METABOLIC SYNDROME IMPAIRS QUALITY OF LIFE AND FUNCTIONAL STATUS IN PATIENTS WITH FIBROMYALGIA SYNDROME

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ABSTRACT

Introduction: *Obesity and insulin resistance are important risk factors for metabolic syndrome (Mets). Studies on Mets frequency and its effects on quality of life in patients with fibromyalgia syndrome (FMS) are inconclusive. We aimed to investigate the frequency of obesity, insulin resistance and Mets in patients with FMS and to examine their effect on quality of life (QoL).*

Materials and methods: *Fifty FMS patients and fifty controls between 20 and 60 ages were included in the study. The diagnosis of Mets was made according to the criteria of the International Diabetes Federation. Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) method. Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 questionnaire (SF-36) were used to evaluate the functional status and QoL. Pain were evaluated on the visual analog scale (VAS).*

Results: *There was no significant difference in BMI values between the groups. Waist circumference was significantly higher in the FMS group (p=0.004). While 28 (56%) patients in the FMS group met the diagnostic criteria for Mets, 9 (18%) patients in the control group met the diagnostic criteria for Mets (p<0.001). Insulin resistance was found in 28 (56%) patients in the FMS group and 19 (38%) patients in the control group (p=0.002). The FIQ score and VAS-pain score were significantly higher in the FMS group (p<0.001). QoL and functional status parameters assessed by SF-36 were significantly lower in the FMS group compared to the control group (p<0.001). While BMI showed significant positive correlations with VAS-pain (p=0.005) and FIQ (p=0.047), it showed significant negative correlations with physical function (p=0.017), emotional limitation (p=0.046), and general health (p=0.01) parameters of the SF-36. HOMA-IR showed a significant positive correlation with waist circumference (p=0.048), but not BMI.*

Conclusions: *The frequency of Mets and insulin resistance are increasing in patients with FMS. As BMI increases, QoL and functional status deteriorate. Increased physical activity and lifestyle changes may be beneficial to improve the QoL by preventing insulin resistance and Mets.*

Keywords: *Fibromyalgia, metabolic syndrome, obesity, quality of life, QoL.*

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Introduction

Fibromyalgia syndrome (FMS) is defined as a chronic syndrome characterized by widespread pain, sleep disturbance, fatigue, anxiety, and cognitive dysfunction. Today, the cause of FMS is not known exactly. In addition to central sensitization, genetic, environmental, and immunological factors are listed among the possible causes[1, 2]. FMS is most common between the ages of 40 and 60, and its prevalence is reported to be 1-2%[2, 3]. The first classification criteria for FMS were established by the American College of Rheumatology (ACR) in 1990, and subsequently new classification criteria including fatigue, somatic symptoms, cognitive dysfunction, and sleep disorders were published in 2010[4]. In 2013, Bennett et al. developed an alternative classification criteria including a 28-area pain score and symptom impact questionnaire[5]. Obesity and metabolic syndrome (MetS) are serious health problems that are increasingly common all over the world. Hypertension, diabetes mellitus,

dyslipidemia, cardiovascular disorders, and musculoskeletal system disorders can occur with obesity, and this situation reveals the importance of obesity in terms of public health[6-8]. It has been reported that 32-50% of patients with FMS are obese and 21-28% are overweight[9-11]. Another relationship between obesity and FMS is sleep disturbance. There are studies supporting the relationship between obesity and short sleep duration in the general population[12-14]. Mets is characterized by visceral (central) obesity, dyslipidemia, hyperglycemia, and hypertension[15-18]. Obesity and insulin resistance are risk factors for Mets 17. Fava et al. reported that insulin resistance may play a role in the development of cognitive dysfunction in patients with FMS[19]. Thus, the link between FMS and Mets may be obesity and insulin resistance.

