Cardiovascular Risk Factors and Events in Fibromyalgia Patients

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ABSTRACT  Background: Several studies have shown that patients with fibromyalgia present with neuroendocrine, inflammatory, and coagulation features linked to cardiovascular disease development. However, the exact profile of cardiovascular risk factors and events in fibromyalgia remains to be defined.

Objectives: To compare the profile of cardiovascular risk factors and events between fibromyalgia outpatients and the general population in Italy.

Methods: Cardiovascular risk factors and events in fibromyalgia females were collected using the criteria adopted in the CUORE Project.

Results: The study comprised 62 female fibromyalgia patients and 4093 female controls from 35 to 75 years of age. The prevalence of hypertension, diabetes, atrial fibrillation, transient ischemic attack, and cardiovascular total burden was significantly higher in fibromyalgia females than in the general Italian population. No difference was found in blood fasting glucose, triglycerides, total and fractionated cholesterol levels, body mass index, and metabolic syndrome (MetS). The MetS rate was underestimated for methodological aspects.

Conclusions: Fibromyalgia is associated with an increased cardiovascular burden, probably through a specific risk factor profile.

KEY WORDS: body mass index (BMI), cardiovascular events, cardiovascular risk factors, fibromyalgia, metabolic syndrome (MetS)

For editorial see page 637

Fibromyalgia is a syndrome of unknown origin, which is characterized by widespread musculoskeletal pain, fatigue, insomnia, depression, and cognitive impairment complaints. Fatigue, insomnia, and depression can favor physical inactivity that, associated with the overweight predisposition [1], may promote the development of metabolic syndrome (MetS). MetS is defined as a combination of glucose intolerance, obesity, hypertension, and atherogenic dyslipidemia; thus, representing a risk factor for cardiovascular disease development [2]. However, the occurrence of MetS in fibromyalgia has been poorly studied.

Although some traditional cardiovascular risk factors may be overrepresented in fibromyalgia populations, recent studies have suggested that fibromyalgia may be considered as an independent cardiovascular risk factor. Specifically, some fibromyalgia neuroendocrine [3] and inflammatory [4] alterations were linked to cardiovascular disease development. Moreover, features associated with a prothrombotic state, which are known to increase the risk of thrombosis-related cardiovascular disease, were commonly observed in fibromyalgia [5]. These findings point to several mechanisms by which fibromyalgia may be associated with an enhanced cardiovascular burden. However, the exact profile of cardiovascular risk factors in fibromyalgia remains to be defined. Furthermore, whether overrepresented traditional cardiovascular risk factors translate into a higher burden of cardiovascular disease in fibromyalgia is still to be established.

In this study, we assessed the prevalence of traditional cardiovascular risk factors and events in fibromyalgia patients compared to those observed in the general population.

PATIENTS AND METHODS

STUDY PARTICIPANTS

In this cross-sectional study, female outpatients fulfilling the modified 2010 American College of Rheumatology (ACR) criteria for fibromyalgia [6] were consecutively included in the study, after giving written informed consent. The study was conducted according to the Declaration of Helsinki and exempt from ethics committee approval because the participants underwent routine hospital clinical assessment.

Following the age limits of the Italian comparative sample, only fibromyalgia patients between 35 and 74 years of age were considered. Exclusion criteria were co-morbid severe medical conditions (e.g., cancer, infections, and neurological and autoimmune diseases).
The Italian population sample included female participants recruited in the 2008–2012 cohort of the CUORE project, a state-funded project aimed at estimating the impact of cardiovascular diseases in the general Italian population [7].

**CLINICAL METHODOLOGY**

Cardiovascular risk factors were collected using the criteria adopted in the CUORE project to allow a valid comparison [7]. Specifically, blood pressure was measured after 5 minutes of rest in a sitting position. Hypertension was defined as the mean of two consecutive blood pressure values of systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg values or if the patient was under pharmacological treatment. Next, a blood sampling was performed to assay total and high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting glucose. Low-density lipoprotein (LDL) cholesterol was calculated (Friedewald formula). Patients with blood glucose ≥ 120 mg/dl or under antidiabetic treatment were considered diabetic.

