UNIVERSITY OF TURKU

This is a self-archived – parallel published version of an original article. This version may differ from the original in pagination and typographic details. When using please cite the original.

AUTHOR Susanna Kuneinen, Risto J. Kaaja, Tero J. Vahlberg, Päivi E. Korhonen

TITLE Metabolic syndrome is not associated with erectile dysfunction in apparently healthy men

YEAR 2020

DOI https://doi.org/10.1016/j.pcd.2019.12.008.

VERSION Author's accepted manuscript

COPYRIGHT Lisence: CC BY NC ND

CITATION Susanna Kuneinen, Risto J. Kaaja, Tero J. Vahlberg, Päivi E. Korhonen Metabolic syndrome is not associated with erectile dysfunction in apparently healthy men,Primary Care Diabetes, Volume 14, Issue 5, 2020, Pages 460-463, ISSN 1751-9918, https://doi.org/10.1016/j.pcd.2019.12.008. (http://www.sciencedirect.com/science/article/pii/S1751991819303882)

Metabolic syndrome is not associated with erectile dysfunction in apparently healthy men

Author names and affiliations:

Kuneinen, Susanna M. [1, 2]

Kaaja, Risto J.[3]

Vahlberg, Tero J.[4]

Korhonen, Päivi E.[1, 2]

[1] Central Satakunta Health Federation of Municipalities, Harjavalta, Finland, Satakunta Hospital District, Pori, Finland

[2] Department of General Practice, Turku University and Turku University Hospital, Turku, Finland

[3] Institute of Clinical Medicine, Internal Medicine, University of Turku and Turku University Hospital, Finland

[4] Department of Biostatistics, University of Turku, Turku, Finland

Corresponding author:
Susanna Kuneinen, MD
Address: Department of General Practice, 20014 Turku University, Finland
Telephone number: +358456507393
E-mail address: smkune@utu.fi

Abstract

Aims:
To investigate whether metabolic syndrome (MetS) is associated with erectile dysfunction (ED) among apparently healthy men when depressive symptoms and serum testosterone levels are taken into account.

Methods:
A study population of 549 men at risk for cardiovascular disease or type 2 diabetes was drawn from the participants of a population survey, the Harmonica Project. MetS was diagnosed with the United States National Cholesterol Education Program Third Adult Treatment Panel (ATPIII) 2005 definition, the International Diabetes Federation (IDF) 2005 definition and the Harmonization 2009 definition. ED was evaluated by the International Index of Erectile Function (IIEF-5) questionnaire. Depressive symptoms were assessed with Beck's Depression Inventory (BDI).

Results:
Of the 549 men (mean age 58.4 ± 6.7 years), 56.5 % reported ED. The prevalence of MetS was 48.6%, 35.5%, and 50.6% according to the IDF, the ATPIII, and the Harmonization criteria, respectively. We found no difference in the prevalence of ED between men with or without MetS. In a multivariate analysis, age, presence of depressive symptoms and lower education were significant predictors of ED.

Conclusions:
The prevalence of ED is quite high even in apparently healthy men. Depressive symptoms are a critical component to consider in men suffering from ED.

Keywords: metabolic syndrome, erectile dysfunction, depressive symptoms, testosterone

Introduction

Both erectile dysfunction (ED) and metabolic syndrome (MetS) are common conditions in the general population, and strongly associated with cardiovascular disease (CVD) [1] and diabetes mellitus [2].

ED has a multifactorial etiology including lifestyle, neural, vascular, hormonal and psychological factors [3]. The prevalence of ED increases with age [4] and it is estimated to affect 150 million men globally [5]. ED shares many risk factors with CVD including age, obesity, smoking, hypertension, diabetes and hypercholesterolemia [5]. ED has been reported to precede clinical CVD by 2-5 years [5].

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors in which central obesity and insulin resistance are essential elements [6]. MetS increases the risk of atherosclerotic CVD, type 2 diabetes (T2D) and overall mortality. It is estimated that one-quarter to one-third of adults meet MetS criteria in multiple ethnic backgrounds [6].

Thus, the risk factors for ED and defining MetS overlap and are strongly associated with CVD. Individuals with a diagnosis of MetS are a heterogeneous group who may have quite mild metabolic disturbance or at the other extreme, complicated T2D. To our knowledge, only one study has investigated the association of ED and MetS in apparently healthy men. [7] In this study of obese men without chronic diseases, neither MetS nor total testosterone was associated with ED. However, psychogenic factors were not evaluated although a recent meta-analysis suggests that depression substantially increases the risk of ED [8]. In the present study, we also aimed at taking into account depressive symptoms and serum free testosterone as contributing factors to ED. We hypothesized that depressive mood is a stronger predictor of ED than MetS in men at risk but without manifested T2D or CVD.