Quality of life (QoL) is the way individuals perceive and evaluate their situation in the context of the cultural structure and value system to which they belong[20]. FMS adversely affects the QoL, causing loss of work performance and increased health expenditures[20, 21]. The goal of FMS treatment is to control pain and symptoms and increase the QoL. Determining the factors that affect QoL is important for the development of new treatment strategies. In our study, we aimed to investigate the frequency of MetS in patients with FMS and to examine the effect of the presence of Mets on QoL.

Materials and methods

Our study was approved by the local ethics committee. All participants included in the study were informed about the study, and their written consents were obtained. All procedures performed in this study were in accordance with the 1964 Declaration of Helsinki and its later amendments.

Fifty female patients between the ages of 20 and 60 who presented to the rheumatology outpatient clinic with complaints of widespread pain (pain in the left or right half of the body, lower or upper half of the body or axial skeleton) for more than three months and were classified as FMS according to 2013 criteria were included in the study. Fifty female patients of similar age who applied to the rheumatology outpatient clinic due to local pain reasons other than FMS (tendinitis, myofascial pain, discogenic pain, osteoarthritis) were included in the control group. Exclusion criteria were determined as cognitively uncommunicative patients, acute or chronic infection during the study, a history of malignancy, having a known neurological disease (hemiplegia, multiple sclerosis, neurodegenerative diseases), lung, heart, liver and kidney diseases requiring treatment, rheumatologic inflammatory diseases (rheumatoid arthritis, spondyloarthropathies, connective tissue diseases), uncontrolled thyroid diseases, pregnancy, and lactation.

Age, height, weight, body mass index (BMI), educational status, smoking and alcohol use and income levels were recorded. The abdominal circumference (from the midpoint of the distance between the arcus costarum and Spina iliaca anterior superior) was measured by the same doctor in all participants. Blood pressure was measured three times in five-minute intervals, and the average was taken. Pain levels were evaluated on the visual analog scale (VAS). The diagnosis of Mets was made according to the criteria of the International Diabetes Federation: metabolic syndrome definition[22].

Accordingly, central obesity (waist circumference measurement >80 cm in women, >94 cm in men, or BMI>30 kg/m^2) and having two or more of the following criteria were classified as metabolic syndrome:

- Triglyceride >150 mg/dL or being treated for this dyslipidemia;
- HDL-cholesterol in women <50 mg/dL/men <40 mg/dL or being treated for this dyslipidemia;
- Blood pressure ≥130/85 mmHg or being treated for hypertension;
- Fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes mellitus[22].

Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) method[23]. In the HOMA-IR method, fasting plasma glucose and fasting insulin level are multiplied, and the resulting value is divided by 405. A result above 2.5 is accepted as insulin resistance [23].

Fibromyalgia Impact Questionnaire (FIQ) was used to evaluate the functional status and QoL in patients with FMS[24, 25]. The FIQ is composed of 10 items. The first item is related to physical functioning. Items 2 and 3 ask the patient to mark the number of days they felt well and the number of days they were unable to work because of FMS. In items 4 through 10, the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. FIQ is completed by the patient, and the maximum score is 100. Except for the felt well section, low scores indicate being less affected by the disease[24]. Short Form-36 questionnaire (SF-

36) can be used to evaluate the QoL in healthy population and in those with various diseases. We used the SF-36 questionnaire, whose validity and reliability in Turkish was proven, to evaluate the QoL in the FMS and control groups[25]. The SF-36 questionnaire contains 36 questions in eight different categories. Physical function, role limitation due to physical problems, role limitation due to emotional problems, vital function, social functionality, mental health, pain, and general health perception are the subcategories of SF-36. Each section is scored in the range of 0-100 points. While 0 indicates poor health, 100 indicates the best health status[26].

Results

The clinical and demographic characteristics of the FMS and control groups are shown in Table 1.

