 (10)</td>
<td>51 (10)</td>
<td>0.009 [c/a, c/m]</td>
</tr>
<tr>
<td>Basic education, N (%)</td>
<td>95 (24)</td>
<td>43 (30)</td>
<td>94 (35)</td>
<td>0.006 [c/m]</td>
</tr>
<tr>
<td>Living alone, N (%)</td>
<td>90 (22)</td>
<td>53 (37)</td>
<td>116 (43)</td>
<td>&lt;0.001 [c/a, c/m]</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.7 (4.5)</td>
<td>28.0 (5.1)</td>
<td>27.9 (6.0)</td>
<td>0.002 [c/a, c/m]</td>
</tr>
<tr>
<td>Waist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>87 (13)</td>
<td>95 (15)</td>
<td>91 (15)</td>
<td>&lt;0.001 [c/a, c/m]</td>
</tr>
<tr>
<td>Male</td>
<td>97 (12)</td>
<td>97 (12)</td>
<td>101 (14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>129 (16)</td>
<td>132 (15)</td>
<td>129 (16)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 (10)</td>
<td>83 (11)</td>
<td>81 (10)</td>
<td>0.057</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean (SD)</td>
<td>5.04 (0.88)</td>
<td>5.05 (1.01)</td>
<td>5.12 (1.04)</td>
<td>0.61</td>
</tr>
<tr>
<td>HDL (mmol/L), mean (SD)</td>
<td>1.57 (0.42)</td>
<td>1.51 (0.43)</td>
<td>1.60 (0.50)</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL (mmol/L), mean (SD)</td>
<td>3.10 (0.82)</td>
<td>3.04 (0.86)</td>
<td>3.06 (0.97)</td>
<td>0.81</td>
</tr>
<tr>
<td>Triglyceride (mmol/L), mean (SD)</td>
<td>1.20 (0.66)</td>
<td>1.40 (0.89)</td>
<td>1.37 (0.83)</td>
<td>0.006 [c/a, c/m]</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 hours</td>
<td>5.67 (0.97)</td>
<td>6.01 (1.66)</td>
<td>5.83 (1.33)</td>
<td>0.029 [c/a]</td>
</tr>
<tr>
<td>2 hours</td>
<td>5.84 (1.78)</td>
<td>6.42 (2.86)</td>
<td>6.19 (2.31)</td>
<td>0.028 [c/a]</td>
</tr>
<tr>
<td>BDI, mean (SD)</td>
<td>3.2 (2.7)</td>
<td>20.3 (7.8)</td>
<td>24.9 (8.0)</td>
<td>&lt;0.001 [c/a, c/m, a/m]</td>
</tr>
<tr>
<td>Smoking, N (%)</td>
<td>66 (16)</td>
<td>38 (26)</td>
<td>90 (33)</td>
<td>&lt;0.001 [c/a, c/m]</td>
</tr>
<tr>
<td>Alcohol use, doses in week</td>
<td>0</td>
<td>63 (16)</td>
<td>31 (22)</td>
<td>59 (22)</td>
</tr>
<tr>
<td>1–9</td>
<td>286 (71)</td>
<td>90 (63)</td>
<td>172 (65)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>51 (13)</td>
<td>21 (15)</td>
<td>34 (13)</td>
<td></td>
</tr>
<tr>
<td>LTPA</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 [c/a, c/m]</td>
</tr>
<tr>
<td>Low</td>
<td>48 (12)</td>
<td>34 (24)</td>
<td>70 (26)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>176 (44)</td>
<td>62 (43)</td>
<td>104 (39)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>176 (44)</td>
<td>48 (33)</td>
<td>93 (35)</td>
<td></td>
</tr>
<tr>
<td>Use of antidepressive medication, N (%)</td>
<td>21 (5)</td>
<td>82 (57)</td>
<td>201 (75)</td>
<td>&lt;0.001 [c/a, c/m, a/m]</td>
</tr>
</tbody>
</table>

a = atypical depression; BDI = Beck Depression Inventory; BMI = body mass index; c = controls; LTPA = leisure-time physical activity; m = melancholic depression.
pathophysiological processes behind the comorbidity of pain and depression. Although melancholic and atypical depression both contribute to variability in associations with biological measures [8], some biological correlations between the subgroups of depression can be found. As melancholic depression is more like a biological condition, a common neurobiological disruption may explain the higher coexistence of melancholic depression and pain, which was not, however, investigated in this study. An overactive HPA axis has been characterized with melancholic depression [7,9], and with chronic pain as well [7], which might explain the strong relationship. On the other hand, atypical depression seems to be more strongly associated with low-grade inflammation and metabolic dysregulation levels [8,11], which our study corroborates to some extent. High fasting glucose and glucose tolerance was observed among atypical depression but not among melancholic depression in this study, which seems to be intrinsic to atypical depression rather than an artifact of high BMI, as could be assumed based on the fact that glucose values are strongly associated with BMI. Furthermore, chronic bodily pain has been shown to be related to high fasting glucose values among the adult population, and among obese women as well [25,26]. In addition, some psychological factors may play a significant role in the association between depression and pain. Living with pain might reduce functioning and social interaction, leading to feelings of loss and thus contributing to the development of depression.

**Strengths and Limitations**

There are several strengths in this study. Diagnosis of depression was based on a diagnostic interview instead of self-reported symptoms. Additionally, the data were based on an extensive and geographically representative sample of middle-aged and elderly men and women. However, due to a lower age limit of 35 years in this study, the results cannot be generalized to younger individuals with depression. While some antidepressants may have pain-relieving effect, the use of medication may have altered the prevalence of musculoskeletal pain to some extent. Moreover, due to a lower age limit of 35 years in this study, the results cannot be generalized to younger individuals with depression. While some antidepressants may have pain-relieving effect, the use of medication may have altered the prevalence of musculoskeletal pain to some extent. However, 75% of those in melancholic depression used an antidepressant, while the amount was lower among those with atypical depression. Due to the cross-sectional design of this study, the causal connection cannot be evaluated, which is one of this study’s limitations. Depressed participants were recruited from health center patients, and thus prevalence of pain may be over-represented to some extent in the depression subgroups.

**Conclusions**

The result of higher prevalence of musculoskeletal pain in melancholic depression in comparison with atypical depression in this study suggests that when studying
depressive disorders, melancholic and atypical depression should be examined separately. Different prevalence of pain might point to different etiological pathways, which is supported by the finding of a stronger association between musculoskeletal pain and melancholic depression, but it also highlights the need for further studies about the mechanisms behind the association between pain and melancholic depression. Additionally, patients with melancholic depression may require more detailed and effective treatment of depression as well, and those with atypical depression may also benefit from lifestyle counseling. The presence of pain may negatively affect recognition and treatment of depression as most often physical causes of pain are assessed instead of examining the broader biopsychosocial context.

Acknowledgments

The authors would like to thank the depression nurse case managers who took part in the practical implementation of the Finnish Depression and Metabolic Syndrome in Adults study (FDMSA): Mari Alanko, Harri Back, Timo Hannula, Anu Holopainen, Ritva Häkkänen, Katja Johansson, Eija Kinnunen, Kajja Luoma, Hannele Niemi, Hillevi Peura, Inga Pöntiö, Kirsi Rouvinen, Tiina Silvennoinen, and Pia Jauhiainen, scientific secretary of the study.

References


Musculoskeletal Pain in Depression Subgroups