The MetS was defined according to the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria [8], which included the presence of at least three of the following criteria: fasting hyperglycemia (≥ 110 mg/dl), high blood pressure (≥ 130/85 mmHg), high triglycerides (≥ 150 mg/dl), low HDL cholesterol (< 50 mg/dl), and central obesity (waist circumference ≥ 88 cm).

In this study, waist circumference was replaced by body mass index (BMI), as a BMI value of ≥ 28.8 kg/m² is equivalent to central obesity [9].

The following cardiovascular events were considered in the assessment of cardiovascular disease prevalence: ischemic heart disease, stroke, transient ischemic attack, heart failure, or peripheral arterial disease.

**STATISTICAL ANALYSIS**

Fibromyalgia patients and the general population were compared on continuous factors and categorical variables. The differences between females with fibromyalgia and the general population of females who were tested were determined with a one-sample z-test. P-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 26 (SPSS, IBM Corp, Armonk, NY, USA).

**RESULTS**

**STUDY DEMOGRAPHICS**

The study population included a total of 62 female patients with fibromyalgia (mean age 53.7 ± 10.7 years) and 4093 female controls. The mean duration of fibromyalgia symptoms in patients was 9.95 ± 10 years.

**CARDIOVASCULAR RISK FACTORS AND EVENTS**

Cardiovascular risk factors and events in the study populations were summarized in Table 1. The fibromyalgia patients did not significantly differ from the Italian population in fasting glucose,

<table>
<thead>
<tr>
<th>Table 1. Cardiovascular risk factors and events in the fibromyalgia population vs. the general population</th>
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<tbody>
<tr>
<td><strong>Number</strong></td>
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<tr>
<td><strong>Traditional cardiovascular risk factors</strong></td>
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<tr>
<td>Systolic, mmHg</td>
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<tr>
<td>Diastolic, mmHg</td>
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<tr>
<td>Anti-hypertensive treatment users, n (%)</td>
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<tr>
<td>Prevalence of hypertension, n (%)</td>
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<tr>
<td>Total cholesterol mg/dl</td>
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<tr>
<td>HDL-cholesterol mg/dl</td>
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<tr>
<td>Calculated LDL-cholesterol mg/dl</td>
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<tr>
<td>Triglyceridemia, mg/dl</td>
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<tr>
<td>Lipid-lowering treatment users, n (%)</td>
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<tr>
<td>Blood fasting glucose, mg/dl</td>
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<tr>
<td>Prevalence of diabetes, n (%)</td>
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<tr>
<td>Prevalence of acute myocardial infarction</td>
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<tr>
<td>Prevalence of transient ischemic attacks, n (%)</td>
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<td>Total cardiovascular events, n (%)</td>
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*statistically significant at P < 0.050

HDL = high-density lipoprotein, LDL = low-density lipoprotein.
DISCUSSION

In this study, we compared the profiles of cardiovascular risk factors and event rates in fibromyalgia patients with those of the general Italian population, as reported by the CUORE Project. The results demonstrated an increased prevalence of certain traditional cardiovascular risk factors and an enhanced cardiovascular burden in fibromyalgia. Although some risk factors were increased in prevalence, this profile did not lead to a higher MetS frequency in fibromyalgia patients, probably suggesting a specific risk profile in this condition.

Our results align with previous studies showing a high rate of hypertension and diabetes in fibromyalgia patients [10]. The presence of lower systolic blood pressure in our fibromyalgia sample may be related to the significantly higher percentage of fibromyalgia female patients undergoing antihypertensive treatment, thus suggesting an increased prevalence of hypertension. Biochemical parameters (fasting glucose, triglycerides, total and fractionated cholesterol levels) did not differ between the two populations. While some previous studies reported higher fasting glucose and lipids levels in fibromyalgia patients [4], others did not find differences compared to healthy controls [11,12]. Similarly, unlike previous studies, our study did not show a higher prevalence of MetS compared to the general population.