Variables		Control (n=50)	FMS (n=50)	p
Age, (years) (Mean±SD)		43.68±7.09	45.82±7.36	0.142
Height, (cm) (Mean±SD)		159.28±4.09	160.20±6.6	0.469
Weight, (kg) (Mean±SD)		75.66±11.62	79.60±11.67	0.074
BMI (kg/m^2) (Mean±SD)		29.87±4.84	31.03±4.51	0.218
Educational Status	Primary school	24 (48%)	35 (70%)	0.214
	High school	18 (36%)	9 (18%)	
	University	8 (16%)	6 (12%)	
Marital status	Married	43 (86%)	44 (88%)	0.766
	Single / Widow	7 (14%)	6 (12%)	
Smoking	Yes	14 (28%)	14 (28%)	1
	No	36 (72%)	36 (72%)	
Income rate	≤2500 Lira	35 (70%)	36 (72%)	0.826
	> 2500 Lira	15 (30%)	14 (28%)	
Postmenopausal	Yes	20 (40%)	26 (52%)	0.229
	No	30 (60%)	24 (48%)	
Metabolic Syndrome	Yes	9 (18%)	28 (56%)	**<0.001**
	No	41 (82%)	22 (44%)	
Insulin Resistance	Yes	19 (38%)	28 (56%)	**0.002**
	No	31 (62%)	22 (44%)	

Table 1: Comparison of clinical and demographic data.
BMI: Body Mass Index, FMS: Fibromyalgia Syndrome, SD: Standard Deviation.

Both groups were similar in terms of age, educational status, marital status, income level, menopause, and smoking. There were no significant differences in height, weight, and BMI values of the groups. However, waist circumference measurement, which is a component of Mets, was significantly higher in the FMS group (p=0.004) (Table 2). While 28 (56%) patients in the FMS group met the diagnostic criteria for Mets, 9 (18%) patients in the control group met the diagnostic criteria for Mets (p<0.001) (Table 1). In the FMS group, arterial blood pressure, triglyceride level, and fasting blood glucose level were found to be significantly higher, and HDL level was found to be significantly lower (Table 2). Insulin resistance was found in 28 (56%) patients in the FMS group and 19 (38%) patients in the control group (p=0.002) (Table 1).

Metabolic Syndrome Components	Control (n=50) (Mean±SD)	FMS (n=50) (Mean±SD)	p
Waist Circumference (cm)	82.50±9.55	88.56±9.03	**0.004**
Systolic BP (mmHg)	113.30±9.56	126.60±10.56	**<0.001**
Diastolic BP (mmHg)	72.70±6.48	79.60±8.00	**<0.001**
Triglyceride (mg/dL)	118.30±53.52	172.36±117.53	**0.004**
HDL (mg/dL)	54.20±10.50	48.96±9.16	**0.009**
Fasting Blood Glucose (mg/dL)	91.42±18.04	99.98±17.25	**0.003**

Table 2: Comparison of metabolic syndrome parameters.
BP: Blood Pressure, FMS: Fibromyalgia Syndrome, HDL: High Density Lipoprotein, SD: Standard Deviation.

The FIQ score and VAS-pain score, indicating being more affected by the disease, were significantly higher in the FMS group (p<0.001) (Table 3). QoL and functional status parameters assessed by SF-36 were significantly lower in the FMS group compared to the control group (p<0.001) (Table 3).

Variables	Control (n=50) (Mean ± SD)	FMS (n=50) (Mean ± SD)	p
VAS-pain	5.44±1.79	8.46±1.48	**<0.001**
FAQ	43.43±12.68	74.05±10.27	**<0.001**
SF-36-Physical Function	68.5±16.78	43.00±18.78	**<0.001**
SF-36-Physical Limitation	56.50±21.05	25.00±27.66	**<0.001**
SF-36-Emotional Limitation	52.00±33.11	28.66±30.12	**<0.001**
SF-36-Energy / Fatigue	42.82±14.72	25.60±14.97	**<0.001**
SF-36-Emotional Well-Being	59.80±18.93	41.44±20.64	**<0.001**
SF-36-Social Function	61.89±19.85	44.94±24.15	**<0.001**
SF-36-Pain	49.50±21.64	18.90±14.38	**<0.001**
SF-General Health	49.40±18.67	25.10±11.27	**<0.001**

Table 3: Comparison of VAS-pain, FIQ, and SF-36 parameters.
FIQ: Fibromyalgia Impact Questionnaire, FMS: Fibromyalgia Syndrome, SF-36: Short Form-36, SD: Standard Deviation, VAS: Visual Analog Scale.

