

FIBROMYALGIA: ABSTRACTS FROM SELECTED JOURNAL ARTICLES, 1999

The abstracts in this collection are intended to provide health professionals and patients with a convenient overview of trends in research on fibromyalgia published in medical journals in the year 1999. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space. The abstracts are arranged in alphabetical order by lead author. Similar collections of abstracts published in 2000 and 2001 can be found on the website of the National Fibromyalgia Partnership: www.fmpartnership.org.

Adler GK, Kinsley BT, Hurwitz S, Mossey CJ, Goldenberg DL
Reduced hypothalamic-pituitary and sympathoadrenal responses to hypoglycemia in women with fibromyalgia syndrome

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

Bennett RM

Disordered growth hormone secretion in fibromyalgia: a review of recent findings and an hypothesized etiology

Growth hormone (GH) deficiency occurs in about 30% of fibromyalgia patients. Treatment of GH deficient fibromyalgia patients with recombinant growth hormone improves several clinical features, including the tender point count. Defective GH secretion in these patients appears to be due to increased somatostatin tone in the hypothalamus. An hypothesis is presented which relates dysfunctional GH secretion to the effects of intermittent hypercortisolemia on upregulating the density of beta-adrenergic receptors in the hypothalamus. The resulting augmentation of beta-adrenergic tone stimulates the release of somatostatin, thus impairing GH secretion.

Z Rheumatol 1998; 57 Suppl 2:72-6

Bennett RM

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

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 non-nociceptive 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."

Mayo Clin Proc 1999 Apr; 74(4):38-98

Berman BM, Swyers JP

Complementary medicine treatments for fibromyalgia syndrome

Fibromyalgia is a chronic-pain-related syndrome associated with high rates of complementary and alternative medicine (CAM) use. Among the many CAM therapies frequently used by fibromyalgia patients, empirical research data exist to support the use of only three: (1) mind-body, (2) acupuncture, and (3) manipulative therapies for treating fibromyalgia. The strongest data exist for the use of mind-body techniques (e.g. biofeedback, hypnosis, cognitive behavioral therapy), particularly when utilized as part of a multidisciplinary approach to treatment. The weakest data exist for manipulative techniques (e.g., chiropractic and massage). The data supporting the use of acupuncture for fibromyalgia are only moderately strong. Also, for some fibromyalgia patients, acupuncture can exacerbate symptoms, further complicating its application for this condition. Further research is needed not only in these three areas, but also for other treatments being frequently utilized by fibromyalgia patients.

Baillieres Best Pract Res Clin Rheumatol 1999 Sep; 13(3):487-92

Breau LM, McGrath PJ, Ju LH

Review of juvenile primary fibromyalgia and chronic fatigue syndrome

This article reviews the current literature on childhood fibromyalgia and chronic fatigue syndrome. In doing so, it questions assumptions about the presumed nature of the disorders--that they are distinct from each other and are duplicates of their adult counterparts. It also attempts to synthesize the available data to reach some preliminary judgments about these disorders: that fibromyalgia and chronic fatigue syndrome may be related in children and may not be duplicates of the adult disorders; that psychological and psychosocial factors are unlikely contributors to the etiology of these disorders; and that the evidence is increasingly pointing to a role for genetic factors in their etiology. A discussion of the research into treatments for childhood fibromyalgia and chronic fatigue syndrome highlights the lack of well-designed, controlled studies. Finally, directions for future research are offered where results of the current literature are unclear.

