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Metabolic syndrome in women with chronic pain

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Abstract

Fibromyalgia is a prevalent syndrome characterized by chronic pain, fatigue, and insomnia. Patients with fibromyalgia commonly have an elevated body mass index and are physically inactive, 2 major risk factors for metabolic syndrome. Yet little is known about the relationship between chronic pain conditions and metabolic disturbances. Our study evaluated the risk for, and neuroendocrine correlates of, metabolic syndrome in this patient population. Women with fibromyalgia (n = 109) were compared with control healthy women (n = 46), all recruited from the community. Metabolic syndrome was identified by using criteria from the Adult Treatment Panel III with glycosylated hemoglobin concentrations substituted for serum glucose. Catecholamine and cortisol levels were determined from 12-hour overnight urine collections. Women with fibromyalgia were 5.56 times more likely than healthy controls to have metabolic syndrome (95% confidence interval, 1.25-24.74). Fibromyalgia was associated with larger waist circumference (P = .04), higher glycosylated hemoglobin (P = .01) and serum triglyceride (P < .001) levels, and higher systolic (P = .003) and diastolic (P = .002) blood pressure. Total and low-density lipoprotein cholesterol were also significantly higher in women with fibromyalgia (P = .001 and .02, respectively), although high-density lipoprotein cholesterol was in the reference range. These associations were not accounted for by age or body mass index. Meeting criteria for more metabolic syndrome components was related to higher urinary norepinephrine (NE)/epinephrine and NE/cortisol ratios (P < .001 and P = .009, respectively). Women with chronic pain from fibromyalgia are at an increased risk for metabolic syndrome, which may be associated with relatively elevated NE levels in conjunction with relatively reduced epinephrine and cortisol secretion.

1. Introduction

Fibromyalgia is a chronic pain syndrome of unknown etiology. Of the more than 3.7 million Americans estimated to be affected by fibromyalgia [1], 85% to 92% are women [1,2], most of whom are sedentary [3] and overweight or obese [4]. Fibromyalgia is further characterized by fatigue, sleep disturbances, and disability [2], which may contribute to the habitual physical inactivity. Prevalence rates of metabolic syndrome are known to increase with increasing body mass index (BMI) and physical inactivity [5]. Sleep deprivation has also been linked to the development of the metabolic syndrome [6]. Because these clinical features intrinsic to fibromyalgia are also associated with the metabolic syndrome, it seemed possible that patients with fibromyalgia might be at greater risk for metabolic disturbances. However, little is known about the relationship between fibromyalgia or other chronic pain conditions and metabolic syndrome.

Recent reports by the Adult Treatment Panel III (ATP III) providing diagnostic and management guidelines have focused clinical attention on the importance of identifying patients with metabolic syndrome because it indicates risk for cardiovascular disease, diabetes mellitus, and all-cause mortality [5,7]. As defined by the ATP III, metabolic syndrome is composed of central obesity, dyslipidemia, hypertension, and glucose intolerance [8]. Both obesity and physical inactivity predispose to the development of insulin resistance, which, in turn, appears to be a driving force in the development of dyslipidemia and hypertension [9]. Pain accompanying physical trauma, such as surgery [10], as well as acute experimental pain [11], also has been found to induce insulin resistance. Furthermore, chronic widespread pain has been diagnosed in 62% of diabetic women and labeled as fibromyalgia in 17% to 23% [12-14]. Yet, the prevalence of diabetes mellitus in patients with chronic pain is not known.

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To our knowledge, there are no previous systematic studies of metabolic syndrome in chronic pain patients.

Although the diagnosis of fibromyalgia has been controversial, the American College of Rheumatology 1990 diagnostic criteria settled on both a history of chronic widespread musculoskeletal pain and pain on digital palpation of 11 or more of 18 well-defined tender points [2], facilitating confirmation by physical examination for both clinical and research purposes. More recently, fibromyalgia has been conceptualized as the extreme end on a continuum of chronic widespread pain accompanied by fatigue and distress [15]. Therefore, women with fibromyalgia constitute an ideal chronic pain population in which to study the prevalence and phenomenology of metabolic disturbances.

