

## Research Abstracts FMS & ME/CFS

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1999

### *Authors*

Adler GK, Kinsley BT, Hurwitz S, Mossey CJ, Goldenberg DL

### *Title*

**Reduced hypothalamic-pituitary and sympathoadrenal responses to hypoglycemia in women with fibromyalgia syndrome.**

### *Source*

Am J Med 1999 May;106(5):534-43

### *Author's Affiliation*

Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA

### *Abstract*

**PURPOSE:** To perform a detailed comparison of the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system in women with and without fibromyalgia.

**SUBJECTS AND METHODS:** Fifteen premenopausal women who met the 1990 American College of Rheumatology criteria for the diagnosis of fibromyalgia and 13 healthy, premenopausal women were enrolled. We measured baseline 24-hour urinary free cortisol levels and evening and morning adrenocorticotrophic hormone (ACTH) and cortisol levels, performed stepped hypoglycemic hyperinsulinemic clamp studies in which serum glucose levels were decreased from 5.0 to 2.2 mmol/L, and compared the effects of infusions of placebo and ACTH.

**RESULTS:** Women with fibromyalgia had normal 24-hour urinary free cortisol levels and normal diurnal patterns of ACTH and cortisol. There was a significant, approximately 30%, reduction in the ACTH and epinephrine responses to hypoglycemia in women with fibromyalgia compared with controls. Prolactin, norepinephrine, cortisol, and dehydroepiandrosterone responses to hypoglycemia were similar in the two study groups. In subjects with fibromyalgia, the epinephrine response to hypoglycemia correlated ( $P = 0.01$ ) inversely with overall health status as measured by the fibromyalgia impact questionnaire. Graded ACTH infusion revealed similar increases in cortisol in women with fibromyalgia and healthy controls.

**CONCLUSIONS:** **Patients with fibromyalgia have an impaired ability to activate the hypothalamic-pituitary portion of the hypothalamic-pituitary-adrenal axis as well as the sympathoadrenal system, leading to reduced ACTH and epinephrine responses to hypoglycemia.**

### *Authors*

Bennett RM

### *Title*

**Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia.**

*Source*

Mayo Clin Proc 1999 Apr;74(4):385-98

*Author's Affiliation*

Division of Arthritis and Rheumatic Diseases, Oregon Health Sciences University, Portland 97201, USA.

*Abstract*

Chronic pain often differs from acute pain. The correlation between tissue pathology and the perceived severity of the chronic pain experience is poor or even absent. Furthermore, the sharp spatial localization of acute pain is not a feature of chronic pain; chronic pain is more diffuse and often spreads to areas beyond the original site. Of importance, chronic pain seldom responds to the therapeutic measures that are successful in treating acute pain. Physicians who are unaware of these differences may label the patient with chronic pain as being neurotic or even a malingerer. During the past decade, an exponential growth has occurred in the scientific underpinnings of chronic pain states. **In particular, the concept of nonnociceptive pain has been refined at a physiologic, structural, and molecular level.** This review focuses on this new body of knowledge, with particular reference to the chronic pain state termed "fibromyalgia."

*Authors*

Bounous G, Molson J

*Title*

**Competition for glutathione precursors between the immune system and the skeletal muscle: pathogenesis of chronic fatigue syndrome**

*Source*

Med Hypotheses 1999 Oct;53(4):347-9

*Author's Affiliation*

Department of Surgery, McGill University, and Medical Research Council of Canada.

*Abstract*

The chronic fatigue syndrome (CFS) is typically associated or follows a recognized or presumed infection. Abnormalities of both humoral and cellular immunity have been demonstrated in a substantial proportion of patients with CFS. The most consistent findings are of impaired lymphocyte responses to mitogen. As an antioxidant, glutathione (GSH) is essential for allowing the lymphocyte to express its full potential without being hampered by oxiradical accumulation. Hence, protracted challenge of the immunocytes may lead to cellular GSH depletion. **Because GSH is also essential to aerobic muscular contraction, an undesirable competition for GSH precursors between the immune and muscular systems may develop. It is conceivable that the priority of the immune system for the survival of the host has drawn to this vital area the ever-diminishing GSH precursors, thus depriving the skeletal muscle of adequate GSH precursors to sustain a normal aerobic metabolism resulting in fatigue and eventually myalgia.**

*Authors*

Dessein PH, Shipton EA, Joffe BI, Hadebe DP, Stanwix AE, Van der Merwe BA

*Title*

## **Hyposecretion of adrenal androgens and the relation of serum adrenal steroids, serotonin and insulin-like growth factor-1 to clinical features in women with fibromyalgia.**

### *Source*

Pain 1999 Nov;83(2):313-9

### *Authors Affiliation*

Rheumatology Unit, Milpark Hospital, Johannesburg, South Africa.

### *Abstract*

Neuroendocrine deficiencies have been implicated in fibromyalgia (FM). In the present study, adrenal androgen metabolites and their relationship with health status in FM were investigated. For comparison, serum levels of other implicated neuroendocrine mediators were correlated with health status. Fifty-seven consecutive women with FM completed the Fibromyalgia Impact Questionnaire (FIQ). Fasting blood samples were taken for measurement of dehydroepiandrosterone sulphate (DHEAS), free testosterone (T), cortisol, serotonin and insulin-like growth factor-1. Normal value for DHEAS and T were obtained from 114 controls. DHEAS levels were decreased significantly in pre- and postmenopausal patients ( $P < 0.0001$  and  $P < 0.0005$ , respectively). T levels were decreased significantly in premenopausal and insignificantly in postmenopausal patients ( $P < 0.0001$  and  $P = 0.06$ , respectively). The following correlations between neurohormonal levels and FIQ scores were found: DHEAS (after adjustment for age) vs. pain ( $P < 0.001$ ) and T (after adjustment for age) versus physical functioning ( $P = 0.002$ ). None of the other neurohormonal levels correlated significantly with any of the FIQ scores. IGF-1 levels were lower in the obese patients as compared to those who were non-obese ( $P = 0.03$ ). The BMI correlated positively with pain ( $P < 0.001$ ) and inversely with DHEAS levels ( $P = 0.006$ ). After further adjustment for BMI, the correlation between age adjusted DHEAS and pain was no longer significant. **Hyposecretion of adrenal androgens was documented in FM. This was more pronounced in obese patients. Low serum androgen levels correlated with poor health status in FM. Longitudinal studies are needed to elucidate whether these are cause and/or effect relationships.**

### *Authors*

Ernberg M, Hedenberg-Magnusson B, Alstergren P, Kopp S

### *Title*

**The level of serotonin in the superficial masseter muscle in relation to local pain and allodynia.**

### *Source*

Life Sci 1999;65(3):313-25

### *Author's Affiliation*

Department of Clinical Oral Physiology, Karolinska Institutet, Huddinge, Sweden.  
malin.ernberg@ofa.ki.se

### *Abstract*

The aim of this study was to investigate if serotonin is present in the human masseter muscle and if so, whether it is involved in the modulation of local muscle pain or allodynia. Thirty-five patients with pain and tenderness of the masseter muscle as well as ten healthy individuals were included in the study. Of the patients, 18 suffered from fibromyalgia and 17 had localized myalgia, e.g. myofascial pain in the temporomandibular system. The participants were examined clinically with special consideration to the masseter muscle and the pressure pain threshold as well as tolerance levels of

this muscle were assessed. Intramuscular microdialysis was performed in order to sample serotonin and a venous blood sample was collected for analysis of the serum level of serotonin. Serotonin was present in the masseter muscle and the level was significantly higher in the initial sample than in the sample collected during steady state. The level of serotonin in the masseter muscle in relation to the level of serotonin in the blood serum was calculated. This fraction of serotonin was higher in the patients with fibromyalgia than in healthy individuals and high level of serotonin was associated with pain as well as allodynia of the masseter muscle. **In conclusion, the results of this study show that serotonin is present in the human masseter muscle both immediately following puncture and in a subsequent steady state and that it is associated with pain and allodynia. The origin of the serotonin seems partly to be the blood, but our results indicate that peripheral release also occurs.**

*Authors*

Ernberg M, Hedenberg-Magnusson B, Alstergren P, Lundeberg T, Kopp S

*Title*

**Pain, allodynia, and serum serotonin level in orofacial pain of muscular origin.**

*Source*

J Orofac Pain 1999 Winter;13(1):56-62

*Author's Affiliation*

Department of Clinical Oral Physiology, Karolinska Institutet, Stockholm, Sweden.  
malin.ernberg@ofa.ki.se

*Abstract*

This study was conducted to investigate the serum level of serotonin (S-5-HT) in patients with temporomandibular disorders (TMD) of muscular origin, i.e., localized myalgia, and to compare it to that found in healthy individuals and patients with fibromyalgia. A second aim was to investigate the association between S-5-HT and pain parameters.