J Dev Behav Pediatr 1999 Aug; 20(4):278-88

Buskila D

Drug therapy

Because of the lack of understanding of the basis of fibromyalgia, therapy remains empiric. This article reviews the different drug elements used in fibromyalgia, including psychotropic agents (anti-depressants, sedatives and hypnotics), anti-inflammatories, analgesics and other pharmacological

compounds. The strength of evidence for the therapeutic effect of each medicinal modality is presented, with the emphasis on results of randomized controlled trials. The importance of the expected effects of the current drug modalities, and whether these drugs have short- or long-term effects, are also discussed. Future directions, including testing of newer antidepressants, analgesics and non-steroidal anti-inflammatory drugs (Cox-2 selective inhibitors), as well as the need for long-term comparative trials of both drug efficacy and toxicity, are discussed. *Baillieres Best Pract Res Clin Rheumatol* 1999 Sep; 13(3):479-85

Crofford LJ

The hypothalamic-pituitary-adrenal stress axis in fibromyalgia and chronic fatigue syndrome

HPA axis abnormalities in FM, CFS, and other stress-related disorders must be placed in a broad clinical context. We know that interventions providing symptomatic improvement in patients with FM and CFS can directly or indirectly affect the HPA axis. These interventions include exercise, tricyclic antidepressants, and serotonin reuptake inhibitors. There is little direct information as to how the specific HPA axis perturbations seen in FM can be related to the major symptomatic manifestations of pain, fatigue, sleep disturbance, and psychological distress. Since many of these somatic and psychological symptoms are present in other syndromes that exhibit HPA axis disturbances, it seems reasonable to suggest that there may be some relationship between basal and dynamic function of the HPA axis and clinical manifestations of FM and CFS.

Z Rheumatol 1998; 57 Suppl 2:67-71

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

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.

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

Giovengo SL, Russell IJ, Larson AA

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

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 (\pm 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 that a central mechanism, involving abnormalities in neuropeptides such as NGF, may be a factor in the pathogenesis of FM.

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

Grace GM, Nielson WR, Hopkins MA, Berg MA

Concentration and memory deficits in patients with fibromyalgia syndrome

The present study compared 30 patients with fibromyalgia syndrome (FS) to 30 healthy control subjects matched for age, sex, and estimated intellectual level on standardized measures of attention, concentration, and memory as well as subjective ratings of memory abilities and sleep quality. In addition, in order to investigate the relationship between cognitive functioning and other physical and psychological symptoms, subjects with FS completed psychological measures of pain severity, trait anxiety, and depression. Results indicated that patients with FS performed more poorly on tests of immediate and delayed recall, and sustained auditory concentration, and their ratings of both their memory abilities and sleep quality were lower than those of controls. Furthermore, perceived memory deficits of the FS subjects were disproportionately greater than their objective deficits. Results indicated significant correlations between performance on memory and concentration measures and scores on questionnaires of pain severity and trait anxiety. Implications of these results for multidisciplinary treatment programs are discussed.

Clin Exp Neuropsychol 1999 Aug; 21(4):477-87

Heim C, Ehlert U, Hellhammer DH

The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders

Representing a challenge for current concepts of stress research, a number of studies have now provided convincing evidence that the adrenal gland is hypoactive in some stress-related states. The phenomenon of hypocortisolism has mainly been described for patients who experienced a traumatic event and subsequently developed post-traumatic stress disorder (PTSD). However, as presented in this review, hypocortisolism does not merely represent a specific correlate of PTSD, since similar findings have been reported for healthy individuals living under conditions of chronic stress as well as for patients with several bodily disorders. These include chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis, and asthma, and many of these disorders have been related to stress. Although hypocortisolism appears to be a frequent and widespread phenomenon, the nature of the underlying mechanisms and the homology of these mechanisms within and across clinical groups remain speculative. Potential mechanisms include dysregulations on several levels of the hypothalamic-pituitary-adrenal axis. In addition, factors such as genetic vulnerability, previous stress experience, coping and personality styles may

determine the manifestation of this neuroendocrine abnormality. Several authors proposed theoretical concepts on the development or physiological meaning of hypocortisolism. Based on the reviewed findings, we propose that a persistent lack of cortisol availability in traumatized or chronically stressed individuals may promote an increased vulnerability for the development of stress-related bodily disorders. This pathophysiological model may have important implications for the prevention, diagnosis and treatment of the classical psychosomatic disorders. *Psychoneuroendocrinology* 2000 Jan; 25(1): 1-35