The relationships of BMI with VAS-pain, FIQ, and SF-36 in the FMS group are shown in Table 4. While BMI showed significant positive correlations with VAS-pain and FIQ, it showed significant negative correlations with physical function, emotional limitation, and general health parameters, which are among the SF-36 parameters (Table 4).

While there was no significant correlation between insulin resistance (HOMA-IR) and BMI in the FMS group (p=0.116), a weak but significant correlation was found between HOMA-IR and waist circumference (p=0.048, r=0.281).

Variables	BMI	
	Spearman r	p
VAS-pain	**0.389**	**0.005**
FAQ	**0.283**	**0.047**
SF-36-Physical Function	**-0.337**	**0.017**
SF-36-Physical Limitation	-0.269	0.059
SF-36-Emotional Limitation	**-0.283**	**0.046**
SF-36-Energy / Fatigue	-0.99	0.495
SF-36-Emotional Well-Being	-0.212	0.140
SF-36-Social Function	-0.20	0.888
SF-36-Pain	-0.249	0.081
SF-36-General Health	**-0.362**	**0.01**

Table 4: Correlation between BMI and VAS-pain, FIQ, and SF-36 parameters in the FMS group.
BMI: Body Mass Index, FIQ: Fibromyalgia Impact Questionnaire, FMS: Fibromyalgia Syndrome, SF-36: Short Form-36, VAS: Visual Analog Scale.

Discussion

FMS is an important health problem that causes an increase in health expenditures, deterioration in QoL, and decrease in work performance. Patients with FMS often prefer a sedentary lifestyle due to widespread body pain and fatigue. A sedentary lifestyle is an important risk factor for obesity. Obesity, which has become an important health problem, creates a predisposition to musculoskeletal problems, metabolic disorders, and cardiovascular diseases. There are studies showing a relationship between obesity and FMS[27, 28]. It has been reported that the severity of symptoms increases with increasing BMI in patients with FMS[29]. In our study, it was shown that the waist circumference was greater and the frequency of insulin resistance and Mets increased in patients with FMS. In addition, according to the results of our study, it was observed that as BMI increases, pain intensity increases (VAS), functional status and QoL worsens (FIQ and SF-36 scores). In the study conducted by Lily et al., obesity was shown to be associated with an increase in tender point sensitivity[9]. The mechanisms underlying the link between obesity and pain sensitivity are not yet fully understood. It has been shown that decreased physical condition increases pain sensitivity, and aerobic exercise programs reduce sensitivity to tender point pain in patients with FMS[30, 31]. Another possible mechanism could be linked to the endogenous opioid system. In animal studies, it has been shown that obesity can affect the sensitivity to painful stimuli by causing changes in the endocrine and opioid systems[32, 33]. In our study, a significant positive correlation was found between BMI and VAS-pain in the FMS group.

With the increasing frequency of obesity in patients with FMS, the risk of insulin resistance and Mets also increases[34]. The results of our study showed that waist circumference was greater, and Mets and insulin resistance were more common in patients with FMS compared to the control group.

It has been suggested that memory impairment seen in patients with FMS is associated with insulin resistance and that insulin resistance may be an independent risk factor for cognitive dysfunctions[19]. In the study conducted by Svetvold et al., it was shown that the probability of insulin resistance in patients with FMS with memory deficiency was 2.6 times higher than in controls[35]. It has been reported that cognitive dysfunctions can be seen in Mets accompanied by insulin resistance[36]. It is thought that the effect of insulin resistance on cognitive functions may be through glucose metabolism and neurotransmitter modulation[19]. Low-dose insulin can reverse the amnestic effects of cholinergic blockade[37]. Hyperinsulinemia, which is an indicator of insulin resistance, has been shown to trigger sympathetic nervous system activity and cause an increase in noradrenaline concentrations in plasma, urine, and cerebrospinal fluid[38, 39]. In our study, it was observed that the risk of insulin resistance was increased in patients with FMS, and there was a significant positive correlation between insulin resistance (HOMA-IR) and waist circumference measurement.

