Metabolic Syndrome Predisposes to Depressive Symptoms: A Population-Based 7-Year Follow-Up Study

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Objective: Previous cross-sectional studies have suggested that patients with depression have a high risk for metabolic syndrome. As there is a paucity of data concerning the temporal relationship of depression and metabolic syndrome, we decided to evaluate the risk for developing depressive symptoms in patients with metabolic syndrome in a population-based follow-up study.

Method: The prevalence of depressive symptoms and metabolic syndrome at baseline in 1998 and at 7-year follow-up in 2004/2005 was studied in a large, middle-aged, population-based sample collected from Central Finland. Depressive symptoms were measured with the Beck Depression Inventory, with a cutoff score of 10 points. Metabolic syndrome was assessed using the modified National Cholesterol Education Program Adult Treatment Panel III criteria.

Results: Nondepressed women and men with metabolic syndrome at baseline were twice as likely to have depressive symptoms at follow-up (OR = 2.2, 95% CI = 1.1 to 4.5 for women; OR = 2.2, 95% CI = 0.8 to 5.9 for men) as compared with the nondepressed cohort members without metabolic syndrome at baseline.

Conclusions: The higher rate of depressive symptoms in the subgroup with metabolic syndrome suggests that the metabolic syndrome may be an important predisposing factor for the development of depression. Effective prevention and treatment of metabolic syndrome could also be important for the prevention of depression.

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Metabolic syndrome is a cluster of risk factors for type 2 diabetes and cardiovascular diseases.[1] In previous years, different diagnostic criteria have been suggested for metabolic syndrome.[2,3] The U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) criteria proposed easily applicable cutoff limits for waist circumference, lipid levels, blood glucose, and blood pressure,[4] and these have been widely used in both clinical practice and epidemiologic studies. The recent modification of the criteria[1] uses a lower cutoff point for glucose and takes the antihypertensive, antidiabetic, or antidyslipidemic medication into account in the criteria. In previous cross-sectional studies, metabolic syndrome has been observed to have a higher prevalence in depressed than in nondepressed subgroups.[4–6] The only existing long-term study focusing on the interaction between metabolic syndrome and depression showed a reciprocal association between anger and anxiety and metabolic syndrome in an exclusively female study population.[7] These previous study results thus suggest that depression and metabolic syndrome are related. There is, however, a paucity of data concerning the temporal relationship between metabolic syndrome and depression in men and women despite the high prevalence of depression (the 12-month prevalence of any depressive disorder

TAKE-HOME POINTS

- Patients with depression have a high risk for developing metabolic syndrome.
- The metabolic syndrome may be an important predisposing factor for the development of depression.
- Effective prevention and treatment of the metabolic syndrome could aid in the prevention of depression.

is 6.5% in the Finnish population,[8] and the prevalence of metabolic syndrome was 38% in a recent Finnish study [J. Miettola, M.D.; L. K. Niskanen, M.D.; H. Viinamäki, M.D.; et al., manuscript submitted]).

Obesity is also a risk factor for diabetes and cardiovascular diseases, and it may be used as a proxy to metabolic syndrome. In the population-based cohort follow-up studies of Roberts et al.[9] and Herva et al.,[10] obese individuals had a 2-fold risk of developing depression. In addition, alleviation of depression in association with surgically induced weight loss suggests that being overweight may induce or exacerbate depression.[11] The results are, however, equivocal, as in a cross-sectional study, a higher body mass index (BMI) was associated with lower depression scores.[12] Besides the association of weight with depression, the presence of diabetes has been reported to double the odds of comorbid depression.[13] Arterial hypertension is also associated with depression,[14] and it has been suggested that depression lowers high-density lipoprotein (HDL) cholesterol[15] and elevates triglyceride levels.[16]

The aim of our study was to evaluate the putative risk of developing depressive symptoms in patients having metabolic syndrome at baseline in a large population-based study sample. In addition, the sex differences in risk levels were scrutinized.