Hodgson MJ, Kipen HM

Gulf War illnesses: causation and treatment

Soldiers returning from the Gulf War in 1991 described a range of symptoms, including some consistent with the chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. Well-defined adverse health events attributable to service in the Gulf occurred. However, controlled epidemiological studies in Gulf War veterans and controls describe significant excesses of symptoms that were not clearly associated with pathologic disease. At least 12% of veterans currently receive some form of disability from the Department of Veterans Affairs [USA]. A number of reports outline theories proposed to explain the excess, but few are scientifically supported. Management guidelines for this spectrum of disorders resembles that of many of "emerging overlap syndromes," including multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. They include the establishment of a trusting doctor-patient relationship, negotiations around a common ground of scientific and etiologic beliefs, non-labeling of the disorder, and work toward recovery in the absence of clear etiologic answers.

J Occup Environ Med 1999 Jun; 41(6):443-52

Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, Haus E, Demitrack MA, Crofford L

Melatonin levels in women with fibromyalgia and chronic fatigue syndrome

OBJECTIVE: Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are stress-associated disorders mainly affecting women. FM is characterized primarily by widespread musculoskeletal pain, and CFS by profound debilitating fatigue, but there is considerable overlap of clinical symptoms between these 2 syndromes. Neuroendocrine abnormalities have been noted in both FM and CFS, and desynchronization of circadian systems has been postulated in their etiology. The pineal hormone melatonin is involved in synchronizing circadian systems, and the use of

exogenous melatonin has become widespread in patients with FM and CFS. **METHODS:** We examined the characteristics and relationship of melatonin and cortisol levels in premenopausal women with FM (N=9) or CFS (N=8), compared to age and menstrual cycle phase matched controls. Blood was collected from an indwelling intravenous catheter every 10 min over 24 h, and plasma melatonin and cortisol were determined by radioimmunoassay at 60 and 10 min intervals, respectively. **RESULTS:** Night-time (23:00-06:50) plasma melatonin levels were significantly higher in FM patients compared to controls ($p < 0.05$), but there was no significant difference in melatonin levels between CFS patients and controls. No differences in the timing of cortisol and melatonin secretory patterns and no internal desynchronization of the 2 rhythms were found in either patient group, compared to controls. **CONCLUSION:** Raised plasma melatonin concentrations have been documented in several other conditions that are associated with dysregulation of neuroendocrine axes. Increased melatonin levels may represent a marker of increased susceptibility to stress-induced hypothalamic disruptions. These data indicate that there is no rationale for melatonin replacement therapy in patients with FM and CFS.
J Rheumatol 1999 Dec; 26(12):2675-80

Lentz MJ, Landis CA, Rothermel J, Shaver JL

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

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.

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

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

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

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-IR 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 (≥ 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.

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

Miller CS

Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abidction

Toxicant-induced loss of tolerance (or TILT) describes a two-step disease process in which (1) certain chemical exposures, e.g., indoor air contaminants, chemical spills, or pesticide applications, cause certain susceptible persons to lose their prior natural tolerance for common chemicals, foods, and drugs (initiation); (2) subsequently, previously tolerated exposures trigger symptoms. Responses may manifest as addictive or abidctive (avoidant) behaviors. In some affected individuals, overlapping responses to common chemical, food, and drug exposures, as well as habituation to recurrent exposures, may hide (mask) responses to particular triggers. Accumulating evidence suggests that this disease process might underlie a broad array of medical illnesses including chronic fatigue, fibromyalgia, migraine headaches, depression, asthma, the unexplained illnesses of Gulf War veterans, multiple chemical sensitivity, and attention deficit disorder.

Toxicol Ind Health 1999 Apr-Jun; 1 5(3-4):28-9

Neeck G, Riedel W

Hormonal perturbations in fibromyalgia syndrome

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.

Ann NY Acad Sci 1999; Jun 22;876:325-38

Pennacchio EA, Borg-Stein J, Keith DA

The incidence of pain in the muscles of mastication in patients with fibromyalgia

This study recognizes the high incidence of temporomandibular symptoms in a group of patients with documented fibromyalgia. Findings indicate that the diagnosis and treatment of temporomandibular disorders and fibromyalgia have many similarities.