The neuroendocrine concomitants of fibromyalgia also overlap with those of metabolic syndrome. Both fibromyalgia and metabolic syndrome have been characterized by sympathetic nervous system (SNS) activation as evidenced by lowered heart rate variability [16-18] and elevated norepinephrine (NE) levels, although this finding is not always demonstrable in peripheral samples [19-22]. Both experimentally induced and naturally occurring states of hyperinsulinemia, an indicator of insulin resistance, provoke SNS activity as measured by elevations in plasma and urinary NE concentrations [23,24]. Furthermore, increased urinary NE concentration in the context of reduced urinary epinephrine (Epi) has been seen in abdominal obesity [25,26] as well as the metabolic syndrome [25]. These observations raised the question of whether the NE-to-Epi balance might also be skewed in fibromyalgia. High NE is thought to contribute to hypertension, whereas low Epi is associated with dyslipidemia [24-26]. Finally, both metabolic syndrome and fibromyalgia have been associated with perturbations of the hypothalamic-pituitary-adrenal (HPA) axis, but the literature is mixed, with reports of mild hypocortisolism, hypercortisolism, and a flattening of the cortisol diurnal curve [16,21,27-30]. Our analyses thus focused on whether SNS activation in conjunction with adrenal dysregulation contributed to both fibromyalgia [31] and metabolic syndrome [32,33].

This study evaluated the hypothesis that there would be a higher prevalence of metabolic syndrome in patients with fibromyalgia. Neuroendocrine and clinical features of fibromyalgia including measures of urinary catecholamines and cortisol, pain, fatigue, sleep quality, and perceived stress were tested for association with metabolic syndrome.

2. Methods

2.1. Participants

Metabolic, anthropometric, neuroendocrine, and clinical measures were available for 109 women with fibromyalgia and 46 control healthy women, who had participated in 2 phases of the University of Wisconsin Mind/Body Center's study of fibromyalgia. Phase 1 had been designed to assess clinical and physiological phenomena in women with fibromyalgia compared with age-matched healthy controls [34]. Phase 2 participants had been assessed at a baseline evaluation for a trial of mindfulness-based stress reduction for fibromyalgia. Only baseline data were included in this analysis to preclude potential effects of the subsequent intervention. Inclusion and exclusion criteria were identical, except that the upper age range for phase 2 women was extended from 45 to 49 years. All participants were recruited from the community by advertisements in a local newspaper. Written informed consent was obtained from all participants and the studies were approved by the institutional review board.

Eligibility criteria for the fibromyalgia cohort were female sex because most fibromyalgia patients are women and fibromyalgia may manifest differently in men [35]; age 21 to 45 years for phase 1, which assessed menstrual cycle influences and found no differences in tender point counts or other measures of pain across the menstrual cycle [34], and 21 to 49 years for phase 2; a diagnosis of fibromyalgia made by a physician; and meeting 1990 American College of Rheumatology criteria for fibromyalgia on our evaluation, which included tender point examination. The healthy control women were 21 to 45 years old and free of any chronic physical illness. Exclusion criteria for all subjects included medical conditions causing other pain or chronic symptoms, uncontrolled endocrine disorders (e.g., diabetes, polycystic ovary syndrome), autoimmune or other rheumatologic conditions, malignancy, substance abuse, severe psychiatric disorders (e.g., schizophrenia, psychotic disorders, active suicidality), severe physical impairment (ie, unable to maintain employment or education), and use of steroid, narcotic, or antipsychotic medications.

