# Fibromyalgia, Hepatitis C Infection, and the Cytokine Connection

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Fibromyalgia and chronic hepatitis C infection share many clinical features including prominent somatic complaints such as musculoskeletal pain and fatigue. There is a growing body of evidence supporting a link between cytokines and somatic complaints. This review discusses alterations of cytokines in fibromyalgia, including increased serum levels of interleukin (IL)-2, IL-2 receptor, IL-8, IL-1 receptor antagonist; increased IL-1 and IL-6 produced by stimulated peripheral blood mononuclear cell in patients with FM for longer than 2 years; increased gp130, which is a neutrophil cytokine transducing protein; increased soluble IL-6 receptor and soluble IL-1 receptor antagonist only in patients with fibromyalgia who are depressed; and IL-1 β, IL-6, and TNF-α by reverse transcriptase-polymerase chain reaction in skin biopsies of some patients with fibromyalgia. In addition, this review describes the mechanism by which alterations in cytokines in fibromyalgia and chronic hepatitis C infection can produce hyperalgesia and other neurally mediated symptoms through the presence of cytokine receptors on glial cells and opiate receptors on lymphocytes and the influence of cytokines on the hypothalamus-pituitary-adrenal axis such as IL-1, IL-6, and TNF-α activating and IL-2 and IFN-α down-regulating the HPA axis, respectively. The association between chronic hepatitis C infection and fibromyalgia is discussed, including a description of key cytokine changes in chronic hepatitis C infection. Future studies are encouraged to further characterize these immunologic alterations with potential pathophysiologic and therapeutic implications.

## Introduction

Fibromyalgia is a syndrome characterized by widespread musculoskeletal pain, fatigue, and nonrestorative sleep that affects approximately 2% of adults in the United States. Clinically, the symptoms of fibromyalgia are reminiscent of a viral syndrome. This observation has led investigators to search for underlying chronic viral infections in patients with fibromyalgia. Fibromyalgia syndrome has been documented in 10% to 16% of patients with chronic hepatitis C virus (HCV) infection, a rate significantly higher than in the general population [1,2]. It is unknown why fibromyalgia occurs so commonly in association with this chronic viral infection. One hypothesis is that chronic hepatitis C infection causes persistent upregulation of the cellular immune response, accompanied by abnormal cytokine responses. Altered proinflammatory cytokine levels could cause perturbations in the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis and also may directly cause some of the symptoms that are common to fibromyalgia. In this paper, the existing literature on cytokines and their possible role in the pathogenesis of fibromyalgia and hepatitis C are discussed.

## Fibromyalgia and the Immune System

Fibromyalgia is a complex syndrome of widespread pain in muscles and joints accompanied by tenderness in specific anatomic locations referred to as tender points. Fibromyalgia is estimated to effect approximately 2% of the population, with more than 90% of the patients being women diagnosed between the ages of 20 and 40 years [3–5]. Patients with fibromyalgia syndrome often have associated symptoms including fatigue, irregular sleep patterns, cognitive dysfunction, and autonomic symptoms such as lightheadedness, irritable bowel, and irritable bladder. The pathophysiology of fibromyalgia is not understood completely, but is thought to involve perturbations in the immune system, the hypothalamic-pituitary axis, and the sympathetic nervous system (SNS). The interactions between these systems are complex and there is mounting evidence that the clinical manifestations of the disease, including myalgias, fatigue, autonomic dysfunction, and sleep and mood disorders, may result from abnormalities in any one of these systems [6•,7].

The immune system is thought to play a role in the pathogenesis of fibromyalgia through its interactions with the HPA and SNS, but the precise mechanisms continue to be elucidated. Numerous studies have examined the overall function of the immune system in patients with fibromyalgia [8]. A subset of patients with fibromyalgia exhibit low-level autoantibodies (antinuclear antibody) or immunoglobulins (Ig; rheumatoid factor) and may have

evidence of low-level systemic inflammation [8]. However, most patients with fibromyalgia exhibit relatively normal immune function, which is measured by lymphocyte subsets, IgG subclasses, and circulating immune complexes [9]. Recent research has focused on the possible role of abnormal cytokine regulation in producing the symptoms of fibromyalgia. The rationale for these studies is derived from the observation that cytokines are important in orchestrating the interactions of the immune system with the SNS and HPA. In addition, abnormalities in cytokine levels have been shown to be associated with some of the most common symptoms of fibromyalgia such as depression, sleep disorders, and pain [6•,10–12].