J Mass Dent Soc 1998 Fall; 47(3):8-12

Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, Hewett JE, Johnson JC

A meta-analysis of fibromyalgia treatment interventions

OBJECTIVE: To evaluate and compare the efficacy of pharmacological and non-pharmacological treatments of fibromyalgia syndrome (FMS). **METHODS:** This meta-analysis of 49 fibromyalgia treatment outcome studies assessed the efficacy of pharmacological and non-pharmacological treatment across four types of outcome measures—physical status, self-report of FMS symptoms, psychological status, and daily functioning. **RESULTS:** After controlling for study design, antidepressants resulted in improvements on physical status and self-report of FMS symptoms. All non-pharmacological treatments were associated with significant improvements in all four categories of outcome measures with the exception that physically-based treatment (primarily exercise) did not significantly improve daily functioning. When compared, non-pharmacological treatment appears to be more efficacious in improving self-report of FMS symptoms than pharmacological treatment alone. A similar trend was suggested for functional measures. **CONCLUSION:** The optimal intervention for FMS would include non-pharmacological treatments, specifically exercise and cognitive-behavioral therapy, in addition to appropriate medication management as needed for sleep and pain symptoms.

Ann Behav Med 1999 Spring;21(2):180-91

Russell IJ

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

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. However, 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.

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

Russell IJ, Michalek JE, Kang YK, Richards AB

Reduction of morning stiffness and improvement in physical function in fibromyalgia syndrome patients treated sublingually with low doses of human interferon-alpha

One hundred and twelve fibromyalgia syndrome (FMS) patients were randomized into one of four demographically similar groups (N=28/group). Sequential primary FMS patient volunteers were to receive daily sublingual placebo or interferon-alpha (IFN-alpha) at 15, 50, or 150 IU. After a screening evaluation, analgesic or sedative hypnotic medications were withdrawn. Two weeks later, daily IFN-alpha or placebo was initiated with follow-up evaluations at 2-week intervals ending with week 6. One primary, three secondary, and seven tertiary variables were assessed. Study outcome was based on improvement in the tender point index (TPI). The TPI did not improve with any IFN-alpha dose. However, significant improvement was seen in morning stiffness and in physical function with the 50 IU IFN-alpha ($p < 0.01$). None of the other outcome means changed significantly and no adverse events were attributable to IFN-alpha therapy.

J Interferon Cytokine Res 1999 Aug; 19(8):96-8

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

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

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.

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

Schwarz MJ, Spath M, Muller-Bardorff H, Pongratz DE, Bondy B, Ackenheil M
Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients

The serotonergic system has repeatedly been discussed to be involved in the pathophysiology of fibromyalgia (FM), which is a syndrome of widespread pain and sleep disturbance. Elevated levels of substance P (SP), a mediator of nociception, have been described in FM. In this study the possible relationship between SP and serotonin (5-HT) together with its precursor tryptophan (TRP) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) was evaluated in 51 serum samples of fibromyalgia patients. These parameters were compared with clinical data such as pain intensity or sleep quality. A strong negative correlation between SP and 5-HIAA ($p=.000$) as well as between SP and TRP ($p=.009$) could be demonstrated. High serum concentrations of 5-HIAA and TRP showed a significant relation to low pain scores (5-HIAA: $p=.030$; TRP: $p=.014$). Moreover, 5-HIAA was strongly related to good quality of sleep ($p=.000$), while SP was related to sleep disturbance ($p=.005$). These data are valid to support the hypothesis of a systemic involvement of 5-HT and SP in fibromyalgia.