2.2. Fibromyalgia-related symptoms

Pain was measured by tender point count and by a 10-cm Visual Analogue Scale (VAS) labeled as 0 = no pain and 10 = pain as bad as it could be. The revised Piper Fatigue Scale (PFS) [36] was used to measure the extent to which fatigue interfered with activities (eg, work, school, socializing, sexual activity) and current feelings of energy (eg, wakefulness, energy level, clarity of thinking). Sleep quality was measured using the Pittsburgh Sleep Quality Index, a 19-item self-rated inventory, which has been well validated in clinical populations [37]. As a gauge of the individual's perception of the stressfulness of her life over the last week, the Perceived Stress Scale, a psychometrically sound self-report questionnaire, was administered [38]. PFS was administered only in study 1 and Pittsburgh Sleep Quality Index only in study 2.

2.3. Metabolic measures

Phlebotomy for blood analyses and anthropometric measurements was performed at the University of Wisconsin-Madison General Clinical Research Center (GCRC) by GCRC nurses who verified that participants had no cold or flu symptoms and had eaten only a light, low-fat breakfast.

With the participant standing, waist circumference was measured at the narrowest point between the ribs and ileac crest and hip circumference at the maximal buttocks. Sitting systolic and diastolic blood pressure was measured after 5 minutes of rest.

The ATP III clinical definition of metabolic syndrome requires meeting 3 or more of the following criteria: (1) abdominal obesity (waist circumference >88 cm in women); (2) high triglyceride level (≥150 mg/dL); (3) low high-density lipoprotein (HDL) cholesterol level (<50 mg/dL in women); (4) high blood pressure (≥130/85 mm Hg); and (5) high fasting plasma glucose level (≥110 mg/dL) [8]. Use of antihypertensive medication was counted as meeting criteria for high blood pressure. Our studies measured serum lipids and glycosylated hemoglobin (A_{1c}) but not glucose. A_{1c} provides a measure of glucose levels over several months' time. An A_{1c} level of 5.5% or higher defined the top quartile in the Women's Health Study cohort of middle-aged women [39]. The top quartile for A_{1c} and other biological parameters has been used to define those at greater health risk [40] and, consistent with the intent of the ATP III definition, the Women's Health Study data showed that an A_{1c} level greater than 5.5% was associated with a significantly elevated cardiovascular risk [39]. Therefore, A_{1c} with a criterion of 5.5% or more was substituted for the fifth metabolic syndrome criterion.

In addition, because the ATP III report identifies low-density lipoprotein (LDL) cholesterol as the primary target of hypercholesterolemia treatment and recommends a complete lipoprotein profile (total, LDL and HDL cholesterol, and triglycerides) as the preferred screening test for all adults older than 20 years, we included LDL and total cholesterol levels in our analyses [8]. Similarly, we included commonly used clinical anthropometric measures that are outside of the metabolic syndrome diagnostic criteria.

2.4. Neuroendocrine measures

Participants completed an overnight urine collection that began 12 hours before their wake-up time. The overnight collection protocol minimizes potentially confounding effects of physical activity because most of the collection period is spent at home and in bed. Urinary catecholamines (NE and Epi) and free cortisol concentrations were determined by high-pressure liquid chromatography. NE, Epi, and cortisol results are reported as micrograms per gram creatinine to adjust for body size and partial voids, providing integrated measures of basal SNS, adrenal medullary, and HPA axis activity, respectively.

2.5. Statistical analysis

The Mantel-Haenszel statistic was used to test the association between metabolic syndrome and fibromyalgia status while controlling for age, which was stratified as 21 to 29, 30 to 39, or 40 to 49 years [41]. All other statistics were conducted with SPSS for Macintosh, version 10.0 (SPSS, Chicago, IL). An odds ratio was calculated to determine the risk of having metabolic syndrome in women with fibromyalgia as compared with healthy controls. Further differences between the healthy control and fibromyalgia groups were analyzed by using analysis of variance (ANOVA) with age as a covariate. Relationships between metabolic variables and clinical or neuroendocrine variables were analyzed by using Pearson correlation coefficients. The metabolic syndrome component (MSC) sum denotes the number of MSCs for which ATP III criteria were met (range, 0 to 5). *P* values less than .05 (two tailed) were considered significant. Any variables with skewed distribution were logarithmically transformed, including NE, Epi, cortisol, and NE/Epi and NE/cortisol ratios. For ease of interpretation, untransformed mean values are presented in tables.