**METHODS:** Twenty patients with localized myalgia participated in the study. Twenty age- and gender-matched healthy individuals and twenty patients with fibromyalgia served as controls. The participants were examined clinically as to the condition of the temporomandibular region and S-5-HT.

**RESULTS:** The levels of S-5-HT did not differ significantly between the groups. However, in patients with localized myalgia there was a negative correlation between S-5-HT and tenderness of the temporomandibular muscles.

**CONCLUSION:** **The results of this study indicate that allodynia of orofacial muscles in patients with TMD is significantly related to S-5-HT concentration.**

*Authors*

Giovengo SL, Russell IJ, Larson AA

*Title*

**Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia.**

*Source*

J Rheumatol 1999 Jul;26(7):1564-9

*Author's Affiliation*

AA Department of Veterinary Pathobiology, University of Minnesota, St. Paul 55108, USA.

*Abstract*

**OBJECTIVE:** To determine whether there is a difference in the concentration of nerve growth factor (NGF) in the cerebrospinal fluid (CSF) from patients diagnosed with primary fibromyalgia syndrome (FM), fibromyalgia associated with other secondary conditions (SFM), patients with other painful conditions but lacking fibromyalgia (OTHER), and healthy controls.

**METHODS:** The clinical measures of pain threshold included the tender point index, a measure of pain threshold intensity measured by digital pressure, and the average pain threshold measured by dolorimetry. Concentrations of NGF in the CSF were measured using a 2 site enzyme immunoassay.

**RESULTS:** The mean (+/- SEM) concentration of NGF measured in patients with FM was significantly increased (41.8 +/- 12.7 pg/ml) compared to controls (9.1 +/- 4.1 pg/ml), but with large variability. Concentrations of NGF in SFM (8.9 +/- 4.4 pg/ml) and OTHER (16.2 +/- 8.4 pg/ml) were not elevated compared to controls.

**CONCLUSION:** **The findings of increased concentrations of NGF in patients with FM suggest a central mechanism, involving abnormalities in neuropeptides such as NGF, may be a factor in the pathogenesis of FM.**

*Authors*

Gordon R, Michalewski HJ, Nguyen T, Gupta S, Starr A

*Title*

**Cortical motor potential alterations in chronic fatigue syndrome.**

*Source*

Int J Mol Med 1999 Nov;4(5):493-9

*Author's Affiliation*

Department of Neurology, University of California, Irvine, Med. Surge I, Room 154, Irvine, CA 92697-4290, USA.

*Abstract*

Premovement, sensory, and cognitive brain potentials were recorded from patients with Chronic Fatigue Syndrome (CFS) in four tasks: i) target detection, ii) short-term memory, iii) self-paced movement, and iv) expectancy and reaction time (CNV). Accuracy and reaction times (RTs) were recorded for tasks i, ii, and iv. Results from CFS patients were compared to a group of healthy normals. Reaction times were slower for CFS patients in target detection and significantly slower in the short-term memory task compared to normals. In target detection, the amplitude of a premovement readiness potential beginning several hundred milliseconds prior to stimulus onset was reduced in CFS, whereas the poststimulus sensory (N100) and cognitive brain potentials (P300) did not differ in amplitude or latency. In the memory task, a negative potential related to memory load was smaller in CFS than normals. The potentials to self-paced movements and to expectancy and RT (CNV) were not different between groups. **The findings in CFS of slowed RTs and**

reduced premovement-related potentials suggest that central motor mechanisms accompanying motor response preparation were impaired in CFS for some tasks. In contrast, measures of neural processes related to both sensory encoding (N100) and to stimulus classification (P300) were normal in CFS.

*Authors*

Henriksson KG

*Title*

**Is fibromyalgia a distinct clinical entity? Pain mechanisms in fibromyalgia syndrome. A myologist's view.**

*Source*

Baillieres Best Pract Res Clin Rheumatol 1999 Sep;13(3):455-61

*Author's Affiliation*

Neuromuscular Unit, University Hospital, Linkoping, Sweden.

*Abstract*

The cause of muscle pain and allodynia may not be the same in all persons fulfilling the American College of Rheumatology (ACR) criteria for fibromyalgia syndrome. In the majority of patients the generalized pain is preceded by localized or regional pain, usually in the musculoskeletal system. **In many patients with fibromyalgia there are findings compatible with tissue injury pain with pain mechanisms involving both the primary afferent neuron and the nociceptive system in the central nervous system. Evidence for these mechanisms is described.**

*Authors*

Lange G, DeLuca J, Maldjian JA, Lee H, Tiersky LA, Natelson BH

*Title*

**Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome**

*Source*

J Neurol Sci 1999 Dec 1;171(1):3-7

*Author's Affiliation*

Department of Psychiatry, UMDNJ-New Jersey Medical School, MSB E-561, 185 S. Orange Avenue, Newark, NJ 07103-2714, USA.

*Abstract*

Presence of MRI brain abnormalities in patients with Chronic Fatigue Syndrome (CFS) was determined and the profile of MRI abnormalities was compared between 39 CFS patients, 18 with (CFS-Psych) and 21 without (CFS-No Psych) a DSM-III-R Axis I psychiatric diagnosis since illness onset, and 19 healthy, sedentary controls (HC). Two neuroradiologists, blind to group membership, separately read the MR films using a detailed protocol for rating and categorizing abnormal signal changes. When findings were incongruent, the two neuroradiologists met to try to reach consensus, otherwise a third neuroradiologist evaluated the MR images and served as a tie-breaker. The CFS-No Psych group showed a significantly larger number of brain abnormalities on T2 weighted images than the CFS-Psych and HC groups. **Cerebral changes in the CFS-No Psych group consisted mostly of small, punctate, subcortical white matter hyperintensities, found predominantly in**

**the frontal lobes.** No significant difference was found when both CFS groups were combined and compared to the HC group. The use of stratification techniques is an important strategy in understanding the pathophysiology of CFS. **This frontal lobe pathology could explain the more severe cognitive impairment previously reported in this subset of CFS patients.**

*Authors*

Leal-Cerro A, Povedano J, Astorga R, Gonzalez M, Silva H, Garcia-Pesquera F, Casanueva FF, Dieguez C

*Title*

**The growth hormone (GH)-releasing hormone-GH-insulin-like growth factor-1 axis in patients with fibromyalgia syndrome.**

*Source*

J Clin Endocrinol Metab 1999 Sep;84(9):3378-81

*Author's Affiliation*

Department of Endocrinology, Hospital Universitario Virgen del Rocio, Sevilla, Spain.

