Depressive Symptoms, Antidepressant Medication Use, and Insulin Resistance

The PPP-Botnia Study

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OBJECTIVE—Although insulin resistance (IR) may underlie associations between depressive symptoms and diabetes, previous findings have been contradictory. We examined whether depressive symptoms associate with IR and insulin secretion, and, additionally, whether antidepressant medication use may modulate such associations.

RESEARCH DESIGN AND METHODS—A total of 4,419 individuals underwent an oral glucose tolerance test (OGTT). Participants with previously or newly diagnosed diabetes are excluded from this sample. The homeostasis model assessment of IR (HOMA-IR) and corrected insulin response (CIR) were calculated. Depressive symptoms and antidepressant medication use were self-reported.

RESULTS—After controlling for confounding factors, depressive symptoms were associated with higher fasting and 30-min insulin during the OGTT and higher HOMA-IR but not CIR. Antidepressant medication use failed to modify these associations.

CONCLUSIONS—Depressive symptoms are associated with IR but not with changes in insulin response when corrected for IR in individuals without previously or newly diagnosed diabetes.

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Depressive symptoms are associated with type 2 diabetes (1) and the metabolic syndrome (2,3), and insulin resistance (IR) is thought to be the underlying factor. However, previous findings have been conflicting because depressive symptoms have been reported to be associated with both higher IR (4) and lower IR (5), whereas some studies have reported null associations (6,7). We examined associations of depressive symptoms with IR and insulin secretion in individuals without diabetes. We also tested if antidepressant medications modulated these associations, as one study suggests that antidepressant medication, such as the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, may improve insulin sensitivity (8). Yet, one study reported that antidepressant medications and insulin sensitivity are not related (9), whereas some studies have reported that antidepressant medications may decrease insulin sensitivity and increase the risk of type 2 diabetes (10,11).

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RESEARCH DESIGN AND METHODS

Of 5,208 randomly selected participants aged 18–75 years from the Prevalence, Prediction, and Prevention of Diabetes (PPP)-Botnia Study (2), representing the adult population residing in the Botnia region of western Finland, 206 individuals with previously diagnosed and 100 individuals with newly diagnosed diabetes were excluded, as were 36 individuals using antipsychotic medications and 5 using lithium. This resulted in a sample of 4,419 participants (2,095 men and 2,324 women) with complete data. Those with incomplete data (n = 442) were older, were more likely to be retired, and consumed less alcohol compared with those with the complete data. The participants gave their written informed consent, and the study protocol was approved by the ethics committee of Helsinki University Central Hospital, Finland.

IR and secretion

During an oral glucose tolerance test (OGTT) (75 g of glucose after a 12-h overnight fast), venous samples for plasma glucose (dehydrogenase method; HemoCue, Ängelholm, Sweden) and insulin (fluoroimmunoassay, Delphia; Perkin-Elmer Finland, Turku, Finland) were drawn at 0, 30, and 120 min ([means ± SD] 5.3 ± 0.6, 8.3 ± 1.5, and 5.2 ± 1.6 mmol/L and 6.6 ± 5.6, 59.7 ± 37.9, and 33.1 ± 35.6 μU/mL, respectively). The homeostasis model assessment of IR (HOMA-IR) (12) and corrected insulin response (CIR) (13) were calculated.

Depressive symptoms and use of antidepressant medications

Depressive symptoms were self-rated using the Short-Form 36/RAND-36 (14). We used the Mental Health Index (MHI), the Vitality Scale (VS), and their sum (20.0 ± 6.7, 9.8 ± 3.7, and 10.2 ± 3.7, respectively) to capture depressive symptoms. The rationale for calculating the sum was based on a Finnish validation study concluding that the VS items also characterize aspects of depression in a Finnish population (15). In the current study, the MHI and VS were significantly correlated (r = 0.70, $P < 0.001$).

We considered self-reported current use of SSRI/serotonin-norepinephrine reuptake inhibitor medication (n = 98), tricyclic medication (n = 36), tricyclic and SSRI/serotonin-norepinephrine reuptake inhibitor medication (n = 10), and antidepressant medications not specified (n = 3) as an indicator of the use of antidepressant medications (n = 147, 110 women and 37 men).

Statistical analyses

Logistic regression analyses, odds ratios (ORs), and 95% CIs were computed to examine associations with HOMA-IR and CIR as dichotomized (top/bottom quartiles vs. the other three). Multiple linear regression analyses examined associations with glucose and insulin during the OGTT. Associations were adjusted first for sex and age and then additionally for regular exercise (yes: >30 min intense physical activity three or more times per week resulting in breathlessness/sweating vs. no: less or no activity), alcohol consumption (grams per week), current smoking status (yes vs. no or former smoker), BMI (kg/m^2), occupational status (manual workers, junior clericals, senior clericals, students, and retirees), and family history of diabetes in at least one first-degree relative. Modulation by antidepressant medication use was examined by entering the interaction term "depressive symptoms × antidepressant medication use" into the regression equation followed by the main effects. Because we found no significant sex-interaction terms (all P values >0.26; data not shown), we report the results in both sexes combined.