Evidence supporting the hypothesis that cytokines are important in fibromyalgia is derived from human and animal models. Glial cells in the central nervous system possess cytokine receptors, an observation indicating that cytokines may help regulate pain responses from the SNS. Experiments with rats exposed to intraperitoneal tumor necrosis factor (TNF)-α demonstrate cytokine-induced hyperalgesia that can be blocked by vagotomy [12]. This observation suggests that cytokines cause hyperalgesia by binding to paraganglia associated with afferent vagal fibers [12]. Furthermore, lymphocytes have been found to express opiate receptors that respond to substance P, a primary modulator of pain in the central nervous system [10,11]. Investigators observed that patients with cancer who underwent therapy with the cytokine interleukin (IL)-2 experienced myalgias, fatigue, malaise, and sleep disturbance symptoms similar to what is experienced in patients with fibromyalgia [13].

In animal and human studies, proinflammatory cytokines such as interleukin 1 (IL-1), TNF-α, and IL-6 have been shown to produce hyperalgesia by directly influencing nociceptive neurons and to cause fatigue, sleep disorders, and depressive symptoms [12,14,15]. Cytokines such as IL-6 can activate the SNS and IL-8 is known to play a role in sympathetic pain [16]. It also is known that IL-1 and TNF-α are somnogenic and that interferon α (IFN-α) can produce disorientation and fatigue [9,17]. Cytokines also influence the function of the HPA axis. IL-1, IL-6 and TNF-α activate and IL-2 and IFN-α down-regulate the HPA axis [18].

Efforts have been made to determine whether patients with fibromyalgia exhibit systematic abnormalities in the levels of serum cytokines or cytokines produced by circulating immune cells. Patients with fibromyalgia were reported to have elevated levels of serum IL-2 and increased production of IL-2 by T lymphocytes when compared with control subjects [13]. Serum levels of IL-1, IL-6, IL-8 and soluble IL-2 receptor (IL-2r) were measured in 113 patients with fibromyalgia and 32 healthy subjects [19]. IL-1 and IL-6 levels did not differ between disease and control groups, but the patients with fibromyalgia had statistically significantly increased levels of IL-8 and IL-2r. Furthermore, higher serum levels of IL-8 were observed to be associated with an increase in self-reported pain intensity [19].

Serum cytokine levels (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-2r, IL-1 receptor antagonist [IL-1ra], IFN-γ, and TNF-α) and cytokines derived from resting and stimulated peripheral blood mononuclear cells (PBMC) were measured in 56 patients with fibromyalgia [20]. These cytokine levels were compared with levels measured in gender- and age-matched healthy control subjects. Investigators observed increased serum levels of IL-8 and IL-1ra in patients with fibromyalgia. Furthermore, patients with a longer duration of disease (> 2 years) had the highest levels of IL-8. The other serum cytokine levels did not appear to differ between patients with fibromyalgia and control subjects. Levels of IL-1ra and IL-6 from resting PBMC were found to be elevated in fibromyalgia patients, with a longer duration of disease compared with control subjects, but no differences were found in those levels between fibromyalgia patients who had the disease for less than 2 years and control subjects [20]. In vitro stimulation of PBMC produced increased levels of IL-1 and IL-6 in fibromyalgia patients with longer disease duration compared with control subjects. The authors hypothesize that the increase in IL-6 and IL-8 is caused by the increased central sensitization and release of substance P and that the elevated level of IL-1ra is a compensatory anti-inflammatory response. The elevation of these proinflammatory cytokines may explain some of the symptoms of fibromyalgia such as hyperalgesia, fatigue, and depression.