Neurosci Lett 1999 Jan 15; 259(3):196-8

Sprott H, Muller A, Heine H

Collagen cross-links in fibromyalgia syndrome

OBJECTIVE: The acceptance of fibromyalgia as a disease entity and its definitive diagnosis have been hampered by a dearth of knowledge concerning the underlying pathophysiology of this disease and the lack of specific biochemical markers applicable to its diagnosis. To determine whether abnormal collagen metabolism is a characteristic of fibromyalgia, we have analyzed collagen metabolites in the urine and serum of patients with fibromyalgia. **METHODS:** The diagnosis of fibromyalgia was made according to the American College of Rheumatology criteria. Urine and serum were collected under standardized conditions from 39 patients and 55 age- and sex-matched controls. Pyridinoline (Pyl) and deoxypyridinoline (Dpyl), which represent products of lysyl oxidase-mediated cross-linking in collagen and are indicators of connective tissue and bone degradation, respectively, were analyzed by ion-paired and gradient HPLC method with fluorescence detection (HPLC). Levels of hydroxyproline (Hyp), a collagen turnover marker, were also measured. The findings were related to creatinine levels and the Pyl/Dpyl ratio determined. **RESULTS:** The Pyl/Dpyl ratios in the urine and serum and the Hyp in the urine were significantly lower in patients with fibromyalgia than in healthy controls. **CONCLUSION:** Decreased levels of collagen cross-linking may contribute to remodeling of the extracellular matrix and collagen deposition around the nerve fibers in fibromyalgia and contribute to the lower pain threshold at the tender points. Analysis of altered collagen metabolism either by histologic examination on biopsy or, preferably, by HPLC analysis of collagen metabolites in urine or serum may aid in understanding more about the pathogenesis of fibromyalgia.

Z Rheumatol 1998; 57 Suppl 2:52-5

Tougas G

The autonomic nervous system in functional bowel disorders

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.

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

White KP, Speechley M, Harth M, Ostbye T

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

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 [Canada]. 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 ($p<0.01$). . . 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%), non-restorative 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.

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

White KP, Speechley M, Harth M, Ostbye T

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

OBJECTIVE: To estimate the prevalence of fibromyalgia syndrome (FM) among non-institutionalized 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 [Canada]. 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% (95% CI 4.7%, 5.1%) of adult women and 1.6% (1.3%, 1.9%) of adult men in London, for a female to male ratio of roughly 3:1. 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.

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

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

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 erythematosus (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 \pm 0.21, 1.95 \pm 0.25, respectively) compared to the seronegative patients (1.83 \pm 0.08, 2.53 \pm 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.

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Wolfe F, Anderson J

Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis

OBJECTIVE: The symptoms of what has been called silicone implant associated syndrome (SIAS) and fibromyalgia (FM) are similar. It has been hypothesized that silicone (filled) breast implants (SBI) might be causally related to the development of FM. This hypothesis was investigated by comparing 508 patients with FM with 1228 control subjects. We also studied the relationship of SBI to the subsequent development of rheumatoid arthritis (RA). METHODS: Utilizing a longitudinal data bank, implantation status was determined in 464 patients with RA, 508 with FM, 261 with osteoarthritis (OA) of the knee or hip, and in 503 randomly selected community controls. We obtained data on the type of implant

and its temporal relationship to the onset of FM and RA. **RESULTS:** No association between SBI and RA was found (OR 1.66, 95% CI 0.33, 8.23, $p=0.538$). No association between prior SBI and subsequent FM was found (OR 1.22, 95% CI 0.30, 4.89, $p=0.781$). But one-third of the SBI in FM occurred after development of the syndrome. When all implants regardless of temporal relationship were considered, the overall relationship between any implant and the diagnosis of FM was significant at $p=0.095$ (OR 2.45, 95% CI 0.86, 7.03). **CONCLUSION:** No relationship between prior SBI and the subsequent development of FM or RA was noted. But implants appear to be more common in patients with than in those without FM ($p=0.095$). A common, predisposing set of psychosocial characteristics may be shared between those who have FM and those who undergo SBI.
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Yunus MB, Khan MA, Rawlings KK, Green JR, Olson JM, Shah S
Genetic linkage analysis of multicase families with fibromyalgia syndrome

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 $> \text{ or } = 60$). We found that the presence of depression did not influence the observed results ($p=0.22$). **CONCLUSION:** Our study of 40 multicase families confirms the 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.
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