*Abstract*

Fibromyalgia (FM) is a painful syndrome of nonarticular origin, characterized by fatigue and widespread musculoskeletal pain, tiredness, and sleep disturbances, without any other objective findings on examination. Interestingly, some of the clinical features of FM resemble the ones described in the adult GH-deficiency syndrome. Furthermore, insulin-like growth factor (IGF)-1 levels are frequently reduced in patients with FM. To gain further insight into the mechanisms leading to dysregulation of the GH-IGF-1 axis in these patients, we assessed 24-h spontaneous GH secretion, GH responses to GHRH, and IGF-1 and IGF binding protein (BP)-3 levels before and after 4 days treatment with human (h)GH. We found that, in comparison with controls, patients with FM exhibited a marked decrease in spontaneous GH secretion as assessed by mean GH secretion (2.5 +/- 0.4 microg/L in controls vs. 1.2 +/- 0.1 microg/L in FM,  $P < 0.05$ ), pulse height (4.7 +/- 0.8 microg/L in controls vs. 2.5 +/- 0.3 microg/L in FM,  $P < 0.05$ ), and pulse area (4.7 +/- 1 min/mg x L in controls vs. 2.3 +/- 0.3 min/mg x L in FM,  $P < 0.05$ ). In contrast, GH responses to GHRH (100 microg, i.v.) were similar in controls (mean peak, 13.5 +/- 2.5 microg/L) and in patients with FM (12.2 +/- 3 microg/L). Finally, treatment with hGH (2 IU, s.c. daily), over 4 days, led to a clear-cut increase in plasma IGF-1 and IGFBP-3 levels in patients with FM. **In conclusion, our data show that patients with FM exhibited a marked decrease in spontaneous GH secretion, but normal pituitary responsiveness to exogenously administered GHRH, thus suggesting the existence of an alteration at the hypothalamic level in the neuroendocrine control of GH in these patients. Furthermore, our finding of increased IGF-1 and IGFBP-3 levels after GH treatment, over 4 days, opens up the possibility of testing the therapeutic potential of hGH in patients with FM.**

*Authors*

Lentz MJ, Landis CA, Rothermel J, Shaver JL

*Title*

**Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women.**

### *Source*

J Rheumatol 1999 Jul;26(7):1586-92

### *Author's Affiliation*

Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle 98195-7266, USA.

### *Abstract*

**OBJECTIVE:** To determine whether disrupted slow wave sleep (SWS) would evoke musculoskeletal pain, fatigue, and an alpha electroencephalograph (EEG) sleep pattern. We selectively deprived 12 healthy, middle aged, sedentary women without muscle discomfort of SWS for 3 consecutive nights. Effects were assessed for the following measures: polysomnographic sleep, musculoskeletal tender point pain threshold, skinfold tenderness, reactive hyperemia (inflammatory flare response), somatic symptoms, and mood state.

**METHODS:** Sleep was recorded and scored using standard methods. On selective SWS deprivation (SWSD) nights, when delta waves (indicative of SWS) were detected on EEG, a computer generated tone (maximum 85 decibels) was delivered until delta waves disappeared. Musculoskeletal tender points were measured by dolorimetry; skinfold tenderness was assessed by skin roll procedure; and reactive hyperemia was assessed with a cotton swab test. Subjects completed questionnaires on bodily feelings, symptoms, and mood.

**RESULTS:** On each SWSD night, SWS was decreased significantly with minimal alterations in total sleep time, sleep efficiency, and other sleep stages. **Subjects showed a 24% decrease in musculoskeletal pain threshold after the third SWSD night. They also reported increased discomfort, tiredness, fatigue, and reduced vigor.** The flare response (area of vasodilatation) in skin was greater than baseline after the first, and again, after the third SWSD night. However, the automated program for SWSD did not evoke an alpha EEG sleep pattern.

**CONCLUSION: Disrupting SWS, without reducing total sleep or sleep efficiency, for several consecutive nights is associated with decreased pain threshold, increased discomfort, fatigue, and the inflammatory flare response in skin. These results suggest that disrupted sleep is probably an important factor in the pathophysiology of symptoms in fibromyalgia.**

### *Authors*

Maes M, Libbrecht I, Delmeire L, Lin A, De Clerck L, Scharpe S, Janca A

### *Title*

**Changes in platelet alpha-2-adrenoceptors in fibromyalgia: effects of treatment with antidepressants.**

### *Source*

Neuropsychobiology 1999 Sep;40(3):129-33

### *Author's Affiliation*

Clinical Research Center for Mental Health, Antwerp, Belgium. m.maes@unicall.be

### *Abstract*

The aim of this study was to determine platelet alpha(2)-adrenergic receptor (alpha(2)-AR) binding sites in fibromyalgia both before and after treatment with sertraline or placebo. The maximum number of binding sites (B(max)) and their affinity (K(d)) for [(3)H]rauwolscine, a selective alpha(2)-AR antagonist, were measured in 13 normal volunteers and 22 fibromyalgia patients. Severity of

illness was evaluated by means of the Hamilton Depression Rating Scale (HDRS) and dolorimetric assessments of tenderness at tender points. Fibromyalgia patients had repeated measurements of [(3)H] rauwolscine binding characteristics both before and after subchronic treatment with sertraline or placebo for 12 weeks. **[(3)H]rauwolscine binding K(d) values were significantly higher in fibromyalgia patients than in normal volunteers. There were significant inverse correlations between [(3)H]rauwolscine binding K(d) values and duration of illness, age and lower energy. Significantly higher [(3)H]rauwolscine binding K(d) values were found in fibromyalgia patients in an early phase of illness (<3 years) than in fibromyalgia patients with a protracted illness (>3 years). Repeated administration of sertraline had no significant effects on [(3)H]rauwolscine binding B(max) or K(d) values. The results suggest that fibromyalgia and, in particular, fibromyalgia in an early phase of illness, is accompanied by lowered affinity of platelet alpha(2)-ARs.**

*Authors*

Maes M, Libbrecht I, Van Hunsel F, Lin AH, De Clerck L, Stevens W, Kenis G, de Jongh R, Bosmans E, Neels

*Title*

**The immune-inflammatory pathophysiology of fibromyalgia: increased serum soluble gp130, the common signal transducer protein of various neurotrophic cytokines.**

*Source*

Psychoneuroendocrinology 1999 May;24(4):371-83

*Author's Affiliation*

H University Department of Psychiatry, Clinical Research Center for Mental Health (CRC-MH), Antwerp, Belgium. m.maes@unicall.be

*Abstract*

Fibromyalgia is a chronic, painful musculoskeletal disorder characterized by widespread pain, pressure hyperalgesia, morning stiffness and by an increased incidence of depressive symptoms. The etiology, however, has remained elusive. The aim of the present study was to examine the inflammatory response system (IRS) in fibromyalgia. Serum interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), sgp130, sIL-1R antagonist (IL-1RA) and sCD8 were determined in 33 healthy volunteers and in 21 fibromyalgia patients, classified according to the American College of Rheumatology criteria. Severity of illness was measured with several pain scales, dolorimetry and the Hamilton Depression Rating Scale (HDRS). Serum sgp130 was significantly higher and serum sCD8 significantly lower in fibromyalgia patients than in healthy volunteers. Serum sIL-6R and sIL-1RA were significantly higher in fibromyalgia patients with an increased HDRS score (> or = 16) than in normal volunteers and fibromyalgia patients with a HDRS score < 16. In fibromyalgia patients, an important part of the variance in sCD8 (50.3%) and IL-1RA (19.3%) could be explained by the HDRS score; 74.3% of the variance in sIL-6R was explained by the combined effects of pain symptoms and the HDRS score; and 25.9% of the variance in serum sgp130 was explained by stiffness. **The results support the contention that pain and stiffness in fibromyalgia may be accompanied by a suppression of some aspects of the IRS and that the presence of clinically significant depressive symptoms in fibromyalgia is associated with some signs of IRS activation.**

*Authors*

McCully KK, Natelson BH

*Title*

**Impaired oxygen delivery to muscle in chronic fatigue syndrome.**

*Source*

Clin Sci (Colch) 1999 Nov;97(5):603-

*Author's Affiliation*

Department of Medicine, Medical College of Pennsylvania and Hahnemann University, Philadelphia, PA 19129, USA. kmccully@coe.uga.edu

*Abstract*

The purpose of this study was to determine if chronic fatigue syndrome (CFS) is associated with reduced oxygen delivery to muscles. Patients with CFS according to CDC (Center for Disease Control) criteria (n=20) were compared with normal sedentary subjects (n=12). Muscle oxygen delivery was measured as the rate of post-exercise and post-ischaemia oxygen-haem resaturation. Oxygen-haem resaturation was measured in the medial gastrocnemius muscle using continuous-wavelength near-IR spectroscopy. Phosphocreatine resynthesis was measured simultaneously using  $(^{31}\text{P})$  magnetic resonance spectroscopy. **The time constant of oxygen delivery was significantly reduced in CFS patients after exercise (46.5 $\pm$ 16 s; mean $\pm$ S.D.) compared with that in controls (29.4 $\pm$ 6.9 s). The time constant of oxygen delivery was also reduced (20.0 $\pm$ 12 s) compared with controls (12.0 $\pm$ 2.8 s) after cuff ischaemia. Oxidative metabolism was also reduced by 20% in CFS patients, and a significant correlation was found between oxidative metabolism and recovery of oxygen delivery. In conclusion, oxygen delivery was reduced in CFS patients compared with that in sedentary controls. This result is consistent with previous studies showing abnormal autonomic control of blood flow.** Reduced oxidative delivery in CFS patients could be specifically related to CFS, or could be a non-specific effect of reduced activity levels in these patients. While these results suggest that reduced oxygen delivery could result in reduced oxidative metabolism and muscle fatigue, further studies will be needed to address this issue.