3. Results

Table 1 shows the clinical and demographic characteristics of the fibromyalgia and healthy control groups. In comparison with healthy women, the fibromyalgia group had higher perceived stress, fatigue-related inactivity, mean tender point counts, VAS pain scores, and lower current energy (all *P*s < .001). Mean waist-to-hip ratio was significantly larger in fibromyalgia than healthy control women ($P = .008$), although weight ($P = .22$) and BMI ($P = .15$) did not differ significantly between the 2 groups. All ANOVAs comparing fibromyalgia participants to healthy controls were age controlled.

3.1. Metabolic syndrome in fibromyalgia

There was a significant association between the occurrence of fibromyalgia and metabolic syndrome ($\chi^2_{MH} = 3.84$,

Table 1
Demographic and clinical characteristics of fibromyalgia and healthy control participants

	Healthy controls (n = 46)	Fibromyalgia patients (n = 109)	P^a
Age (y)	32.9 ± 7.5	36.9 ± 8.0	.005
Education, N (%)			.06
College graduate	29 (63)	85 (78)	
Graduate school	17 (37)	24 (22)	
Income, N (%)			.61
<$20 000	14 (30)	29 (27)	
$20 000-29 000	6 (13)	19 (17)	
>$30 000	26 (57)	61 (56)	
Tender point count	1.8 ± 2.8	14.8 ± 2.3	<.001
Pain VAS	0.5 ± 0.9	5.4 ± 2.3	<.001
Fatigue[b]	2.3 ± 2.1	7.2 ± 2.4	<.001
Energy[b]	7.1 ± 1.5	4.5 ± 1.9	<.001
Perceived stress[c]	12.8 ± 7.1	21.1 ± 7.4	<.001
Waist-to-hip ratio	0.74 ± 0.05	0.77 ± 0.06	.008
Weight (lb)	155 ± 29	166 ± 41	.22
BMI (kg/m^2)	25.3 ± 4.	27.5 ± 6.5	.15

Except where indicated otherwise, values are mean ± SD.

[a] *P* values are from age-controlled ANOVAs comparing fibromyalgia and control groups.

[b] Fatigue and energy were measured with subscales of the PFS.

[c] Perceived stress was measured with the Perceived Stress Scale.

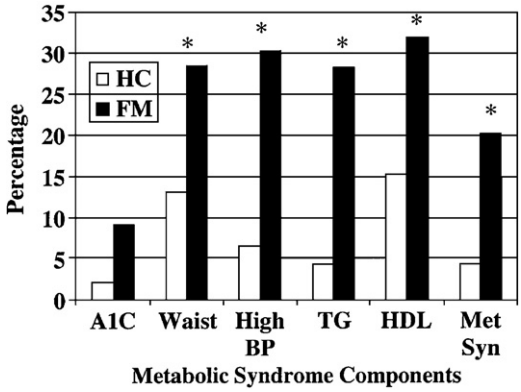

Fig. 1. Percentages of fibromyalgia (FM) and healthy control (HC) groups with metabolic syndrome and components. *In χ^2 analyses, proportion of fibromyalgia group with each component was significantly greater than that of controls (Ps < .05), with the exception of A_{1c} (P = .12). BP indicates blood pressure; TG, triglycerides; HDL, HDL cholesterol; Met Syn, metabolic syndrome.

