"Beyond the Tender Points: The Liver's Crucial Role in Fibromyalgia"

Introduction:

Fibromyalgia (FM), a chronic pain condition characterized by widespread musculoskeletal pain and tenderness, poses diagnostic challenges for physicians due to its multifaceted nature. Unlike conventional diseases, FM doesn't stem from a singular cause but involves a complex interplay of factors across various bodily systems, including the nervous, digestive, immune, and muscular systems. While the traditional focus has been on symptoms and tender points, recent research suggests that central sensitization, a theoretical framework for chronic pain syndromes, may not fully capture the nuanced intricacies of FM's pathophysiology.

This exploration delves into a ground-breaking perspective that extends beyond the well-established tender points, shedding light on the often-overlooked influence of liver health in fibromyalgia. The liver, traditionally viewed as a detoxifying organ, emerges as a pivotal player with multifaceted implications for cognitive health, muscle function, and the notorious fibro fog. As we navigate this uncharted territory, the aim is to broaden our understanding of fibromyalgia, re-evaluate diagnostic approaches, and consider the liver as a central component in comprehensive FM management.

1. Understanding Fibromyalgia Diagnosis:

Why is Fibromyalgia (FM) challenging to diagnose for doctors? Unlike conventional diseases, FM doesn't stem from a single cause; rather, it involves various factors. FM is intricately linked to stress and dysfunction across multiple bodily systems, including the nervous system, digestive system, brain, detoxification system, endocrine system, immune system, and, notably, the muscular system. While muscle stiffness and pain are common complaints, FM is not simply about these symptoms; it's a complex interplay of systemic issues.

- **Central Sensitization: Unraveling the Concept:**

  What exactly is Central Sensitization, and is it a bona fide diagnosis? You might have heard this term from your doctor or online sources. Central sensitization is a theoretical framework aiming to explain various chronic pain syndromes but is not officially recognized as a medical diagnosis. As of now, there's no definitive test for confirming its presence. The criteria for central sensitization include experiencing pain with an unknown cause, persistent chronic pain unresponsive to physical treatments, and heightened sensitivity to pain. [1]

- **Delving Deeper into Central Sensitization:**

  Researchers are still unraveling the complexities of central sensitization. It's characterized by altered central nervous system (CNS) pain processing. Potential causes include neuroinflammation in the brain and spinal cord triggered by traumatic conditions, injuries leading to sensitized neurons, and psychological factors influencing pain perception.

- **The Problem with Labeling: Central Sensitization vs. Fibromyalgia**

Labeling FM patients with centralized sensitization can be misleading and may not address the core issue of muscle pain. This label diverges from the traditional approach of treating individual tender points, neglecting recent findings in FM. Instead, FM might be better understood as a result of a multifactorial breakdown across physiological systems, each of which can be addressed through targeted treatment.

1. The Role of Liver Health in Fibromyalgia

Among the various physiological systems affected in FM, one organ which stands out is the liver. Maintaining optimal liver health is crucial for FM patients. This perspective challenges the notion of central sensitization as the primary cause and emphasizes the importance of addressing systemic breakdowns for effective FM management.

2.1 Why Our Livers Are in Trouble:

The liver is the largest internal organ in the human body and plays a crucial role in filtering out toxins and impurities. It can be compared to the oil and gas filter of a car, which needs to be changed regularly to prevent engine breakdown. The liver filters out waste and toxins that build up in the body due to daily exposure to impurities and toxins. These impurities come from various sources, including the food and drinks we consume, herbicides, and pesticide residues, as well as other man-made chemicals used as drying, coloring, flavoring agents, and preservatives. [2], [3]

2.2 The Role of Sugar:

The liver is responsible for processing and detoxifying these toxins, and the most toxic ingredient that the liver has to process each day is processed sugar. The liver already holds about 100 grams of sugar in reserve, which supplies us with enough energy to run about 20 miles. However, most Americans consume an excessive amount of sugar, with an average intake of around 70 grams per day. An excessive intake of added sugar increases the risk of chronic diseases, and too much-refined sugar and high-fructose corn syrup cause a fatty buildup that can lead to liver disease. Sugar can be as damaging to the liver as alcohol, even if you're not overweight.

Excessive sugar turns into fat, and any excess glucose in the blood is turned into fat cells. The liver is one of the places in our bodies that is remarkable at storing excess fat. Over time, liver cells are gradually replaced by fat cells, leading to non-alcohol-related fatty liver disease (NAFLD). NAFLD is a liver containing 5% or more fat and affects 30-40% of adults in the US. NAFLD is emerging as the leading cause of chronic liver disease worldwide, and it is diagnosed when fat is more than 5% of the weight of the liver. The recommended daily limit for sugar is 9 teaspoons for men and 6 teaspoons for women.