However, using the NCEP ATP III MetS definition to conform to the CUORE project, patients with normal blood pressure or lipid profile due to a successful treatment did not meet hypertension or hypertriglyceridemia criteria. The significantly high rates of fibromyalgia patients treated with antihypertensive and/or lipid-lowering medications compared to the general population may have underestimated MetS cases in the fibromyalgia sample.

The finding of the elevated rate of atrial fibrillation in fibromyalgia females agrees with a recent study [13], which showed that some electrocardiographic parameters predicting atrial and/or ventricular arrhythmias were more frequent in fibromyalgia females than in healthy controls. However, no fibromyalgia patients presented with myocardial infarction or stroke in our sample. These results conflict with a Taiwanese study showing high coronary heart disease and stroke rates in fibromyalgia popula-

tions [14], probably due to different genetic and environmental factors.

The global cardiovascular burden was strongly increased in fibromyalgia, whereas not all traditional cardiovascular risk factors or events were consistently overrepresented. How this specific profile of cardiovascular risk factors translates into real cardiovascular risk remains to be established and should be the object of future studies. Unravelling the associations between this cardiovascular risk profile and clinical features is warranted.

The study limitations included the small number of fibromyalgia females recruited and the failure to assess the lifestyle factors and depression, a common fibromyalgia co-morbidity known to be associated with high rates of cardiovascular disease [15].

CONCLUSIONS

There is an enhanced cardiovascular burden and a specific cardiovascular risk factors profile in fibromyalgia patients, which seems to be independent of MetS.

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References


There is no greater fallacy than the belief that aims and purposes are one thing, while methods and tactics are another.

Emma Goldman (1869-1940), Russian-born anarchist, political activist, and writer

**Capsule**

**Seeing Parkinson’s disease**

Parkinson’s disease is characterized by the misfolding and aggregation of α-synuclein protein in the brain. Radioactive tracers that bind to pathological protein aggregates have enabled the study of other neurodegenerative disorders with positron emission tomography (PET); however, a method of imaging α-synuclein aggregates in vivo has been lacking. Xiang et al. synthesized a new radioactive tracer, [18F]-F0502B, that binds misfolded α-synuclein in vitro and enables PET imaging of α-synuclein aggregates in the brains of nonhuman primates. [18F]-F0502B was specific for α-synuclein and did not bind substantially to aggregates of tau or amyloid-β, which are characteristic of Alzheimer’s disease but are also commonly found in individuals with Parkinson’s disease.

*Cell 2023; 84 (16): 3350*

Eitan Israel

**Capsule**

**CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer’s disease**

Aggregated insoluble tau is one of two defining features of Alzheimer’s disease. Because clinical symptoms are strongly correlated with tau aggregates, drug development and clinical diagnosis need cost-effective and accessible specific fluid biomarkers of tau aggregates; however, recent studies have suggested that the fluid biomarkers currently available cannot specifically track tau aggregates. Horige and colleagues showed that the microtubule-binding region (MTBR) of tau containing the residue 243 (MTBR-tau243) is a new cerebrospinal fluid (CSF) biomarker specific for insoluble tau aggregates and compared it to multiple other phosphorylated tau measures (p-tau181, p-tau205, p-tau17 and p-tau231) in two independent cohorts (BioFINDER-2, n=448; and Knight Alzheimer Disease Research Center, n=219). MTBR-tau243 was most strongly associated with tau-positron emission tomography (PET) and cognition, whereas showing the lowest association with amyloid-PET. In combination with p-tau205, MTBR-tau243 explained most of the total variance in tau-PET burden (0.58 ≤ R² ≤ 0.75) and the performance in predicting cognitive measures (0.34 ≤ R² ≤ 0.48) approached that of tau-PET (0.44 ≤ R² ≤ 0.52). MTBR-tau243 levels longitudinally increased with insoluble tau aggregates, unlike CSF p-tau species. CSF MTBR-tau243 is a specific biomarker of tau aggregate pathology, which may be utilized in interventional trials and in the diagnosis of patients. Based on these findings, the authors proposed to revise the A/T(N) criteria to include MTBR-tau243 as representing insoluble tau aggregates (‘T’).

*Nature Med 2023; 29: 1956*

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