*Authors*

Michiels V, de Gucht V, Cluydts R, Fischler B

*Title*

**Attention and information processing efficiency in patients with Chronic Fatigue Syndrome.**

*Source*

J Clin Exp Neuropsychol 1999 Oct;21(5):709-29

*Author's Affiliation*

Free University of Brussels (VUB), Belgium

*Abstract*

In this study a battery of attentional tests and a verbal memory task were administered to outpatients with Chronic Fatigue Syndrome (CFS) in order to evaluate aspects of attention that have not been explored in this group to date. In addition, this study was designed to further examine memory function and to extend the few reports investigating the rate of cognitive processing independent of motor speed and the possibility of a modality-specific impairment of information processing. Twenty-nine patients with CFS and 22 healthy controls matched for age, gender, intelligence, and education were included in this study. The results show that patients with CFS do not seem to be impaired for modification of phasic arousal level, nor for visual selective attention requiring shifting of attention in

the visuospatial field. **The results further support the presence of reduced information processing speed and efficiency, and strengthen the evidence of a global non-modality-specific attentional dysfunction in patients with CFS. In this study the poor performance of patients with CFS on recall of verbal information was due to poor initial storage rather than to a retrieval failure.**

*Authors*

Moss RB, Mercandetti A, Vojdani A

*Title*

**TNF-alpha and chronic fatigue syndrome.**

*Source*

J Clin Immunol 1999 Sep;19(5):314-6

*Author's Affiliation*

The Immune Response Corporation, Carlsbad, California 92008, USA. shotdoc@imnr.com

*Abstract*

Based upon the clinical presentation of chronic fatigue syndrome (CFS), we hypothesized that proinflammatory cytokines may play a role in the pathogenesis of the disease. We therefore undertook a retrospective cross-sectional study to examine the role of TNF-alpha in patients with CFS. **Our results suggest a significant increase serum TNF-alpha in patients with CFS (P<0.0001) compared to non-CFS controls. This study supports the further examination of the role of proinflammatory mediators in CFS. Furthermore, the clinical testing of TNF-alpha blockers and other antiinflammatory agents for the treatment of this disease is warranted.**

*Title*

**Multiple chemical sensitivity: a 1999 consensus**

*Source*

Arch Environ Health 1999 May-Jun;54(3):147-9

*Abstract*

Consensus criteria for the definition of multiple chemical sensitivity (MCS) were first identified in a 1989 multidisciplinary survey of 89 clinicians and researchers with extensive experience in, but widely differing views of, MCS. A decade later, their top 5 consensus criteria (i.e., defining MCS as [1] a chronic condition [2] with symptoms that recur reproducibly [3] in response to low levels of exposure [4] to multiple unrelated chemicals and [5] improve or resolve when incitants are removed) are still unrefuted in published literature. Along with a 6th criterion that we now propose adding (i.e., requiring that symptoms occur in multiple organ systems), these criteria are all commonly encompassed by research definitions of MCS. Nonetheless, their standardized use in clinical settings is still lacking, long overdue, and greatly needed--especially in light of government studies in the United States, United Kingdom, and Canada that revealed 2-4 times as many cases of chemical sensitivity among Gulf War veterans than undeployed controls. In addition, state health department surveys of civilians in New Mexico and California showed that 2-6%, respectively, already had been diagnosed with MCS and that 16% of the civilians reported an "unusual sensitivity" to common everyday chemicals. **Given this high prevalence, as well as the 1994 consensus of the American Lung Association, American Medical Association, U.S. Environmental Protection Agency, and the U.S. Consumer Product Safety Commission that "complaints [of MCS]**

should not be dismissed as psychogenic, and a thorough workup is essential," we recommend that MCS be formally diagnosed--in addition to any other disorders that may be present--in all cases in which the 6 aforementioned consensus criteria are met and no single other organic disorder (e.g., mastocytosis) can account for all the signs and symptoms associated with chemical exposure. The millions of civilians and tens of thousands of Gulf War veterans who suffer from chemical sensitivity should not be kept waiting any longer for a standardized diagnosis while medical research continues to investigate the etiology of their signs and symptoms.

*Authors*

Neeck G, Riedel W

*Title*

**Hormonal perturbations in fibromyalgia syndrome**

*Source*

Ann N Y Acad Sci 1999 Jun 22;876:325-38; discussion 339

*Author's Affiliation*

Department of Rheumatology, University of Giessen, Bad Nauheim, Germany.

*Abstract*

The symptomatology characterizing fibromyalgia (FM) comprises three systems: the musculoskeletal system with widespread muscular pain, neuroendocrine disorders, and psychological distress including depression. Though the most prominent symptom of FM is pain in defined points of the musculoskeletal system, the numerous other somatoform and psychological disorders suppose a **common primary disturbance which we consider to originate within higher levels of the central nervous system. Recent studies of the entire endocrine profile of FM patients following a simultaneous challenge of the hypophysis with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone, growth hormone-releasing hormone, and luteinizing hormone-releasing hormone support the hypothesis that an elevated activity of CRH neurons determines not only many symptoms of FM but may also cause the deviations observed in the other hormonal axes. Hypothalamic CRH neurons thus may play a key role not only in "resetting" the various endocrine loops but possibly also nociceptive and psychological mechanisms as well.**

*Authors*

Ng SY

*Title*

**Hair calcium and magnesium levels in patients with fibromyalgia: a case center study.**

*Source*

J Manipulative Physiol Ther 1999 Nov-Dec;22(9):586-93

*Abstract*

BACKGROUND: Fibromyalgia is not an uncommon condition. Because its cause has yet to be identified. Treatment of the condition has been empirical; frequently, outcomes are unsatisfactory. Some patients with fibromyalgia were observed to have high hair calcium and magnesium levels

compared with healthy subjects. Because of this and because supplementing calcium with magnesium to fibromyalgia subjects reduced the number of tender points detected by digital palpation, it is worth investigating if patients with fibromyalgia have significantly higher hair calcium and magnesium levels than their healthy counterparts.

**OBJECTIVES:** To determine the degree of difference between the hair calcium and magnesium levels in patients with fibromyalgia and in healthy subjects.

**METHODS:** The study was retrospective and of paired design. Twelve patients who had hair analysis performed and met the criteria of fibromyalgia defined by American College of Rheumatology (1990) were selected consecutively from clinical files. These patients were then matched by age and sex to 12 healthy subjects selected consecutively from the same patient files who had hair analysis performed for check-up purposes. Nonparametric Wilcoxon rank sum tests were used to determine if the hair calcium and magnesium levels in patients with fibromyalgia were significantly higher than that of the control subjects.

**RESULTS:** Wilcoxon rank sum tests showed that patients with fibromyalgia had significantly higher calcium and magnesium levels than the control subjects at  $\alpha = .025$  and  $.05$ , respectively. **CONCLUSION:** In the presence of high hair calcium and magnesium levels, calcium and magnesium supplements may be indicated as an adjunctive treatment of fibromyalgia.