2.3 The Physiological Consequences of a Clogged, Fatty Liver:

The physiological consequences of a clogged, fatty liver are significant. NAFLD diagnosis starting at 5% liver fat increase creates decreased liver function. The downstream effects from this are not often considered when treating patients, yet the science is there. There is a drop in the liver's ability of detoxification, and one byproduct of this is an increase in ammonia, which is damaging to the brain. The

signs of a sick fatty liver include fatigue, weakness, unexplained weight loss, and a dull or aching pain over the lower right side of the ribs. [4]

Ammonia is a by-product of protein metabolism and is essential for various bodily functions, including protein synthesis, hormone production, brain function, and immune system support. However, when the liver becomes clogged and sluggish, excess unfiltered nitrogen in the form of ammonia can back up in the blood, leading to potential brain damage.

2.4 Ammonia and Brain Health:

Excess ammonia in the bloodstream can be detrimental to brain health. The brain is particularly sensitive to ammonia, and its presence can lead to various adverse effects. Ammonia causes astrocytes to swell and can lead to a leaky blood-brain barrier, which is a major cause of brain fog. High levels of ammonia in the blood are toxic to the central nervous system and can lead to cognitive disturbances. Additionally, elevated ammonia levels in the brain are associated with alterations in synaptic function, neuroinflammation, and memory function. Furthermore, high ammonia levels can trigger rapid and severe breakdown of the blood-brain barrier, leading to cognitive decline in the aged brain.

2.5 Impact on Muscle and Liver Health:

In addition to its effects on the brain, excessive ammonia can also impact muscle and liver health. Hyperammonemia, or high levels of ammonia in the blood, is a consistent abnormality in cirrhosis, leading to impaired skeletal muscle protein synthesis and breakdown. In the liver, the accumulation of ammonia can lead to inflammation, stellate cell activation, and fibrogenesis, which may contribute to the progression of fatty liver disease to more severe stages, such as cirrhosis and hepatocellular carcinoma. Systemic hyperammonemia can also have negative effects on other organs, compromising immune function and increasing the risk of liver cancer

2.6 Gut-Brain Axis and Substance P:

Excessive ammonia can lead to elevated levels of substance P, a neuropeptide associated with inflammatory processes and nociception. Substance P is elevated in the cerebrospinal fluid of fibromyalgia (FM) patients and is involved in the generation of central sensitization. The gut-brain axis plays a crucial role in this process, as excessive ammonia can create havoc in both the gut and the brain. Furthermore, high levels of ammonia can lead to decreased glutathione and the activities of glutathione peroxidase and superoxide dismutase, potentially contributing to liver fibrosis.

2.7 Challenges in Liver Monitoring:

Despite the significant impact of ammonia and fatty liver disease on overall health, the current assessment of liver health primarily revolves around blood tests and the testing of liver enzymes. However, liver enzyme tests may not always be sensitive or reliable indicators of liver health. While these tests can provide valuable information, they may not always lead to a definitive diagnosis, especially in cases where the underlying cause of liver damage is unclear. As a result, there is a need for enhanced knowledge of liver enzyme patterns and improved diagnostic algorithms to accurately assess liver function and health. [5]

2.8 Diagnostic Accuracy of Liver Enzyme Tests:

Liver enzyme tests are commonly used to detect liver disease. However, these tests are not always reliable. According to a study published in the journal "Outpatient Practice Management Tips: Tests of

Liver Injury," all tests of liver injury are neither highly sensitive nor specific. This means that liver enzyme tests may not always detect liver disease, even if it is present. [5]

2.9 Hyperammonemia and Brain Fog:

A sick liver has a poor ability to remove ammonia, which can lead to a state known as hyperammonemia. Ammonia is produced from leftover amino acids, and it must be removed from the body. The liver produces several chemicals (enzymes) that change ammonia into a form called urea, which the body can remove in the urine. A decrease in the liver's ability to remove ammonia can cause it to accumulate in the body, leading to hyperammonemia. [6]

Excess ammonia can cause severe, life-threatening encephalopathy. Even minimal levels of ammonia can drive generalized brain fog. Even small fluctuations in ammonia levels can lead to dramatic cognitive troubles that are contingent on which region of the brain is affected. FM patients often report brain fog as a symptom, and hyperammonemia may be a contributing factor.

3. NAFLD and Liver Function:

Non-alcoholic fatty liver disease (NAFLD) is a condition in which fat accumulates in the liver. This condition affects 30-40% of adults in the US. NAFLD can decrease the liver's ability to function correctly, leading to a decrease in bile production. Bile is essential for the absorption of many vitamins, minerals, and amino acids. A decrease in bile can create a state of malnourishment, which may be a contributing factor to FM.