Materials and methods

Study population

The study population was drawn from the participants of a population survey, the Harmonica Project (Harjavalta Risk Monitoring for Cardiovascular Disease), which was carried out in the rural town of Harjavalta (7 646 inhabitants) in south-western Finland from August 2005 to October 2006. The survey was primarily planned to assist clinicians in estimating their patients' total cardiovascular risk in order to prevent cardiovascular diseases (CVDs).

A two-stage screening strategy was used: a cardiovascular risk factor survey and a type 2 diabetes risk assessment form (Finnish Diabetes Risk Score, FINDRISC, available from www.diabetes.fi/english) were mailed to all home-dwelling inhabitants between 45 and 70 years of age (n = 2856). In the risk factor survey, subjects were asked for their waist circumference measured at the level of the umbilicus, their latest blood pressure, the use of antihypertensive medication, any history of gestational diabetes or hypertension, and any history of coronary artery disease, myocardial infarction or stroke as regards their parents or siblings.
Participation rate was 73% (2085/2856). Individuals with the above mentioned risk factors or at least 12 points in the FINDRISC (n = 1756) were invited for laboratory tests (2-hour oral glucose tolerance test, plasma lipids), a generic health survey and a physical examination performed by a trained nurse. Of the risk subjects, 774 were males, of whom 636 (82%) attended the clinical examination. Participation and all the tests included were free of charge for the participants. For the analyses described here, we excluded patients with previously diagnosed diabetes, CVD or renal disease; this yielded an analytic cohort of 549 male subjects.

Measurements and definitions

Subjects completed self-administrated questionnaires at the clinic before the clinical examination was performed. The 5-item version of the International Index of Erectile Function (IIEF-5) was used to define erectile dysfunction as an IIEF-score <22 [9].

Depressive symptoms were assessed by Beck's Depression Inventory (BDI)[10] and the presence of depressive symptoms was defined as a BDI score ≥ 10[11].

The questionnaires also measured the participants' education level, cohabiting status, current smoking, alcohol consumption (Alcohol Use Disorders Identification Test, AUDIT [12]), and leisure-time physical activity (LTPA) level. An AUDIT score of ≥8 was regarded as the cut-off for harmful alcohol use [12]. LTPA was classified as follows: high: LTPA four or more times a week for at least 30 min at a time ; moderate: LTPA two to three times a week for at least 30 min at a time ; low: LTPA a maximum of once a week for at least 30 min.

MetS was diagnosed according to the criteria of the United States National Cholesterol Education Program Third Adult Treatment Panel (ATP III) 2005 definition [13] the International Diabetes Federation (IDF) 2005 definition [14], and the Harmonization 2009 definition [15] (Table 1).

Table 1. Diagnostic criteria of the metabolic syndrome

Clinical measure	**ATP III** any three of the following	**IDF** WC + any two of the following	**Harmonization** any three of the following
Waist circumference	>102 cm	≥94 cm	≥94 cm
Blood pressure	≥130/85 mmHg or drug therapy	≥130/85 mmHg or drug therapy	≥130/85 mmHg or drug therapy
Fasting plasma glucose	≥5.6 mmol/l * or drug therapy	≥5.6 mmol/l or type 2 diabetes	≥5.6 mmol/l or type 2 diabetes
Triglycerides	≥1.7 mmol/l or drug therapy	≥1.7 mmol/l or drug therapy	≥1.7 mmol/l or drug therapy
HDL-C	<1.03 mmol/l or drug therapy	<1.03 mmol/l or drug therapy	<1.03 mmol/l or drug therapy

Abbreviations: ATP III, the United States National Cholesterol Education Program Third Adult Treatment Panel; IDF, the International Diabetes Federation; HDL, high-density lipoprotein cholesterol

The laboratory tests were determined from blood samples which were obtained after at least 12 hours of fasting. Total cholesterol, HDL cholesterol and triglycerides were measured enzymatically (Olympus® AU640, Japan). LDL cholesterol was calculated according to the Friedewald's formula. A 2-hour oral glucose tolerance test (OGTT) was performed by measuring fasting plasma glucose and a 2-hour plasma glucose after ingestion of a glucose load of 75 g anhydrous glucose dissolved in water. Glucose values were measured from capillary whole blood with HemoCue® Glucose 201+ system (Ängelholm, Sweden). The analyzer converts the result from capillary whole blood to plasma glucose values (conversion factor 1.11). Total serum testosterone levels were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an API 2000 triple quadrupole mass spectrometer (PE Sciex) [16]. SHBG was measured with the immunochemiluminescence method (Abbott Architect i2000SR analyzer) and free testosterone was calculated according to the Anderson's formula: Serum testosterone (nmol/l) x (2.28 – 1.38 x log (SHBG (nmol/l) /10) x 10.