*Authors*

Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Kruger M, Schoeps P, Ackenheil M

*Title*

**Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region.**

*Source*

Arthritis Rheum 1999 Nov;42(11):2482-8

*Author's Affiliation*

University Hospital, Munich, Germany.

*Abstract*

To analyze the genotypes of the promoter region of the serotonin transporter gene (5-HTT) in patients with fibromyalgia (FM). **METHODS:** Genomic DNA from 62 patients meeting the American College of Rheumatology 1990 criteria for FM and 110 healthy controls was analyzed by polymerase chain reaction. Additionally, the psychopathologic state of 52 of the FM patients was evaluated using the Beck Depression Inventory (BDI) and the Symptom Checklist-90-Revised (SCL-90-R). **RESULTS:** The 5-HTTLPR genotypes in FM patients versus controls were distributed as follows: L/L 27% versus 34%, L/S 42% versus 50%, and S/S 31% versus 16%. FM patients with the S/S genotype had higher mean scores on the BDI and the SCL-90-R compared with those in the L/L and L/S groups. **CONCLUSION:** A higher frequency of the S/S genotype of 5-HTT was found in FM patients compared with healthy controls. The S/S subgroup exhibited higher mean levels of depression and psychological distress. These results support the notion of altered serotonin metabolism in at least a subgroup of patients with FM.

*Authors*

Ortiz Z, Shea B, Garcia Dieguez M, Boers M, Tugwell P, Boonen A, Wells G

*Title*

**The responsiveness of generic quality of life instruments in rheumatic diseases. A systematic review of randomized controlled trials.**

*Source*

J Rheumatol 1999 Jan;26(1):210-6

*Author's Affiliation*

Academia Nacional de Medicina de Buenos Aires, Argentina.

*Abstract*

To review the available evidence that has used generic instruments alone or in comparison with disease specific instruments. A systematic review was carried out using the methods recommended by the Cochrane Collaboration. We used MEDLINE and EMBASE searches and we performed a hand search of the abstracts listed under "quality of life" at American College of Rheumatology (ACR) meetings. Selection was limited to randomized controlled trials (RCT) using generic instruments in populations older than 18 years with any of the following diseases: rheumatoid arthritis, fibromyalgia, osteoporosis, osteoarthritis, systemic lupus erythematosus, and ankylosing spondylitis. Language was restricted to English papers. Studies using only disease-specific instruments were excluded. From 488 articles retrieved, 13 reports of 10 randomized controlled trials were selected. There were 101 abstracts on quality of life in ACR abstract books; 78 abstracts contained data on generic instruments, and of these, 9 described their use in RCT. Despite a substantial increase in the number of papers and abstracts addressing different aspects of generic questionnaires, the majority of the papers were descriptive. **The evidence is not yet available to document that any of the generic instruments pass the requirements of the OMERACT Filter.**

*Authors*

Pheley AM, Melby D, Schenck C, Mandel J, Peterson PK

*Title*

**Can we predict recovery in chronic fatigue syndrome?**

*Source*

Minn Med 1999 Nov;82(11):52-6

*Author's Affiliation*

Ohio University College of Osteopathic Medicine, Athens, USA.

*Abstract*

**PURPOSE:** To determine if selected demographic or clinical features of chronic fatigue syndrome (CFS) are associated with recovery.

**PATIENTS AND METHODS:** A follow-up questionnaire was mailed to 341 patients who had been ill on average for nine years to ascertain "recovery" rate (defined as self-reported recovery on a visual analog scale). Baseline demographic and clinical features (functional status and psychological status) recorded at the time of the initial (baseline) clinical visit were analyzed for their association with recovery at the time of follow-up.

**RESULTS:** Of the 177 patients who responded to the follow-up questionnaire, only 21 (12%) reported "recovery." Patients with higher levels of physical and social functioning and lower levels of

anxiety and obsessive-compulsiveness at baseline were more likely to report recovery at follow-up ( $p < 0.05$ ). No specific demographic characteristics were associated with recovery.

**CONCLUSION: These findings support previous research that complete recovery from CFS is rare and that patients with less severe illness at the initial clinic visit are more likely to have a positive prognosis for recovery. However, considerable overlap in illness severity was observed between the recovered and nonrecovered groups, suggesting that accurate prediction of recovery in individual CFS patients is not currently feasible.**

*Authors*

Romano TJ

*Title*

**Patients with fibromyalgia must be treated fairly.**

*Source*

Arch Intern Med 1999 Nov 8;159(20):2481-3

*Authors*

Russell IJ

*Title*

**Is fibromyalgia a distinct clinical entity? The clinical investigator's evidence.**

*Author's Affiliation*

University of Texas Health Science Center, San Antonio, Texas 78284-7868, USA.

*Source* Baillieres Best Pract Res Clin Rheumatol 1999 Sep;13(3):445-54

*Abstract*

**SUBJECTIVE:** Chronic widespread pain with multiple tender points (fibromyalgia syndrome) is a common clinical presentation. Criteria for inclusion of fibromyalgia patients into research studies have led to a medical model which integrates symptoms, signs, epidemiology, pathogenesis, responses to treatment, and prognosis. Controversy regarding fibromyalgia relates mostly to issues of compensation.

**THEORETICAL:** The diagnosis of fibromyalgia has been challenged as an inappropriate extraction from an epidemiological continuum of subjective discomfort. There are many conditions in which normally distributed measures exhibit distinctly unique outcomes at their extremes.

**OBJECTIVE:** Since fibromyalgia patients exhibit lowered pain thresholds, the process of nociception was studied. Samples of fibromyalgia urine, blood, and spinal fluid disclosed abnormalities consistent with a biomedical model of failed neuroregulatory inhibition, altered nociception, central sensitization, and allodynia. All three views support fibromyalgia as a distinct clinical syndrome deserving of informed medical care and continued research to better understand chronic widespread pain.

*Authors*

Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT

*Title*

**Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome.**

*Source*

J Pediatr 1999 Oct;135(4):494-9

*Author's Affiliation*

Department of Pediatrics, Center for Hereditary Eye Diseases, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

*Abstract*

**OBJECTIVE:** To report chronic fatigue syndrome (CFS) associated with both Ehlers-Danlos syndrome (EDS) and orthostatic intolerance.

**STUDY DESIGN:** Case series of adolescents referred to a tertiary clinic for the evaluation of CFS. All subjects had 2-dimensional echocardiography, tests of orthostatic tolerance, and examinations by both a geneticist and an ophthalmologist.

**RESULTS:** Twelve patients (11 female), median age 15.5 years, met diagnostic criteria for CFS and EDS, and all had either postural tachycardia or neurally mediated hypotension in response to orthostatic stress. Six had classical-type EDS and 6 had hypermobile-type EDS.

**CONCLUSIONS:** **Among patients with CFS and orthostatic intolerance, a subset also has EDS. We propose that the occurrence of these syndromes together can be attributed to the abnormal connective tissue in dependent blood vessels of those with EDS, which permits veins to distend excessively in response to ordinary hydrostatic pressures. This in turn leads to increased venous pooling and its hemodynamic and symptomatic consequences. These observations suggest that a careful search for hypermobility and connective tissue abnormalities should be part of the evaluation of patients with CFS and orthostatic intolerance syndromes.**

*Authors*

Russell IJ

*Title*

**Is fibromyalgia a distinct clinical entity? The clinical investigator's evidence.**

*Source*

Baillieres Best Pract Res Clin Rheumatol 1999 Sep;13(3):445-54

*Author's Affiliation*

University of Texas Health Science Center, San Antonio, Texas 78284-7868, USA.

*Abstract*

**SUBJECTIVE:** Chronic widespread pain with multiple tender points (fibromyalgia syndrome) is a common clinical presentation. Criteria for inclusion of fibromyalgia patients into research studies have led to a medical model which integrates symptoms, signs, epidemiology, pathogenesis,

responses to treatment, and prognosis. Controversy regarding fibromyalgia relates mostly to issues of compensation.