Both Mets and FMS have been associated with disruptions in the hypothalamic-pituitary-adrenal axis[40]. Barbara et al. showed in their study that women with FMS had a 5.6 times higher risk of MetS compared to demographically similar women[40]. In

accordance with previous studies, our study showed that Mets were more common in the FMS patients. It has been reported that the risk of being overweight or obese is increased and QoL is lower in patients with FMS compared to healthy controls[9]. In our study, there was no significant difference in BMI when the FMS patients were compared with the controls, but the waist circumference was significantly greater in the FMS group and QoL and functional status deteriorated as BMI increased. The main limitations of our study were that it is a cross-sectional study, the number of patients is relatively small, and it consists of only female patients.

In conclusion, the frequency of Mets and insulin resistance are increasing in patients with FMS. Obesity and a sedentary lifestyle are important risk factors for Mets and insulin resistance in FMS patients. As BMI increases, QoL and functional status deteriorate. Increased physical activity and lifestyle changes may be beneficial to improve the QoL by preventing insulin resistance and Mets.

References

1) Bazzichi L, Giacomelli C, Consensi A, Atzeni F, Batticciotto A, et al. One year in review 2016: fibromyalgia. Clin Exp Rheumatol 2016; 34: S145-149.
2) Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, et al. Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. Pain Res Treat 2012; 2012: 426130.
3) Wolfe F, Ross K, Anderson J, and Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. J Rheumatol 1995; 22: 151-156.
4) Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010; 62: 600-6010.
5) Bennett RM, Friend R, Marcus D, Bernstein C, Han BK, et al. Criteria for the diagnosis of fibromyalgia: validation of the modified 2010 preliminary American College of Rheumatology criteria and the development of alternative criteria. Arthritis Care Res (Hoboken) 2014; 66: 1364-1373.
6) Bastien M, Poirier P, Lemieux I, and Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 2014; 56: 369-381.
7) Puhl RM and Heuer CA. The stigma of obesity: a review and update. Obesity (Silver Spring) 2009; 17: 941-964.
8) Shamseddeen H, Getty JZ, Hamdallah IN, and Ali MR. Epidemiology and economic impact of obesity and type 2 diabetes. Surg Clin North Am 2011; 91: 1163-1172, VII.
9) Neumann L, Lerner E, Glazer Y, Bolotin A, Shefer A, et al. A cross-sectional study of the relationship between body mass index and clinical characteristics, tenderness measures, QoL, and physical functioning in fibromyalgia patients. Clin Rheumatol 2008; 27: 1543-1547.
10) Okifuji A, Bradshaw DH, and Olson C. Evaluating obesity in fibromyalgia: neuroendocrine biomarkers, symptoms, and functions. Clin Rheumatol 2009; 28: 475-478.
11) Yunus MB, Arslan S, and Aldag JC. Relationship between body mass index and fibromyalgia features. Scand J Rheumatol 2002; 31: 27-31.
12) Bjorvatn B, Sagen IM, Ayane N, Waage S, Fetveit A, et al. The association between sleep duration, body mass index and metabolic measures in the Hordaland Health Study. J Sleep Res 2007; 16: 66-76.
13) Di Milia L and Mummery K. The association between job related factors, short sleep and obesity. Ind Health 2009; 47: 363-368.
14) Stamatakis KA and Brownson RC. Sleep duration and obesity-related risk factors in the rural Midwest. Prev Med 2008; 46: 439-444.
15) Fulop T, Tessier D, and Carpentier A. The metabolic syndrome. Pathol Biol (Paris) 2006; 54: 375-386.
16) Grundy SM. Metabolic syndrome: part II. Endocrinol Metab Clin North Am 2004; 33: 267-282.
17) O'Neill S and O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev 2015; 16: 1-12.
18) Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.
19) Fava A, Plastino M, Cristiano D, Spano A, Cristofaro S, et al. Insulin resistance possible risk factor for cognitive impairment in fibromyalgia patients. Metab Brain Dis 2013; 28: 619-627.
20) Homann D, Stefanello JM, Goes SM, Breda CA, Paiva Edos S, et al. Stress perception and depressive symptoms: functionality and impact on the QoL of women with fibromyalgia. Rev Bras Reumatol 2012; 52: 319-330.
21) Campos RP and Vazquez Rodriguez MI. Health-related QoL in women with fibromyalgia: clinical and psychological factors associated. Clin Rheumatol 2012; 31: 347-355.
22) Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet 2005; 366: 1059-1062.
23) Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, et al. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care 2003; 26: 3320-3325.