In comparing 21 patients with fibromyalgia with 33 healthy subjects, investigators found that soluble levels of gp130, a common signal transducer protein for neutrophilic cytokines, were significantly increased in fibromyalgia patients [21]. In contrast, serum levels of IL-6 did not differ and levels of soluble IL-6 receptor (sIL-6r) and soluble IL-1 receptor antagonist (sIL-1a) were elevated only in the subpopulation of fibromyalgia patients with more severe depression [21]. Serum soluble gp130 competes with its membrane-bound counterpart; therefore, it potentially could interfere with signaling from proinflammatory cytokines such as IL-6. The authors interpret the results to indicate that patients with fibromyalgia have a suppressed rather than an overactive immune response.

Levels of cytokines were measured by reverse transcriptase polymerase chain reaction (RT-PCR) in skin biopsies of 53 patients with longstanding fibromyalgia and were compared with those from 10 healthy control subjects [22]. IL-1β was detectable in skin biopsies from 38% of the patients with fibromyalgia, IL-6 was detectable in 27%, and TNF-α was detectable in 32%. In contrast, none of these cytokines could be detected in skin biopsies from the control subjects. In the skin biopsies from the patients with fibromyalgia, immunohistochemistry localized expression of these cytokines to mononuclear cells and fibroblasts near the nerves [22].

Investigations of cytokines in fibromyalgia have been conflicting and have failed to demonstrate a clear pattern of cytokine abnormalities common to patients with fibromyalgia. Some of the disparate results may reflect physiologic differences between subsets of fibromyalgia patients and variations in cytokine patterns with disease duration. Furthermore, it is unclear whether pathophysiologic processes are better reflected in levels of serum cytokines, tissue-specific cytokines, or cytokines derived from circulating immune cells. Nonetheless, it is well substantiated that cytokines play a key role in helping to regulate the immune system and its interactions with the SNS and HPA axis. Additionally, that fibromyalgia-like symptoms can be induced in patients exposed to elevated levels of proinflammatory cytokines makes for an intriguing hypothesis regarding the pathogenesis of fibromyalgia with regard to altered cytokine regulation.

## Fibromyalgia and Hepatitis C

The initial event or events that precipitate the development of fibromyalgia syndrome are unknown. Patients with fibromyalgia often describe a "flu-like" illness preceding the development of their symptoms of chronic musculoskeletal pain and fatigue. In one study [23], a flu-like illness was reported in 50% of the patients. This observation has led some investigators to look for evidence of underlying chronic infections in patients with fibromyalgia and associations have been noted with HCV, Lyme disease, HIV, Coxsackie virus, and parvovirus [24–26].

Hepatitis C virus is a single-stranded RNA virus that causes chronic hepatitis in most of the patients who become infected. In chronic HCV infection, the host immune response acts to control viral replication. If the immune system is unable to eradicate the virus, activated lymphocytes are recruited to the liver and may cause persistent inflammation and hepatocyte damage [27•, 28]. The immune response to HCV also is responsible for some of the extrahepatic manifestations of hepatitis C infection [29,30]. Symptoms referable to the musculoskeletal system, including arthralgias, myalgias, vasculitis, polyarticular arthritis, and fibromyalgia syndrome have been documented to occur in patients with chronic HCV infection.

Several recent studies have examined the epidemiology of fibromyalgia and chronic HCV infection. These studies suggest that fibromyalgia is more common among patients with chronic HCV infection than would be expected based on the chance occurrence of the two syndromes together. Musculoskeletal pain was reported in 70% of 239 patients with a variety of hepatic disorders who attended a hepatology clinic. Musculoskeletal pain was significantly more common in the subset of patients with HCV infection (81%) than in HCV-negative patients (56%) [29,30]. Fatigue also was more common in the subset of patients with isolated hepatitis C infection. The likelihood of reporting myalgia as an extrahepatic manifestation of chronic HCV infection was not related to the severity of liver disease from hepatitis. In a French cohort of 1202 patients with chronic hepatitis C infection, self-reported arthralgia was present in 23% and myalgia in 15% of patients [31]. Female gender and higher body mass index were associated independently with those reporting myalgias in that cohort. In another study, investigators documented fibromyalgia in 16% of 90 patients with HCV infection and in 3% of patients with non-hepatitis C cirrhosis, but in none of the healthy control subjects [2].