Blood pressure was measured by a trained nurse with a mercury sphygmomanometer with subjects in a sitting posture, after resting for at least five minutes with the cuff placed on the arm. For obese arms a larger cuff was used. Systolic and diastolic blood pressures were defined according to the Korotkoff sounds I and V. For each subject the mean of two readings taken at intervals of at least two minutes was used in the study.

Height and weight were measured with the subjects in a standing position without shoes and outer garments. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.1 kg. Digital scales (Seca® 861, Germany) were used, and their calibration was monitored regularly. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters squared).
Waist circumference was measured at the level midway between the lower rib margin and the iliac crest, rounded to the nearest 0.1 cm. The subjects were asked to breathe out gently at the time of the measurement, and the tape was held firmly in a horizontal position.

Ethical approval

The study protocol and consent forms were reviewed and approved by the ethics committee of Satakunta hospital district. All participants provided written informed consent for the project and subsequent medical research.

Statistical analysis

The data is presented as the means with standard deviations (SD) or as frequencies with percentages. The comparisons between the groups for erectile function were done by using the Wilcoxon test, the two sample t-test or chi-square test.
Predictors significantly associated with erectile dysfunction in univariate analysis were included in a multivariate logistic regression model. Results are expressed using odds ratios (OD) with 95% confidence intervals (CI). P-values lower than 0.05 were considered statistically significant. Statistical analysis was made with the SAS System for Windows, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

We evaluated 549 male subjects (mean age 58.4 ± 6.7 years) at risk for CVD or diabetes but without a manifested disease. According to the IIEF-5 questionnaire, 310 (56.5%) of them had ED. The prevalence of MetS was 267/549 (48.6%), 195/549 (35.5%), and 278/549 (50.6%) according to the IDF, the ATPIII, and the Harmonization criteria, respectively. Taking into account all these criteria, there was no difference in the prevalence of ED between men with or without MetS. (Table 2)

Table 2 also shows that the men with ED were older, less educated, and had more often depressive symptoms defined as BDI ≥10 than those with normal erectile function. The men with ED had lower serum testosterone and free testosterone levels, higher 2-hour glucose values, and higher systolic blood pressure. The use of beta blockers was more common in the men with ED than in the men with normal erectile function.

Predictors with a p-value <0.2 in the univariate analysis were included in the multivariate logistic regression model. Serum free testosterone level, instead of serum testosterone, was selected because of its lower p-value. Age [odds ratio (OR) 1.11 (95% CI 1.05 –

1.16)], presence of depressive symptoms [OR 3.54 (95% CI 1.41 – 8.91)] and lower education (primary vs. high school) [OR 3.63 (95% CI 1.39-9.47)] were significant predictors of ED. (Table 3)

Table 2. Baseline characteristics of males (n=549) with or without erectile dysfunction (ED)