**THEORETICAL:** The diagnosis of fibromyalgia has been challenged as an inappropriate extraction from an epidemiological continuum of subjective discomfort. There are many conditions in which normally distributed measures exhibit distinctly unique outcomes at their extremes.

**OBJECTIVE:** Since fibromyalgia patients exhibit lowered pain thresholds, the process of nociception was studied. **Samples of fibromyalgia urine, blood, and spinal fluid disclosed abnormalities consistent with a biomedical model of failed neuroregulatory inhibition, altered nociception, central sensitization, and allodynia.** All three views support fibromyalgia as a distinct clinical syndrome deserving of informed medical care and continued research to better understand chronic widespread pain.

#### *Authors*

Russell IJ, Vipraio GA, Michalek JE, Craig FE, Kang YK, Richards AB

#### *Title*

**Lymphocyte markers and natural killer cell activity in fibromyalgia syndrome: effects of low-dose, sublingual use of human interferon-alpha.**

#### *Source*

J Interferon Cytokine Res 1999 Aug;19(8):969-78

#### *Author's Affiliation*

Department of Medicine, University Clinical Research Center, The University of Texas Health Science Center, San Antonio 78284-7868, USA. russell@uthscsa.edu

#### *Abstract*

A clinical study was designed to utilize flow cytometric immunophenotyping and chromium release from cultured tumor target cells to characterize peripheral blood mononuclear leukocyte (PBML) subpopulations and natural killer activity in healthy normal controls (n = 18) and in patients with fibromyalgia syndrome (FMS) at baseline (n = 124) and again after 6 weeks of treatment with low-doses of orally administered human interferon-alpha (IFN-alpha). Volunteer subjects discontinued all analgesic and sedative hypnotic medications for 2 weeks prior to the baseline phlebotomy. Laboratory measures included a complete blood count; a phenotypic analysis of PBML by flow cytometry; and in vitro natural killer (NK) cell activity. After baseline blood sample collection, the FMS patients were randomized to one of four parallel treatment groups (n = 28/group) to receive sublingual IFN-alpha (15 IU, 50 IU, 150 IU), or placebo every morning for 6 weeks. The tests were repeated at week 6 to evaluate treatment effects. **At baseline, FMS patients exhibited fewer lymphocytes and more CD25+ T lymphocytes than did normal controls. By week 6, the main significant and consistent change was a decrease in the HLA-DR+ CD4+ subpopulation in the 15 IU and 150 IU treatment groups. These data do not support an immunologically dysfunctional PBML phenotype among patients with FMS as has been observed in the chronic fatigue syndrome.**

*Authors*  
Saul JP

*Title*  
**Syncope: etiology, management, and when to refer.**

*Source*  
5: J S C Med Assoc 1999 Oct;95(10):385-7

*Author's Affiliation*  
MUSC, Charleston 29425, USA.

*Abstract*  
An abnormality of blood pressure control is by far the most likely cause of syncope in children; however, syncope in children may be due to primary cardiac dysrhythmias, particularly in the presence of structural heart disease. An appropriate work-up should include an ECG with a 60-second rhythm strip at first presentation. Tilt testing can usually wait until after a second occurrence on non-pharmacologic therapy. **Patients who require more than a history and ECG by the algorithm in the Figure should probably be referred to a cardiologist familiar with the evaluation of syncope. The common form of neurally mediated syncope is also probably related to both breath-holding spells in toddlers, and to many of the cases of chronic fatigue syndrome.**

*Authors*  
Sergi M, Rizzi M, Braghiroli A, Puttini PS, Greco M, Cazzola M, Andreoli A

*Title*  
**Periodic breathing during sleep in patients affected by fibromyalgia syndrome.**

*Source*  
Eur Respir J 1999 Jul;14(1):203-8

*Author's Affiliation*  
Servizio di Fisiopatologia Respiratoria, Azienda Ospedaliera--Polo Universitario L. Sacco, Milano, Italy.

*Abstract*  
Seventeen patients affected by fibromyalgia syndrome (FMS) (16 females and one male) and 17 matched healthy subjects underwent formal polysomnography, a sleep questionnaire and lung function tests. FMS patients slept significantly less efficiently than the healthy controls ( $p < 0.01$ ), had a higher proportion of stage 1 sleep (mean $\pm$ SD, 21 $\pm$ 6% versus 11 $\pm$ 4%;  $p < 0.001$ ), less slow wave sleep ( $p < 0.01$ ) and twice as many arousals per hour of sleep ( $p < 0.001$ ). The respiratory pattern of FMS patients showed a high occurrence of periodic breathing (PB) (15 $\pm$ 8% of total sleep time) in 15/17 patients, versus 2/17 control subjects. The short length of apnoeas and hypopnoeas did not affect the apnoea/hypopnoea index (5.1 $\pm$ 3.5 versus 3.2 $\pm$ 1.6; NS), but FMS patients had a greater number of desaturations per hour of sleep (8 $\pm$ 5 versus 3 $\pm$ 3;  $p < 0.01$ ). Pulmonary volumes did not differ between the two groups, but FMS patients had a lower transfer factor of the lung for carbon monoxide (TL,CO (5.8 $\pm$ 1 versus 7.7 $\pm$ 1 mmol x min<sup>-1</sup> x kPa<sup>-1</sup>);  $p = 0.001$ ). PB occurrence

correlated with TL,CO ( $r=-0.62$ ;  $p=0.01$ ), number of desaturations ( $r=0.76$ ,  $p=0.001$ ) and carbon dioxide tension in arterial blood ( $P_a,CO_2$ ) ( $r=-0.50$ ;  $p=0.05$ ). Stepwise multiple linear regression analysis showed desaturation frequency ( $p=0.0001$ ) and TL,CO ( $p=0.029$ ) to be the best predictors of PB percentage ( $R^2 0.73$ ;  $p=0.0001$ ). **Patients complaining of daytime hypersomnolence had a higher number of tender points, about twice as many arousals per hour and a lower sleep efficiency than patients who did not report this symptom. TL,CO was more impaired and the occurrence of PB was higher. The occurrence of periodic breathing in fibromyalgia syndrome patients, which was previously unreported, and is shown to be linked to a reduction of transfer factor of the lung for carbon monoxide could play a major role in the symptoms of poor sleep of these patients.**

*Authors*

Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, Fich A, Buskila D

*Title*

**Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications**

*Source*

Am J Gastroenterol 1999 Dec;94(12):3541-6

*Author's Affiliation*

Department of Gastroenterology, Soroka Medical Center and Faculty of the Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

*Abstract*

**OBJECTIVE:** The irritable bowel syndrome (IBS) and the fibromyalgia syndrome (FS) coexist in many patients. We conducted complementary studies of the prevalence of FS in IBS patients and matched controls, and of IBS in FS patients and the implications of concomitant IBS and FS on health-related quality of life (HRQOL).

**METHODS:** A study of 79 IBS patients with 72 matched controls (IBS study), and a study of 100 FS patients (FS study). All participants underwent tests of tender point sites and threshold of tenderness and answered questionnaires including personal and medical history, GI symptoms, and indices of HRQOL. **RESULTS:** In the IBS study, 25 of the 79 IBS patients (31.6%) and 3 of the 72 controls (4.2%) had FS ( $p < 0.001$ ). Statistically significant differences were found among the study groups in terms of global well-being ( $p < 0.001$ ), sleep disturbance ( $p < 0.001$ ), physician visits ( $p = 0.003$ ), pain ( $p < 0.001$ ), anxiety ( $p < 0.001$ ), and global severity index (SCL-90-R) ( $p < 0.001$ ), with patients with IBS and FS having the worst results. IBS patients had of the 100 FS patients (32%) had IBS. Patients with both disorders had significantly worse scores for physical functioning ( $p = 0.030$ ) and for all but one of a 16-item quality of life questionnaire.

**CONCLUSIONS:** FS and IBS coexist in many patients. Patients with both disorders have worse scores on HRQOL indices than patients with either disorder alone, or controls. Physicians treating these patients should be aware of the overlap, which can affect the presentation of symptoms, health care utilization, and treatment strategies.