24) Burckhardt CS, Clark SR, and Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991; 18: 728-733.
25) Koçyiğit H, Aydemir Ö, Fişek G, Ölmez N, and Memiş A. Kısa form-36 (SF-36)'nın Türkçe versiyonunun güvenilirliği ve geçerliliği. İlaç ve Tedavi Dergisi 1999; 12: 102-106.
26) Demiral Y, Egor G, Unal B, Semin S, Akvardar Y, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. BMC Public Health 2006; 6: 247.
27) Gota CE, Kaouk S, and Wilke WS. Fibromyalgia and Obesity: The Association Between Body Mass Index and Disability, Depression, History of Abuse, Medications, and Comorbidities. J Clin Rheumatol 2015; 21: 289-295.
28) Rossi A, Di Lollo AC, Guzzo MP, Giacomelli C, Atzeni F, et al. Fibromyalgia and nutrition: what news? Clin Exp Rheumatol 2015; 33: S117-125.
29) Segura-Jimenez V, Castro-Pinero J, Soriano-Maldonado A, Alvarez-Gallardo IC, Estevez-Lopez F, et al. The association of total and central body fat with pain, fatigue and the impact of fibromyalgia in women; role of physical fitness. Eur J Pain 2016; 20: 811-821.
30) Martin L, Nutting A, MacIntosh BR, Edworthy SM, Butterwick D, et al. An exercise program in the treatment of fibromyalgia. J Rheumatol 1996; 23: 1050-1053.
31) McCain GA, Bell DA, Mai FM, and Halliday PD. A controlled study of the effects of a supervised cardiovascular fitness training program on the manifestations of primary fibromyalgia. Arthritis Rheum 1988; 31: 1135-1141.
32) Kutlu S, Canpolat S, Sandal S, Ozcan M, Sarsilmaz M, et al. Effects of central and peripheral administration of leptin on pain threshold in rats and mice. Neuro Endocrinol Lett 2003; 24: 193-196.
33) Roane DS and Porter JR. Nociception and opioid-induced analgesia in lean (Fa/-) and obese (fa/fa) Zucker rats. Physiol Behav 1986; 38: 215-218.
34) Savaş HB and Gültekin F. Insulin Resistance and Clinical Significance. Med J SDU 2017; 24: 116-125.
35) Sletvold H, Stiles TC, and Landro NI. Information processing in primary fibromyalgia, major depression and healthy controls. J Rheumatol 1995; 22: 137-142.
36) Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004; 292: 2237-2242.
37) Blanchard JG and Duncan PM. Effect of combinations of insulin, glucose and scopolamine on radial arm maze performance. Pharmacol Biochem Behav 1997; 58: 209-214.
38) Landsberg L. Role of the sympathetic adrenal system in the pathogenesis of the insulin resistance syndrome. Ann N Y Acad Sci 1999; 892: 84-90.
39) Watson GS, Bernhardt T, Reger MA, Cholerton BA, Baker LD, et al. Insulin effects on CSF norepinephrine and cognition in Alzheimer's disease. Neurobiol Aging 2006; 27: 38-41.
40) Loevinger BL, Muller D, Alonso C, and Coe CL. Metabolic syndrome in women with chronic pain. Metabolism 2007; 56: 87-93.

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