	ED present N= 310	**No ED N= 239**	**P-value**
Age, years, mean (SD)	58.5 (6.2)	54.1 (6.0)	<0.0001
Cohabiting, n (%	262 (84%)	213 (89%)	0.12
Education level			<0.0001
Primary school	232 (78%)	136 (59%)	
Secondary school	43 (15%)	58 (25%)	
High school	21 (7%)	35 (15%)	
Leisure-time physical activity			0.45
Low	113 (37%)	90 (38%)	
Moderate	93 (31%)	82 (35%)	
High	97 (32%)	65 (27%)	
Current smoker, n (%)	189 (63%)	139 (59%)	0.36
Harmful alcohol use (AUDIT ≥8), n (%)	119 (42%)	94 (42%)	0.92
Depressive symptoms (BDI ≥10), n (%)	55 (19%)	19 (9%)	0.0011
Body mass index, kg/m^2, mean (SD)	28.2 (3.9)	28.2 (4.0)	0.90
Waist circumference, cm, mean (SD)	100.1 (10.8)	99.5 (9.8)	0.46
Systolic blood pressure, mmHg (SD)	142 (20)	138 (16)	0.014
Diastolic blood pressure, mmHg (SD)	88 (12)	87 (9)	0.27
Fasting glucose, mmol/l, mean (SD)	5.71 (0.87)	5.64 (0.91)	0.34
2h-glucose, mmol/l, mean (SD)	7.46 (2.39)	6.85 (2.18)	0.002
Total cholesterol, mmol/l, mean (SD)	5.26 (0.94)	5.20 (0.90)	0.43
HDL-cholesterol, mmol/l, mean (SD)	1.41 (0.36)	1.44 (0.39)	0.37
LDL-cholesterol, mmol/l, mean (SD)	3.20 (0.84)	3.12 (0.82)	0.23
Triglycerides, mmol/l, mean (SD)	1.45 (0.78)	1.42 (0.73)	0.67
Metabolic syndrome IDF criteria, n (%)	147 (48%)	120 (50%)	0.61
Metabolic syndrome ATP III criteria, n (%)	113 (37%)	82 (34%)	0.53
Metabolic syndrome Harmonization criteria, n (%)	152 (50%)	126 (53%)	0.47
Serum testosterone, nmol/l, mean (SD)	14.56 (4.86) (N=165)	15.79 (5.05) (N=112)	0.048
Serum free testosterone, pmol/l, mean (SD)	210.4 (54.9) (N=165)	228.3 (54.5) (N=112)	0.0081
SHBG, nmol/l mean (SD)	39.78 (14.29) (N=165)	39.33 (13.56) (N=112)	0.79
Use of betablockers, n (%)	52 (17%)	25 (10%)	0.035
Use of diuretics, n (%)	9 (3%)	2 (0.8%)	0.12

Abbreviations: ED, erectile dysfunction; HDL, high-density lipoprotein; LDL, low-density lipoprotein, AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck's Depression Inventory.

Table 3. Factors predicting erectile dysfunction in multivariate logistic regression analysis, N=243

Variables	Odds ratio (95% CI)	P-value
Age	1.11 (1.05-1.16)	<0.0001
Education - Primary vs high school - Secondary vs high school	 3.63 (1.39-9.47) 2.59 (0.87-7.72)	 0.0086 0.087
Cohabiting status	1.50 (0.62-3.67)	0.37
BDI-score ≥10	3.54 (1.41-8.91)	0.0072
2h-glucose	1.03 (0.90-1.18)	0.65
Systolic blood pressure	0.99 (0.98-1.18)	0.52
Serum free testosterone	0.996 (0.990-1.001)	0.14
Use of betablockers	0.84 (0.38-1.89)	0.68
Use of diuretics	1.91 (0.25-14.68)	0.53

Discussion

Our main finding is that depressive symptoms, age and education level – but not MetS or testosterone level – had a significant effect on the prevalence of ED in men without manifested T2D or CVD.

Our results are in line with the study of Gatti et al. [7]. They investigated 50 obese non-diabetic men and found that the prevalence of ED is independent of the presence of MetS or any single factor of MetS. In addition, the total testosterone level was not associated with MetS. In our study hypogonadism (low serum testosterone) was not present in the men with ED as their mean serum testosterone levels were similar to the controls. Thus, the hypogonadism of our study population was not probably severe enough to indicate associations with ED. We broaden these results to a typical primary care population and highlight the importance of depressive symptoms. In the present study, the presence of depressive symptoms was a significant predictor of ED with odd's ratio of 3.54. Consistent with our results, previous studies show strong evidence that depressive symptoms and ED are closely associated [8], and a bidirectional relationship has been postulated [17]. The meta-analysis of Liu et al. reported that exposure to depression increased the risk of ED by 39% and in addition, exposure to ED was found to increase the risk of depression by 192%. [8]

The interplay between depressive symptoms and ED is likely to be mediated through both biological and behavioral mechanisms [18]. The behavioral model suggests that men with depression are usually less confident and more self-conscious and engage in negative thought which lead to compromised erectile function [18]. In the biological model, it is postulated that depression affects the hypotalamic-pituitary-adrenocortical axis, leading to excess catecholamine production which leads to poor cavernosal muscle relaxation and ED [19].

The vast majority of previous studies indicate a relationship between ED and MetS. Nevertheless, in the present study, the connection was not found. In the comprehensive systematic review and meta-analysis by Besiroglu et al. [20] patients with MetS had a 2.6-fold increased risk of having ED. However, in the majority of the incorporated studies, the study populations included patients with manifested chronic diseases such as CVD or

T2D, or the mean blood glucose levels of the MetS-populations were at a diabetic level. These factors indicate more severe metabolic disturbances than in our study population. Furthermore, the presence of depressive symptoms were not taken into account as contributing factors in the aforementioned studies. These differences largely explain the opposing results in comparison with our study.