METHOD

Subjects

The study was conducted in the Pieksämäki area of South Savo, Finland, to determine the prevalence of risk factors and long-term course of metabolic syndrome between 1998 and 2005. All inhabitants born in the years 1942, 1947, 1952, 1957, and 1962 in Pieksämäki (N = 1294) were invited for a comprehensive health checkup during 1998. The addition of the last group, those born in 1962, extends the age spectrum of the sample as compared with the previously reported 1993 sampling.[17] The participation rate was 923/1294, i.e., 71.3%. The study was carried out in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent, and the study protocol was approved by the Ethics Committee of the Kuopio University Hospital and the University of Kuopio. In 2004/2005, 688 (74.5%) of the participants from 1998 took part in a follow-up visit.

Procedures

At the 1998 and 2004/2005 study visits, all participants filled out a standard questionnaire containing questions about use of medications, including antidepressants. In addition, data were collected on smoking habits, use of alcohol (number of drinks per week), and physical activity (number of > 30-minute exercise sessions per week). The depressive symptoms were evaluated with the Beck Depression Inventory (BDI),[18] for which a score of 10 points was used as a cutoff point for depressive symptomatology. Fasting blood samples, including the glucose and lipid levels, were drawn between 8 a.m. and 11 a.m. after 12 hours of fasting. The physical examination included weight, height, waist circumference, and blood pressure taken at the same study visit. Height and weight were measured in light clothing to the nearest 0.5 cm and 0.1 kg, respectively. The waist circumference was measured to the nearest 1.0 cm at the midpoint between the lateral iliac crest and the lowest rib. Trained nurses measured blood pressure twice with a mercury sphygmomanometer, with subjects in sitting position after a 15-minute rest. In the evaluation of metabolic syndrome, we used the modified NCEP ATP-III criteria with the 100 mg/dL blood glucose cutoff point.[1] Originally, NCEP defined metabolic syndrome as having 3 or more of the following criteria: (1) fasting serum glucose of 110 mg/dL or higher, (2) serum triglycerides of 150 mg/dL or higher, (3) serum HDL cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women, (4) blood pressure of 130/85 mm Hg or higher, and (5) waist circumference greater than 102 cm in men or greater than 88 cm in women.[4] Later, the glucose limit was changed to 100 mg/dL.[1]

Statistical Methods

Logistic regression models were used to examine the relationship between the metabolic syndrome and depressive symptoms by gender. In multivariate analyses, the following possible confounding factors were used: age, BMI, education, marital status, smoking, physical activity, alcohol consumption, and use of antidepressants. To examine the relationship between each compo-

Table 1. Study Population Characteristics at 2004/2005 Follow-Up

Characteristic	Women		Men	
	With Depressive Symptoms (N = 48)	Nondepressed (N = 288)	With Depressive Symptoms (N = 29)	Nondepressed (N = 239)
Age, mean (SD), y	52.3 (6.5)	53.8 (6.0)	52.8 (6.3)	55.1 (5.0)
Current use of antidepressant, %	14.5	2.8	17.2	0.8
Basic education, %				
Elementary school	56.3	45.8	69.0	57.7
Middle school	27.1	28.5	17.2	28.9
College	16.6	25.7	13.8	13.4
Marital status, %				
Single	12.5	6.9	6.9	8.4
Married/cohabiting	81.3	84.4	93.1	86.2
Divorced/widowed	6.2	8.7	NA	5.4
Current smoker, %	16.7	22.2	20.7	28.0
Physically active, %	33.3	26.7	24.1	31.0
Alcohol use, %	4.2	7.6	24.1	28.9
Waist circumference, mean (SD), cm	82.5 (11.4)	86.3 (12.2)	93.6 (10.1)	96.9 (10.3)
BMI, mean (SD)	27.7 (3.8)	26.9 (5.1)	28.2 (4.7)	27.1 (3.8)
Weight, mean (SD), kg	74.1 (11.8)	71.8 (13.8)	88.5 (14.3)	85.1 (13.5)
Systolic BP, mean (SD), mm Hg	132.6 (18.0)	131.5 (19.0)	137.6 (16.5)	137.6 (15.3)
Diastolic BP, mean (SD), mm Hg	79.4 (9.5)	78.3 (9.0)	83.3 (10.0)	85.1 (6.8)
Hypertension (systolic BP ≥ 130 and/or diastolic BP ≥ 85), %	68.8	70.2	89.7	77.8
Triglycerides, mean (SD), mg/dL	1.2 (0.6)	1.4 (0.7)	1.6 (0.8)	2.2 (1.8)
HDL cholesterol, mean (SD), mg/dL	1.5 (0.3)	1.4 (0.3)	1.3 (0.3)	1.3 (0.4)
Glucose, mean (SD), mg/dL	5.6 (0.6)	5.7 (0.6)	5.9 (1.0)	6.0 (0.6)
Metabolic syndrome, %	41.7	24.9	51.7	31.4