In a study from Spain, HCV infection was documented in 15% of 112 fibromyalgia patients compared with 5.3% of the control subjects with rheumatoid arthritis. In the same report, 53% of the patients with hepatitis C infection reported diffuse musculoskeletal pain, but only 10% met diagnostic criteria for fibromyalgia [1]. This is compared with a control group of surgery clinic patients in which 22% reported widespread pain and 1.7% met criteria for fibromyalgia. The risk of developing fibromyalgia in the setting of chronic HCV infection was not associated with the level of liver damage, which was measured by transaminase elevation or autoimmune markers, because transaminase levels were normal in approximately 50% of the patients with fibromyalgia [1].

Studies have documented decreased pain thresholds in patients with fibromyalgia at the fibromyalgia tender points and at the control points [3,32–34]. Levels of pain perception after repetitive thermal stimulation were higher in patients with fibromyalgia indicating increased temporal summation, supporting the hypothesis that modulation of pain in these patients is abnormal [35]. Fibromyalgia patients with chronic hepatitis C infection also have been found to exhibit reduced pain thresholds when measured by dolorimetry compared with healthy control subjects. Ninety patients with chronic HCV infection were examined for tender points and pain thresholds [36]. The tender point count was significantly higher and the pain thresholds were significantly lower in the subset of patients with fibromyalgia compared with patients with chronic HCV who did not have fibromyalgia.

Numerous authors have hypothesized that a viral infection may be the triggering event that results in the development of fibromyalgia. The epidemiologic studies outlined previously support the contention that fibromyalgia occurs more commonly in HCV-infected patients than in healthy control subjects or in patients with non-HCV chronic liver disease. Furthermore, HCV is found more commonly amongst patients with fibromyalgia than in healthy age- and gender-matched control subjects. The mechanism by which chronic HCV infection may cause the development of fibromyalgia syndrome is unknown. Investigators have proposed that anxiety caused by the knowledge of a chronic infectious diagnosis may result in the stress-related development of fibromyalgia [37]. However, in some studies, more than 50% of the patients

with fibromyalgia who were examined had no prior knowledge of their hepatitis C status, making it difficult to implicate a psychologic response to their HCV status as a causative mechanism [1].

Alternatively, active viral replication or the release of inflammatory modulators in response to viral infection may result in symptoms of fibromyalgia. The next section examines the existing evidence regarding inflammatory cytokines and their role in acute and chronic HCV infection.

## Cytokines and Hepatitis C

Most patients exposed to HCV will develop chronic infection. The host defense against HCV is complex and appears to involve components of the humoral and cellular immune systems. The relative contributions of the innate immune system, B cells, and CD4+ and CD8+ T cells in eradicating the virus are unclear. Most patients exposed to the virus develop an HCV-directed antibody response, but many are unable to clear the virus. This is thought to be a result of the quasispecies nature of the virus that enables selection of strains that are able to avoid the immune system.

In addition to an antibody response, the host exhibits CD4+ and CD8+ cellular immune responses to HCV infection. Type-I (Th1) CD8+ T-cell immune responses are characterized by the release of certain cytokines (IL-2, IFN-$\gamma$, TNF-$\alpha$) that are important in host defense against intracellular pathogens such as viruses. However, the host's humoral response to pathogens is based on a Type-II (Th2) CD4+ T-cell response and is characterized by the production of a different set of cytokines (IL-4, IL-5, IL-10) [38].

The Chimpanzee model has been studied extensively with regard to the cellular immune response to HCV. In this animal model, the Chimpanzee's ability to eradicate the virus depends on an early, Th1 cytotoxic lymphocyte response. Animals in which the response is directed too narrowly or that do not develop a CD8+ HCV-specific response are more likely to develop chronic infection. Similar observations have been made in humans suggesting that clearing of the virus requires an early, broad CD8+ cytotoxic lymphocyte response (ThI response).