RESULTS

The sample age averaged 48.5 ± 15.4 years, 52.6% were women, and the average BMI was 26.3 ± 4.3 kg/m^2. A total of 54.7% of subjects reported regular exercise; 14.7% reported smoking; 46.4 and 28.1% reported a weekly alcohol consumption of 12–60 g and >60 g, respectively; and 28.6 reported having a family history of diabetes. In addition, 17.4% of subjects were of senior clerical, 30.2% were of junior clerical, and 26.1% were of manual worker occupational status, whereas 21.8% were retired and 4.6% were students.

Depressive symptoms were associated with increased odds for antidepressant medication use (total score: OR 2.64 [95% CI 2.22–3.13]; MHI: 2.42 [2.05–2.85]; and VS: 2.52 [2.10–3.02] per each SD unit increase in symptoms).

Antidepressant medication use was significantly associated with a higher odds for belonging to the top quartile of HOMA-IR but not with CIR (Table 1) or with insulin and glucose values during an OGTT (Supplementary Table A1) in models adjusted for confounding and mediating factors.

Although depressive symptoms were significantly associated with higher odds for belonging to the top quartile of HOMA-IR (Table 1), with higher fasting and 30-min insulin (Supplementary Table A1), they were not associated with CIR (Table 1) in models adjusted for confounding and mediating factors.

Analyses addressing interactions between antidepressant medication use and depressive symptoms showed that depressive symptoms were associated with higher 120-min glucose in participants using antidepressants (total score: 5.6% increase [95% CI 0.8–10.5], P = 0.02, and VS: 5.9% [0.08–11.0], P = 0.02, per SD unit increase in symptoms). In contrast, the associations were not significant in those who were not using antidepressants (P values >0.24) (P values <0.05 for antidepressant medication use × depressive symptoms − interactions). There were no additional significant interactions.

CONCLUSIONS

The current study examined the associations between depressive symptoms and IR and insulin secretion in a large, population-based sample of adult men and women without previously or newly diagnosed diabetes. Depressive symptoms were associated with higher odds for being insulin resistant but not with changes in insulin response when corrected for IR (CIR). These associations were not modulated by antidepressant medication use. Taken together, our findings suggest that depressive symptoms are associated with IR, even in individuals without diabetes, and that the use of antidepressant medications may neither augment nor explain these effects. Although our study was cross-sectional, constituting

Table 1—*Associations between depressive symptoms, the use of antidepressant medications, and HOMA-IR and CIR as indices of IR and secretion*

	HOMA-IR*	*P*	CIR†	*P*
Depression				
Antidepressant medication (no vs. yes)‡				
Sex- and age-adjusted model	1.82 (1.29–2.58)	0.001	1.21 (0.83–1.76)	0.320
Full model§	1.66 (1.11–2.48)	0.014	1.36 (0.92–2.01)	0.121
Depressive symptoms				
Total score (SD units)				
Sex- and age-adjusted model	1.17 (1.09–1.25)	0.001	0.99 (0.92–1.06)	0.681
Full model§	1.12 (1.03–1.21)	0.007	0.98 (0.91–1.06)	0.679
MHI (SD units)				
Sex- and age-adjusted model	1.11 (1.04–1.19)	0.003	0.99 (0.93–1.07)	0.848
Diagnosed diabetes excluded§	1.09 (1.01–1.18)	0.038	0.99 (0.92–1.07)	0.810
VS (SD units)				
Sex- and age-adjusted model	1.20 (1.12–1.29)	0.001	0.98 (0.91–1.05)	0.496
Full model§	1.13 (1.04–1.22)	0.004	0.98 (0.91–1.06)	0.580

Data are OR (95% CI). *HOMA-IR was dichotomized contrasting the highest quartile (referent) with the other three quartiles, n = 1,105 vs. 3,314. †CIR was dichotomized contrasting the lowest quartile (referent) with the other three quartiles, n = 1,104 vs. 3,315. ‡Number of individuals using antidepressant medications is 147. §Full model refers to adjustments for age, sex, regular exercise (yes: >30 min intense physical activity three or more times per week resulting in breathlessness/sweating vs. no: less or no activity), alcohol consumption (grams per week), current smoking status (yes vs. no or former smoker), BMI (kg/m^2), occupational status (manual workers, junior clericals, senior clericals, students, and retirees), and family history of diabetes in at least one first-degree relative.

an obvious and major study limitation, the fact that the associations characterized participants without diagnosed diabetes suggests that depressive symptoms should be regarded as a clinically important risk factor for both metabolic syndrome and type 2 diabetes. Thus, the detection and prevention of depressive symptoms are of importance in everyday clinical practice.

Additional study limitations include a lack of opportunity to address potential mechanisms underlying the reported associations, generalizability from our findings to non-whites, a lack of information regarding psychiatric disorders and/or the duration of antidepressant medication use, and the low prevalence of antidepressant medication use, which may have attenuated our ability to detect stronger associations, thereby limiting generalizability from the findings to less healthy populations.

In conclusion, depressive symptoms are associated with IR but not with changes in insulin response when corrected for IR in individuals without diabetes. Thus, the detection of individuals with higher depressive symptoms may benefit programs of early prevention of type 2 diabetes and related disorders.

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A.-J.P. researched data, contributed to discussion, and wrote the manuscript. K.R., T.T., J.G.E., L.G., and B.I. researched data, contributed to discussion, and reviewed and edited the manuscript.

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