Abbreviations: BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, NA = not applicable.

nent of the metabolic syndrome and depressive symptoms, we performed multiple multivariate logistic regression analyses with depressive symptoms as the dependent variable and each component of metabolic syndrome as the independent variable, adjusting for the above-mentioned confounding factors. All statistical testing was performed at a 5% level of significance, using SAS for Windows, version 9.1 (SAS Institute Inc., Cary, N.C.).

RESULTS

The key variables for the 604 members of the 1998 initial study population not depressed at baseline and participating in the 7-year follow-up in 2004/2005 are shown in Table 1. The 84 excluded participants who had depressive symptoms at baseline in 1998 did not differ from the study group with regard to age, demographic status, or life habits. In addition, there were no differences in the prevalence of metabolic syndrome in 1998 in various subgroups (22.6% and 27.3% for women and men, respectively, with depressive symptoms; 27.2% and 33.6%, respectively, for nondepressed women and men). When participants were subdivided according to their BMI, the 2005 prevalence rates of depressive symptoms did not differ between the subgroups (the prevalence of depressive symptoms was 14% in the subgroup with a BMI less than 25, 22% in the group with a BMI of 25–30, 22% in the group with a BMI of 31–40, and 20% in the group with a BMI over 40; $p = .09$). At the 2005 visit, 38 individuals in the study population had type 2 diabetes (6%), and cardiovascular diseases were encountered in 34 individuals (5%).

After adjusting for age, BMI, education, physical activity, smoking, alcohol use, marital status, and the use of antidepressants, the logistic regression analysis showed a 2-fold risk for the nondepressed cohort members with metabolic syndrome at baseline to have depressive symptoms at follow-up (OR = 2.1, 95% CI = 1.2 to 3.8). Of the individual criteria for metabolic syndrome, the lipid levels had the most substantial contribution to the odds ratio in our study population (Table 2).

DISCUSSION

The novel finding in our study is the observation of a 2-fold prevalence of depressive symptoms, as defined by a score of 10 points or more on the BDI scale, after a 7-year follow-up in initially nondepressed men and women with metabolic syndrome at baseline. The predisposing influence of metabolic syndrome on depressive symptoms in a large, prospective, middle-aged, population-based study sample is, in this study, reported for the first time in both sexes, as the only previously published long-term study reported increased rates of anger and anxiety, but not depression, after 7 years' follow-up in the Healthy Women Study population with metabolic syndrome at baseline.[7] Besides including only women, the study population of Räikkönen et al.[7] differed from ours in that the prevalence of metabolic syndrome was

Table 2. Logistic Regression Models for Each Component of the Metabolic Syndrome Adjusted for Age, Education, Smoking, Physical Activity, BMI, Alcohol Use, Marital Status, and Use of Antidepressant