P = .047). Women with fibromyalgia were 5.56 times as likely as healthy controls to have metabolic syndrome (95% confidence interval, 1.25-24.74) (Fig. 1). Women in the fibromyalgia group met criteria for a significantly greater number of MSCs (ie, had higher MSC sum scores) (P = .001), as illustrated in Fig. 1. Because the number of healthy controls meeting criteria for metabolic syndrome and for some components was less than 5, confirmatory, age-controlled analyses using continuous metabolic variables were performed. Fibromyalgia status was associated with significantly higher mean levels of each component, that is, for A_{1c} (P = .01), waist (P = .04), systolic (P = .003) and diastolic (P = .002) blood pressure, and serum triglycerides (P < .001) (Table 2). Total and LDL cholesterol (P = .001 and .02, respectively) concentrations were also significantly higher in fibromyalgia than healthy controls, although HDL cholesterol was in the reference range (P = .42). Controlling for BMI did not alter any of these findings. Only 2 healthy controls manifested metabolic syndrome, and both had BMIs greater than 33, whereas 59% of the 22 fibromyalgia participants with metabolic syndrome had BMIs less than 33.

Table 2
Metabolic and neuroendocrine measurements in women with fibromyalgia and healthy controls

	Healthy controls (n = 46)	Fibromyalgia patients (n = 109)	P[a]
Metabolic syndrome components			
A_{1c} (%)	4.8 ± .33	5.0 ± .36	.01
Waist (cm)	75 ± 10	82 ± 15	.04
Systolic blood pressure (mm Hg)	112 ± 10	120 ± 16	.003
Diastolic blood pressure (mm Hg)	65 ± 9	72 ± 12	.002
Triglycerides (mg/dL)	85 ± 32	131 ± 70	<.001
HDL cholesterol (mg/dL)	59 ± 9	57 ± 15	.42
Cholesterol levels:			
LDL cholesterol (mg/dL)	100 ± 26	115 ± 33	.02
Total cholesterol (mg/dL)	175 ± 29	201 ± 39	.001
Urinary neuroendocrine levels:			
NE/Epi	11.1 ± 7.3	13.6 ± 7.4	.03
NE/cortisol[b]	1.2 ± 0.6	1.7 ± 1.1	.03
NE[b]	22.7 ± 7.1	27.0 ± 12.5	.38
Epi[b]	2.9 ± 0.3	2.5 ± 1.6	.17
Cortisol[b]	23.9 ± 1.8	22.0 ± 15.9	.06

Values are mean ± SD.

[a] P values are from age-controlled ANOVAs comparing fibromyalgia and control groups; neuroendocrine variables were log-transformed in these analyses.

[b] Twelve-hour urinary norepinephrine, epinephrine, and cortisol are expressed in micrograms per gram creatinine.

Table 3
Pearson correlation coefficients showing association between NE ratios and metabolic risk factors in women with fibromyalgia

	NE/Epi[a] (n = 107)		NE/cortisol[a] (n = 102)	
	Pearson r	P	Pearson r	P
Waist	0.38	<.001	0.22	.03
Systolic BP	0.33	.001	0.27	.006
Diastolic BP	0.30	.002	0.26	.008
Triglycerides	0.33	<.001	0.15	.14
HDL cholesterol	−0.16	.10	0.07	.49
A_{1C}	0.06	.58	0.10	.32
MSC sum score	0.39	<.001	0.26	.009
Total cholesterol	0.23	.02	0.05	.60
Waist-to-hip ratio	0.35	<.001	0.15	.12
Weight	0.36	<.001	0.18	.07
BMI	0.36	<.001	0.21	.03

MSC sum score indicates the number of MSCs for which the threshold criterion was met (range, 0 to 5).

[a] Log-transformed neuroendocrine ratios were used in these analyses.

3.2. Clinical correlates of metabolic syndrome

Within the fibromyalgia group, neither individual differences in pain severity (tender point count and VAS scores) nor fatigue-related inactivity were significantly associated with metabolic syndrome or related variables (MSCs, MSC sum score, LDL and total cholesterol, waist-to-hip ratio, BMI, and weight). Levels of perceived stress also did not account for any metabolic variables. Energy level had an