*Authors*

Swezey RL, Adams J

*Title*

**Fibromyalgia: a risk factor for osteoporosis.**

*Source*

J Rheumatol 1999 Dec;26(12):2642-4

*Author's Affiliation*

Osteoporosis Prevention and Treatment Center, Santa Monica, California 90404, USA.

*Abstract*

**OBJECTIVE:** To investigate associations of bone mineral density (BMD) and osteoporosis in patients with fibromyalgia (FM) and healthy controls.

**METHODS:** Twenty-four women meeting the American College of Rheumatology criteria for FM (23 Caucasians, one Asian) were each compared to 2 age (+/-3 years) and ethnically matched controls by bone densitometry of the femoral neck and lumbar spine. The patients' ages were 33 to 60 years. No patient or control used steroids or other bone demineralizing agents. Simple T tests were used to compare hip and lumbar spine BMD of FM cases to controls by 3 decades (31-40, 41-50, 51-60 years).

**RESULTS:** The patients with FM in all 3 decades had a lower mean BMD of the spine ( $p < 0.05$ ). The femoral neck BMD were also lower, but reached significance ( $p < 0.05$ ) only in the 51-60 age group.

**CONCLUSION:** **FM in this pilot study was frequently associated with osteoporosis.** Early detection and implementation of appropriate nutritional supplementation (calcium/vitamin D), resistive and weight bearing exercise, and specific bone mineral enhancing pharmacological therapy may be indicated in pre, peri, and postmenopausal subjects.

*Authors*

Tougas G

*Title*

**The autonomic nervous system in functional bowel disorders.**

*Source*

Can J Gastroenterol 1999 Mar;13 Suppl A:15A-17A

*Author's Affiliation*

Digestive Diseases Research Program, Division of Gastroenterology, McMaster University, Hamilton, Canada. tougasg@fhs.mcmaster.ca

*Abstract*

Communications along the brain-gut axis involve neural pathways as well as immune and endocrine mechanisms. The two branches of the autonomic nervous system are integrated anatomically and functionally with visceral sensory pathways, and are responsible for the homeostatic regulation of gut function. The autonomic nervous system is also a major mediator of the visceral response to central influences such as psychological stress. As defined, functional disorders comprise a constellation of symptoms, some of which suggest the presence of altered perception, while other symptoms point to disordered gastrointestinal function as the cause of the symptoms. **A growing number of reports have demonstrated disordered autonomic function in subgroups of functional bowel patients.** While a number of different methods were used to assess autonomic

function, the reports point to a generally decreased vagal (parasympathetic) outflow or increased sympathetic activity in conditions usually associated with slow or decreased gastrointestinal motility, while other studies found either an increased cholinergic activity or a decreased sympathetic activity in patients with symptoms compatible with an increased motor activity. Under certain conditions, altered autonomic balance (including low vagal tone and increased sympathetic activity) may alter visceral perception. **Autonomic dysfunction may also represent the physiological pathway accounting for many of the extraintestinal symptoms seen in irritable bowel syndrome patients and some of the frequent gastrointestinal complaints reported by patients with disorders such as chronic fatigue and fibromyalgia.**

*Authors*

White KP, Harth M

*Title*

**The occurrence and impact of generalized pain.**

*Source*

Baillieres Best Pract Res Clin Rheumatol 1999 Sep;13(3):379-89

*Author's Affiliation*

Department of Medicine, London Health Sciences Center, Ontario, Canada.

*Abstract*

A major problem with estimating the impact of chronic generalized pain is that the term remains undefined. It appears to encompass several distinct clinical entities, including rheumatoid arthritis and fibromyalgia, which can exist alone or together in a given individual. Nonetheless, chronic generalized pain appears to have a sizable impact on both the individual and society. Although little is known about causal relationships, demographic risk factors for chronic generalized pain are female sex, age in the forties and fifties, lower income, lower education, and being divorced or separated. Chronic generalized pain affects the individual in several ways, **including physical and psychological distress, losses of function, quality of life, employment and income, and prolonged litigation for many. Its impact on society includes increased utilization of health care resources, loss of work productivity, disability and insurance cost, cost of litigation and social policy.** Future research into the impact of chronic generalized pain must begin by defining this term in a way that is both valid in construct and convenient to use. Research is also warranted to develop and validate diagnostic tools that may better distinguish various subsets of chronic generalized pain, both to better understand the pathological processes involved and to allow for estimates of the relative contribution of each subset to societal costs.

*Authors*

White KP, Speechley M, Harth M, Ostbye T

*Title*

**The London Fibromyalgia Epidemiology Study: comparing the demographic and clinical characteristics in 100 random community cases of fibromyalgia versus controls.**

*Source*

J Rheumatol 1999 Jul;26(7):1577-85

*Author's Affiliation*

Department of Medicine, University of Western Ontario, London, Canada. kevin.white@lhsc.on.ca

*Abstract*

**OBJECTIVE:** To identify demographic and clinical features that distinguish fibromyalgia (FM) from other chronic widespread pain. **METHODS:** We identified 100 confirmed FM cases, 76 widespread pain controls, and 135 general controls in a random community survey of 3395 noninstitutionalized adults living in London, Ontario. FM cases were distinguished from pain controls using the 1990 American College of Rheumatology (ACR) classification criteria for FM.

**RESULTS:** The mean age of FM cases was 47.8 years (range 19 to 86), the same as for pain controls; 86% of FM cases were female versus 67.1% of pain controls ( $p < 0.01$ ). FM cases were less educated than general controls ( $p = 0.03$ ). Male and female FM cases were similar, except females were older and reported more major symptoms (both  $p = 0.02$ ). FM cases reported more severe pain and fatigue, more symptoms, more major symptoms, and worse overall health than pain controls or general controls. The most commonly reported major symptoms among FM cases were musculoskeletal pain (77.3%), fatigue (77.3%), severe fatigue lasting 24 h after minimal activity (77.0%), nonrestorative sleep (65.7%), and insomnia (56.0%). Subjects with 11-14 tender points were more similar to those with 15-18 tender points than to those with 7-10 points in 11 of 14 clinical variables. **On multivariate analysis, 4 symptoms distinguished FM cases from pain controls: pain severity ( $p = 0.004$ ), severe fatigue lasting 24 h after minimal activity ( $p = 0.006$ ), weakness ( $p = 0.008$ ), and self-reported swelling of neck glands ( $p = 0.01$ ).** **CONCLUSION:** In the general population, adults who meet the ACR definition of FM appear to have distinct features compared to those with chronic widespread pain who do not meet criteria.

*Authors* White KP, Speechley M, Harth M, Ostbye T

*Title* The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario

*Source* J Rheumatol 1999 Jul;26(7):1570-6

*Authors' Affiliation* Department of Medicine, University of Western Ontario, London, Canada.

[Keven.white@lhsc.on.ca](mailto:Keven.white@lhsc.on.ca)

*Abstract* **OBJECTIVE:** To estimate the point prevalence of fibromyalgia syndrome (FM) among noninstitutionalized Canadian adults; and to assess the effect of demographic variables on the odds of having FM. **METHODS:** A screening questionnaire was administered via telephone to a random community sample of 3395 noninstitutionalized adults residing in London, Ontario. Individuals screening positive were invited to be examined by a rheumatologist to confirm or exclude FM using the 1990 American College of Rheumatology classification criteria. **RESULTS:** One hundred confirmed cases of FM were identified, of whom 86 were women. Mean age among FM cases was 49.2 years among women, 39.3 years among men ( $p < 0.02$ ). FM affects an estimated 4.9% of adult women and 1.6% (1.3%, 1.9%) of adult men in London, for a female to male ratio of roughly 3 to one. In women, prevalence rises steadily with age from  $< 1\%$  in women aged 18-30 to almost 8% in women 55-64. Thereafter, it declines. The peak prevalence in men also appears to be in middle age (2.5%; 1.1%, 5.7%). FM affects 3.3% (3.2%, 3.4%) of noninstitutionalized adults in London. Female sex, middle age, less education, lower household income, being divorced, and being disabled are associated with increased odds of having FM. **CONCLUSION:** FM is a common musculoskeletal disorder among Canadian adults, especially among women and persons of lower socioeconomic status.