Strengths and limitations

The major limitation of our study is the cross-sectional design which prevents us from making any causal interpretations. We assessed depressive symptoms with a questionnaire, not with a clinical interview. Our study was conducted with participants who were white men aged 45-70 years, thus the generability to other populations is limited. However, our study population is typical in a primary health care setting. The clinical measurements were made by trained medical staff and we were able to take into account many different demographic and lifestyle associated factors.

In conclusion, depressive symptoms – but not MetS without manifested T2D – are strongly associated with ED in apparently healthy men. This is important information for clinicians treating men who suffer from ED.

Funding

This research was supported by the State Provincial Office of Western Finland and the Central Satakunta Health Federation of Municipalities.

Declarations of interest: none.

References

[1] WHO Fact Sheet Cardiovascular diseases (CVDs), Https://www.who.int/news-Room/fact-Sheets/detail/cardiovascular-Diseases-(Cvds). Visited: February 24, 2019. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

[2] WHO Fact Sheet Diabetes mellitus, Https://www.who.int/news-Room/fact-Sheets/detail/diabetes. Visited: February 24 2019. https://www.who.int/news-room/fact-sheets/detail/diabetes.

[3] T.F. Lue, Erectile dysfunction, N. Engl. J. Med. 342 (2000) 1802–1813.

[4] C.B. Johannes, A.B. Araujo, H.A. Feldman et al. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study, J Urol (2000) 460–463.

[5] O.A. Orimoloye, D.I. Feldman, M.J. Blaha, Erectile dysfunction links to cardiovascular disease—defining the clinical value, Trends Cardiovasc. Med. (2019) 1–8.

[6] S.L. Samson, A.J. Garber, Metabolic Syndrome, Endocrinol. Metab. Clin. NA. 43 (2014) 1–23.

[7] A. Gatti, E. Mandosi, M. Fallarino et al. Metabolic syndrome and erectile dysfunction among obese non-diabetic subjects, J Endocrinol Invest. (2009) 542–545.

[8] Q. Liu, Y. Zhang, J. Wang, et al. Erectile Dysfunction and Depression : A Systematic Review and Meta-Analysis, J. Sex. Med. 15 (2018) 1073–1082.

[9] R. Rosen, J. Lipsky, J. Cappelleri et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction, Int. J. Impot. Res. 11 (1999) 319–326.

[10] E.G. Beck AT, Rush AJ, Shaw BF, Cognitive therapy of depression. Guilford Press, New York 1979.

[11] H. Koponen, J. Jokelainen, S. Keinänen-Kiukaanniemi, M. Vanhala, Depressive symptoms and 10-year risk for cardiovascular morbidity and mortality, World J. Biol. Psychiatry. 11 (2010) 834–839.

[12] T.F. Babor, J.R. de la Fuente, J. Saunders, AUDIT: the alcohol use disorders identification test: guidelines for use in primary healthcare. WHO/MNH/DAT 89.4, Geneva: World Health Organization; 1989.

[13] S.M. Grundy, J.I. Cleeman, S.R. Daniels et al. Diagnosis and management of the

metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary., Cardiol. Rev. 13 (2005) 322–7.

[14] K.G.M.M. Alberti, P. Zimmet, J. Shaw for the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome - a new worldwide definition, Lancet. 366 (2005) 1059–1062.

[15] K.G.M.M. Albreti, R.H. Eckel, S.M. Grundy et al. Harmonizing the Metabolic Syndrome, Circulation. 120 (2009) 1640–1645.

[16] U. Turpeinen, S. Linko, O. Itkonen, E. Hämäläinen, Determination of testosterone in serum by liquid chromatography-tandem mass spectrometry, Scand. J. Clin. Lab. Investig. 68 (2008) 50–57.

[17] R. Shiri, J. Koskimäki, T.L.J. Tammela et al. Bidirectional Relationship Between Depression and Erectile Dysfunction, J. Urol. 177 (2007) 669–673.

[18] A. Makhlouf, A. Kparker, C.S. Niederberger, Depression and Erectile Dysfunction, Urol. Clin. North Am. 34 (2007) 565–574.

[19] I. Goldstein, The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction, Am. J. Cardiol. 86 (2000) 41–45.

[20] H. Besiroglu, A. Otunctemur, E. Ozbek, The Relationship Between Metabolic Syndrome, Its Components, and Erectile Dysfunction: A Systematic Review and a Meta-Analysis of Observational Studies, J. Sex. Med. 12 (2015) 1309–1318.