Studies comparing patients with chronic HCV infection with those who are able to clear the HCV infection show that patients who mount a strong Th1 response without a detectable Th2 response are more likely to clear the virus. In contrast, patients who develop chronic infection with active liver damage are more likely to exhibit a milder Th1 response along with a Th2 response to HCV infection [27•]. Cytotoxic lymphocytes specific for HCV are abundant in liver tissue in patients with chronic hepatitis C infection and, in vitro, these cells are capable of producing a Th1 cytokine response [38,39]. Therefore, it does not appear to be a complete absence of appropriate cellular immune response, but qualitative differences in immune response that account for persistence of HCV infection.

Cytokine release plays an important role in the inflammatory cascade that results in fibrosis in patients with chronic HCV. T cells isolated from hepatic tissue from patients with chronic HCV are CD8+ Th1 cells that produce IFN-$\gamma$, TNF-$\alpha$, IL-8, GM-CSF, and IL-10 in response to stimulation with hepatitis C-specific antigens [40]. These cytokines would be expected to be important in host eradication of a viral infection. TNF-$\alpha$ is known to have direct antiviral activity against HCV while also enhancing proliferation of lymphocytes, IFN-$\gamma$ inhibits viral replication, and IL-2 has antiviral effects against hepatitis B with unknown effects against hepatitis C.

However, with a chronic HCV infection, persistent T-cell activation and the release of these cytokines leads to ongoing recruitment of inflammatory cells and can contribute to hepatocyte damage and liver fibrosis. TNF-$\alpha$ and IFN-$\gamma$ can contribute to hepatocyte necrosis, apoptosis, and fibrosis. The Th2 cytokines Il-4 and IL-10 act to downregulate the Th1 cytokine response and to control fibrotic and necrotic effects of the proinflammatory cytokines. This is supported by the observation that the amount of liver damage on biopsy is proportional to the level of Th1 cytokines in patients with chronic hepatitis C [41]. Furthermore, patients with chronic hepatitis C with elevated Th1 cytokines are less likely to respond to interferon therapy [42].

Cacciarelli *et al.* [43] measured Th1 and Th2 cytokine levels in 11 patients with chronic hepatitis C and compared them with levels in control subjects who did not have liver disease. At baseline, the patients infected with HCV had significantly elevated levels of IL-2, IL-4, IL-10, and IFN-$\gamma$ compared with control subjects. Levels of IL-4 and IL-10 were noted to drop after interferon therapy and levels paralleled a decreased in HCV RNA. The authors concluded that the HCV infection results in an activated T-cell response and that interferon treatment may work partly through a diminution of Th2 cytokine response. In another study, serum cytokine levels were measured in 134 patients infected with HCV and in 54 uninfected control subjects [44]. The chronic HCV-infected patients exhibited significantly elevated Th1 cytokines, IL-2, IL-2R, and IFN-$\gamma$ levels; however, the levels of Th2 cytokines IL-4 and IL-6 were significantly lower than they were in the control subjects [44].

These studies illustrate the complexity of the immune system response to the HCV infection. Patients with chronic HCV infection and patients being treated with interferon for HCV infection experience many symptoms that overlap with the symptom complex typically seen in patients with fibromyalgia. It remains unclear whether the fatigue, myalgias, sleep disorders, and depression commonly experienced by patients with HCV may be the result of perturbations in cytokine levels that develop from the immune response to the virus. It also is unclear whether subsets of patients with HCV infection may be more prone to develop fibromyalgia as a result of cytokine abnormalities. Further studies should help elucidate these relationships.

## Conclusions

Fibromyalgia and chronic hepatitis C infection share many clinical features. This review demonstrates that the immunologic abnormalities identified in both conditions may be the reason for some of the clinical similarities. However, much work remains to identify the origins of immunologic perturbations in fibromyalgia, particularly the subset in which no clear initiating or chronic infection is evident. Similarly, the somatic complaints identified frequently in patients with chronic hepatitis C infection may share immune-mediated pathophysiologic changes identified in fibromyalgia. However, more studies are needed to identify mechanisms whereby immunologic alterations produce central nervous perturbations, which are thought to be involved centrally in the fibromyalgia symptom generation.

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