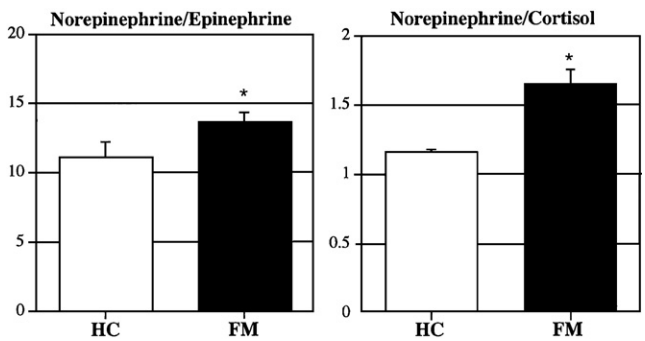

Fig. 2. Urinary NE/Epi and NE/cortisol ratios in women with fibromyalgia and healthy controls. *P = .03.

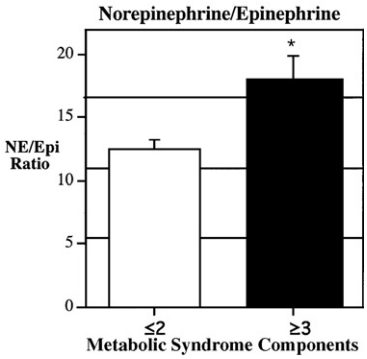

Fig. 3. Urinary NE/Epi ratio in women with fibromyalgia who have comorbid metabolic syndrome (≥3 components) (n = 21) compared with women with fibromyalgia who do not (≤2 components) (n = 86). *P = .002.

inverse relationship with A_{1c} (P = .003). Poor global sleep quality scores were associated with total and LDL cholesterol (Ps = .04).

3.3. Neuroendocrine correlates of fibromyalgia and metabolic syndrome

Both the ratios of NE/Epi and NE/cortisol proved to be more strongly associated with fibromyalgia status (Table 2) and metabolic syndrome status (Table 3) than were the individual hormones. Both urinary NE/Epi and NE/cortisol ratios (Ps = .03) were significantly higher in women with fibromyalgia (Fig. 2). Women with fibromyalgia tended to excrete less urinary cortisol, but NE and Epi levels were not significantly different (P = .06, P = .38, and P = .17, respectively). In these between-group ANOVAs, the effect of age (entered as a covariate) on neuroendocrine variables was significant only for NE (P < .001). Age was positively correlated with urinary NE (r = 0.34, P < .001).

Within the fibromyalgia group, the ratios for NE/Epi and NE/cortisol were more robustly associated with individual metabolic variables (Table 3). The NE/Epi ratio showed positive correlations with the MSC sum score, waist circumference, triglycerides, and systolic and diastolic blood pressure, as well as total cholesterol, waist-to-hip ratio, BMI, and weight. The NE/cortisol ratio was associated positively with the MSC sum score, waist circumference, systolic and diastolic blood pressure, and BMI.

When looked at individually, NE had a modest association with waist circumference, blood pressure, BMI, and weight as well as the MSC sum score (Ps < .05). Epi had an inverse correlation with the MSC sum score, triglycerides, and waist-to-hip ratio (Ps <. 05). Cortisol was not related to the MSC sum score (P = .20), although it had a positive association with LDL cholesterol (P = .04). Further associations between individual hormones and metabolic variables were not significant. The potential physiological significance of the association between the NE/Epi ratio and metabolic syndrome in fibromyalgia patients was further demonstrated by subdividing the fibromyalgia participants into those meeting and those not meeting metabolic syndrome criteria. Women with fibromyalgia comorbid with metabolic syndrome had significantly higher NE/Epi ratios (P = .002, Fig. 3) and a tendency toward higher NE/cortisol (P = .072). Controlling for age did not affect the association between metabolic syndrome and NE/Epi, but the association with NE/cortisol became nonsignificant (P = . 184).