*Authors*

White KP, Speechley M, Harth M, Ostbye T

*Title*

**Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario: the London Fibromyalgia Epidemiology Study.**

*Source*

Arthritis Rheum 1999 Jan;42(1):76-83

*Author's Affiliation*

University of Western Ontario, London, Canada.

*Abstract*

**OBJECTIVE:** To compare function and disability in fibromyalgia syndrome (FMS) cases in the community versus controls, and to identify variables predicting poor function and disability.

**METHODS:** We identified 100 FMS cases, 76 pain controls, and 135 general controls in a random survey of 3,395 noninstitutionalized adults.

**RESULTS:** FMS cases reported worse function ( $P < 0.00001$ ), more days in bed ( $P < 0.001$ ), and more healthy years of life lost ( $P < 0.0001$ ). More FMS cases were disabled ( $P < 0.00001$ ) and receiving pensions ( $P < 0.00001$ ). Risk factors for disability included middle age and previous heavy manual labor. Pain, fatigue, and weakness were most often claimed to affect the ability to work. Variables predicting work disability were the Fibromyalgia Impact Questionnaire (FIQ) score, a prior diagnosis of FMS, nonrestorative sleep, and past heavy physical labor. Variables influencing the FIQ score were the number of major symptoms, self-reported health satisfaction, tender point count, and education level. **CONCLUSION: FMS commonly results in loss of function and work disability.**

*Authors*

Wilson RB, Gluck OS, Tesser JR, Rice JC, Meyer A, Bridges AJ

*Title*

**Antipolymer antibody reactivity in a subset of patients with fibromyalgia correlates with severity.**

*Source*

J Rheumatol 1999 Feb;26(2):402-7

*Author's Affiliation*

Autoimmune Technologies, L.L.C., New Orleans, Louisiana 70112, USA. rwilson@communique.net

*Abstract*

**OBJECTIVE:** To determine the prevalence of antipolymer antibodies (APA) in patients with fibromyalgia (FM) and autoimmune disease control groups and to determine if the presence of these antibodies correlates with severity in patients with FM.

**METHODS:** Sera from patients with FM ( $n = 47$ ), osteoarthritis (OA) ( $n = 16$ ), and rheumatoid arthritis (RA) ( $n = 13$ ) were analyzed. Patients with implants of any kind and patients with concurrent

autoimmune conditions were excluded from study. Banked sera from autoimmune disease controls including poly/dermatomyositis (n = 15), RA (n = 30), systemic lupus erythmatosus (SLE) (n = 30), and systemic sclerosis (SSc) (n = 30) were also analyzed. To determine if seroreactivity correlates with severity, banked sera from patients with FM assessed as severe (n = 28) or mild (n = 37) and from controls (n = 21) were assayed.

**RESULTS:** Following analysis, the prevalence of seroreactivity was found to be higher in patients with FM (22/47, 47%) compared to patients with OA (3/16, 19%; p<0.1) or RA (1/13, 8%; p<0.05) and the autoimmune disease control sera from poly/dermatomyositis (2/15, 13%; p<0.05), and patients with RA (3/30, 10%; p<0.01), SLE (1/30, 3%; p<0.01), and SSc (1/30, 3%; p<0.01). The prevalence of APA seroreactivity was also significantly higher in patients with severe FM (17/28, 61%) compared to patients with mild FM (11/37, 30%; p<0.05) and controls (4/21, 19%; p<0.01). In addition, both mean threshold and mean tolerance dolorimetry scores were significantly lower in the seropositive patients with mild FM (1.33+/-0.21, 1.95+/-0.25, respectively) compared to the seronegative patients (1.83+/-0.08, 2.53+/-0.11; p<0.05 for both comparisons, respectively).

**CONCLUSION:** **These results reveal that an immunological response, production of anti-polymer antibodies, is associated with a subset of patients with FM. The results also suggest that the APA assay may be an objective marker in the diagnosis and assessment of FM and may provide additional avenues of investigation into the pathophysiological processes involved in FM.**

*Authors*  
Wolfe F

*Title*  
**Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia.**

*Source*  
Rheumatology (Oxford) 1999 Apr;38(4):355-61

*Author's Affiliation*  
Arthritis Research Center and University of Kansas School of Medicine, Wichita 67214, USA

*Abstract*  
**OBJECTIVES:** The Western Ontario MacMaster (WOMAC) is a validated instrument designed specifically for the assessment of lower extremity pain and function in osteoarthritis (OA) of the knee or hip. In the clinic, however, we have noted that OA patients frequently have other musculoskeletal and non-musculoskeletal problems that might contribute to the total level of pain and functional abnormality that is measured by the WOMAC. In this report, we investigated back pain and non-articular factors that might explain WOMAC scores in patients with OA, rheumatoid arthritis (RA) and fibromyalgia (FM) in order to understand the specificity of this instrument.

**METHODS:** RA, OA and FM patients participating in long-term outcomes studies completed the WOMAC and were assessed for low back pain, fatigue, depression and rheumatic disease symptoms by mailed questionnaires.

**RESULTS:** **Regardless of diagnosis, WOMAC functional and pain scores were very much higher (abnormal) among those complaining of back pain.** On average, WOMAC scores for back pain (+) patients exceeded those of back pain (-) patients by approximately 65%, and 52% of

OA patients reported back pain. In regression analyses, study symptom variables explained 42, 44 and 38% of the variance in WOMAC function, pain and stiffness scores, respectively. In the subset of OA patients, radiographic scores added little to the explained variance. The strongest predictor of WOMAC abnormality in bivariate and multivariate analyses was the fatigue score, with correlations of 0.58, 0.60 and 0.53 with WOMAC function, pain and stiffness, respectively. The WOMAC performed well in RA and FM, and correlated strongly with the Health Assessment Questionnaire (HAQ) disability scale and a visual analogue scale (VAS) pain scale.

**CONCLUSION:** The WOMAC captures more than just knee or hip pain and dysfunction, **and is clearly influenced by the presence of fatigue, symptom counts, depression and low back pain.** WOMAC scores also appear to reflect psychological and constitutional status. These observations suggest the need for care in interpreting WOMAC scores as just a measure of function, pain or stiffness, and indicate the considerable importance of psychological factors in rheumatic disease and rheumatic disease assessments.

#### *Authors*

Yunus MB, Khan MA, Rawlings KK, Green JR, Olson JM, Shah S

#### *Title*

**Genetic linkage analysis of multicase families with fibromyalgia syndrome.**

#### *Source*

J Rheumatol 1999 Feb;26(2):408-12

#### *Abstract*

**OBJECTIVE:** Based on the reports of familial aggregation of fibromyalgia (FM) syndrome, we investigated its possible genetic linkage to HLA by studying multicase families.

**METHODS:** Forty Caucasian multicase families with a diagnosis of FM (American College of Rheumatology criteria) in 2 or more first degree relatives were investigated. Eighty-five affected and 21 unaffected members of 41 sibships were studied. Depression symptomology was assessed by Zung Self-rating Depression Scale (SDS). HLA typing was performed for A, B, and DRB 1 alleles, and haplotypes were determined with no knowledge of the subject's diagnosis. We investigated genetic linkage to the HLA region by evaluating sibships in multicase families.

**RESULTS:** Sibship analysis showed significant genetic linkage of FM to the HLA region ( $p = 0.028$ ). Subgroup analysis was also performed for 17 families where the proband was also noted to have depression (with an SDS index value  $\geq 60$ ). We found that the presence of depression did not influence the observed results ( $p = 0.22$ ).

**CONCLUSION:.** **Our study of 40 multicase families confirms existence of a possible gene for FM that is linked with the HLA region. Our results should be regarded as preliminary** and their independent confirmation by other studies is warranted.