	Women		Men	
Component	Prevalence of Depressive Symptoms, %	OR (95% CI)	Prevalence of Depressive Symptoms, %	OR (95% CI)
Blood pressure				
Normal	15.8	…	7.4	…
High	13.0	0.6 (0.3 to 1.2)	12.3	2.8 (0.8 to 9.8)
Triglycerides				
Normal	12.7	…	8.0	…
High	21.7	1.7 (0.8 to 3.9)	16.1	2.1 (0.9 to 4.9)
HDL cholesterol				
Normal	12.1	…	9.8	…
Low	19.6	2.0 (1.0 to 3.9)	16.3	2.5 (0.9 to 6.6)
Glucose				
Normal	12.2	…	12.2	…
High	16.7	1.1 (0.6 to 2.1)	9.7	0.6 (0.2 to 1.7)
Waist circumference				
Normal	12.9	…	10.3	…
Large	18.4	1.4 (0.7 to 2.8)	13.0	1.3 (0.5 to 3.5)
Metabolic syndrome				
No	11.4	…	7.8	…
Yes	21.7	2.2 (1.1 to 4.5)	16.7	2.2 (0.8 to 5.9)

Abbreviations: BMI = body mass index, HDL = high-density lipoprotein.
Symbol: … = reference.

low (5.9% at baseline), thus restricting the variance of the key variables. The prevalence of metabolic syndrome in the general population has been rising worldwide,[19,20] and the same has been true also in Finland.[21] The observed prevalence of metabolic syndrome in patients with depression has ranged from 8% to 34%.[5–7] Our prevalence figures at 1998 and during follow-up are quite similar to those observed in recent Finnish studies by Heiskanen et al.[6] and Miettola et al. (J. Miettola, M.D.; L. K. Niskanen, M.D.; H. Viinamäki, M.D.; et al., manuscript submitted). Taking into account the rapidly increasing rates of metabolic syndrome, our result suggests that metabolic syndrome may be an important nonconventional risk factor for depression.

Multiple factors appear to predispose to metabolic syndrome, e.g., genetic deficits in insulin signaling pathways, adipose tissue disorders, physical inactivity, mitochondrial dysfunction, individual genetic variability, advancing age, and certain drugs. The metabolic syndrome is a useful clinical concept, as it identifies patients who have twice the risk for atherosclerotic cardiovascular disease and 5 times the risk for diabetes.[22] In addition, insulin resistance, the key feature in metabolic syndrome, has been suggested to be a metabolic link between depressive disorder and atherosclerotic vascular diseases.[23] Biological mechanisms that may explain the association between metabolic syndrome and depression include cytokine-mediated inflammation, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and the effects of insulin resistance on neurotransmission. Proinflammatory cytokines play an important role in metabolic disorders,[24] and they may induce malfunctioning of the serotonergic neurotransmission in the brain, resulting in depression.[25] Insulin resistance may also contribute to the diminished serotonergic activity in the central nervous system.[8] Cortisol excess is often associated with insulin resistance and may result in a state resembling HPA-axis hyperactivity also encountered in depression.[26] The psychological factors may also be important, as metabolic syndrome is associated with a sedentary lifestyle and a negative perception of self. These factors may also be important contributing factors for the development of depression.

There are some limitations in this study. The identification of depressive symptoms was based on a self-report scale, not a diagnostic interview, which is a limitation. Although not initially constructed as a diagnostic scale, the BDI (with a cutoff score of 10 points) has been shown to be a useful instrument for detecting depressive disorders in follow-ups in various adult populations (e.g., see references 27 and 28). Second, the 7-year follow-up period is lengthy, and some depressive episodes may have occurred unnoticed. Thus, the reported results reflect differences at the 7-year follow-up, not in the incidence rates. Third, our genetically homogenous study population may hamper the generalizability of the results.

The higher rate of development of depressive symptoms in both women and men with metabolic syndrome at baseline suggests that the metabolic syndrome may be an important predisposing factor for the development of depression. Thus, effective prevention and treatment of metabolic syndrome could also be important for the prevention of depression. In the future, new long-term studies are needed to elucidate the long-term course and prognosis, proper treatment, and specific symptom picture of depression related to metabolic syndrome.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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