4. Discussion

In this sample of young adult and middle-aged women drawn from the community, those with fibromyalgia had a 5.6 times higher risk of metabolic syndrome than demographically similar women without chronic pain. Women with fibromyalgia presented with larger waist measurements, higher blood pressure, and higher levels of A_{1c} and triglycerides as well as total and LDL cholesterol not attributable to age or BMI. Both waist circumference and waist-to-hip ratio, but not BMI or weight, were higher in women with fibromyalgia, suggesting that obesity in many women with fibromyalgia [4] may, in fact, include a bias toward central adiposity. Given that our sample was composed of relatively young, largely premenopausal women and that we excluded women with diabetes mellitus, polycystic ovary syndrome, and functional disability, thereby removing many of those at highest risk, the increased prevalence of metabolic syndrome in these women with fibromyalgia, as well as the occurrence of higher levels of the individual components is striking.

Women with fibromyalgia presented with an imbalance in the secretion of NE and Epi, captured in the NE/Epi ratio, which within this group was closely associated with the presence of metabolic syndrome and central obesity, consistent with a previous report in Hong Kong Chinese [25]. This relatively increased NE and decreased Epi excretion was also related to dyslipidemia and raised blood pressure. Interestingly, fibromyalgia has been postulated to be maintained by chronic SNS hyperactivity as evidenced by studies showing sympathetic nerve involvement in fibromyalgia pain, animal models of sympathetically maintained pain, and assessments of heart rate variability [42]. Furthermore, it has been hypothesized that the hyperinsulinemia of obesity plays a role in stimulation of the SNS (NE) and diminution of adrenal medullary activity (Epi) thereby contributing to the development of hypertension and dyslipidemia, respectively [24]. Our finding of a trend for increasing age to be associated with enhanced NE secretion is similar to that seen over time in aging nuns [43] and supportive of a hypothesized role of the SNS in the higher incidence of both fibromyalgia [2] and metabolic syndrome [5] with age. A skew in the excretion of NE/cortisol was also associated with both fibromyalgia and metabolic disturbance. A dysregulation of the HPA axis with hypocortisolism and/or flattening of diurnal rhythms resulting from chronic stress, including that from chronic pain,

has been hypothesized to play a role in the downstream development of insulin resistance and metabolic syndrome [33,44,45], as well as fibromyalgia [31,33,46]. Our data are consistent with these hypothesized pathogenetic mechanisms and, furthermore, suggest the possibility that the elevated risk for metabolic syndrome in patients with fibromyalgia may be related to SNS activation in conjunction with relatively low-to-normal Epi and cortisol.

It is important to point out that not all women with fibromyalgia are overweight or will develop metabolic syndrome. In this cohort of women with fibromyalgia, which excluded some of the highest risk individuals, 20.2% had reached the full criteria for metabolic syndrome. Some of the inferences from this study may be limited by the cross-sectional design and relatively small sample size and may apply primarily to young to middle-aged, female, and fairly high functioning fibromyalgia patients. Nonetheless, the magnitude, consistency, and biological plausibility of the association between fibromyalgia and metabolic syndrome suggest that it warrants clinical attention as well as further examination in large population-based studies that are inclusive of those known to be at greater risk, particularly older men and women.

Although metabolic syndrome has been observed in patients with fibromyalgia in clinical settings, this study provides the first empirical evidence that fibromyalgia per se, not merely the associated obesity and physical inactivity, may be a risk factor for metabolic syndrome. The implications of this study are that women with fibromyalgia, and perhaps those with other chronic pain syndromes of unknown etiology, should be followed clinically to identify those with metabolic syndrome. First-line interventions for all metabolic syndrome risk factors are increased physical activity and weight reduction [8]. Because patients with fibromyalgia have both muscle and generalized hyperalgesia, there has been concern about risk for symptom aggravation and muscle injury with exercise [3]. However, a number of recent studies have indicated that both aerobic exercise and progressive strength training can be well tolerated and effective at improving both functional and cardiovascular status as well as pain in patients with fibromyalgia [3]. Weight loss in women with fibromyalgia also may reduce pain and other fibromyalgia symptoms [47]. Women with fibromyalgia should be educated about the benefits of physical exercise and weight loss, when appropriate, for lowering metabolic risk as well as for improving pain and general health.

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