3.1 Bile and Gut Health:

Bile is a major function of the liver, and it is crucial for health. Many studies have found that gut dysbiosis and NAFLD are closely related to a malfunction in bile acid signaling. Our gut microbiota is crucial for the synthesis of essential amino acids and vitamins and the breakdown of indigestible components in the diet such as plant polysaccharides (complex carbohydrates, starches, and fiber). Dysbiosis can be categorized into three types: loss of beneficial bacteria, the expansion of harmful bacteria, and a general loss of diversity of bacteria. Gut dysbiosis is implicated in many diseases, including inflammatory bowel disease, metabolic disorders, obesity, type 2 diabetes, and colorectal cancer. [7]

3.2 Association Between Bile Acids and Fibromyalgia:

Recent research has shown that alterations in the composition of bile acids and gut bile-metabolizing bacteria are associated with fibromyalgia and its symptom severity.[8] Women with fibromyalgia exhibit significant changes in serum bile acids and gut bile-metabolizing bacteria, which are correlated with syndrome symptom severity [9]. Specifically, a secondary bile acid called alpha-muricholic acid (aMCA) was found to be significantly less present in fibromyalgia patients than in healthy participants, and its presence was negatively correlated with most of the syndrome symptoms, including pain and fatigue.

- **Implications of Bile Acid Alterations in Fibromyalgia:**

The study also revealed that statistical learning algorithms could accurately detect individuals with fibromyalgia using the concentration of these serum bile acids. These findings suggest that serum bile acid alterations are implicated in nociplastic pain, which is characteristic of fibromyalgia. Furthermore,

alterations in the relative abundance of certain bacterial species known to metabolize bile acids were observed in women with fibromyalgia, indicating a potential link between gut microbiome changes and fibromyalgia symptom severity.

4. Glutathione Production and Liver Detoxification:

Glutathione (GSH) is one of the body's main antioxidants, and its production occurs in the liver. The effects of GSH on health are diverse. However, in the case of a sick liver, such as in non-alcoholic fatty liver disease (NAFLD), there can be a decrease in the production or ability of the body to produce GSH. This reduction in GSH production can have significant implications for overall health.

- **Liver Detoxification Pathways:**

  The liver plays a crucial role in detoxifying harmful chemicals and free radicals in the body. Liver detoxification consists of two pathways, known as Phase I and Phase II liver detoxification pathways. In Phase I, a group of enzymes known as the cytochrome P450 family neutralizes substances like alcohol and caffeine.[10] However, the byproducts of Phase I can still pose a toxic threat to the body. Phase II detoxification neutralizes these byproducts and other remaining toxins by making them water-soluble for excretion from the body. Glutathione, sulphate, and glycine are the primary molecules responsible for this process.

- **Implications:**

  Glutathione is essential for both Phase I and Phase II detoxification pathways. Its deficiency may result in liver damage, as it is needed for the elimination of heavy metals like mercury and lead. [11]Methionine and cysteine ensure adequate amounts of glutathione and protect the liver from toxic damage. Furthermore, impaired detoxification enzyme systems in the liver have been associated with certain diseases, including fibromyalgia. This suggests that the liver's ability to efficiently detoxify and remove toxins may influence the development of fibromyalgia and other chronic disease processes.

5. Albumin and Liver Health:

Furthermore, longitudinal studies have explored the association between serum albumin and changes in muscle mass, strength, and power in older men. While low serum albumin within the normal range has been posited as a risk factor for muscle-related parameters, the results demonstrated modest and inconsistent trends with loss of muscle mass and function, suggesting that low serum albumin may not be a significant risk factor for this process among elderly men.

In the context of liver health, albumin serves as a marker for liver biosynthesis and can be measured to assess the liver's biosynthetic capacity. However, it is important to note that serum albumin values can be normal in states of chronic liver disease and abnormal in cases of normal liver function, highlighting the complexity of interpreting albumin levels in the context of liver health.[12]

The degradation of albumin can occur in various tissues, including the liver, kidney, and muscle, further emphasizing the multifaceted role of albumin in the body and its potential implications for liver and muscle health.

5.1 The Interplay Between Albumin, Muscle Mass, and Liver Health:

The relationship between albumin, muscle mass, and liver health is a complex interplay that has garnered significant attention in recent research. Albumin, the most abundant circulating protein synthesized by the liver, plays a crucial role in regulating blood volume, fluid distribution, and the transport of various bioactive molecules. Low albumin levels have been associated with a range of health implications, including abnormal fluid retention, decreased muscle mass, and potential consequences for liver function. Several studies have shed light on the intricate connections between albumin, muscle measures, and liver health, providing valuable insights into their interrelatedness.

- **Albumin and Muscle Mass:**

  A cross-sectional study highlighted a significant loss of muscle mass in elderly individuals with low albumin levels, emphasizing the potential impact of albumin on muscle-related parameters.[13] The study also revealed correlations between albumin levels and health-related physical fitness, with higher albumin levels being associated with improved vital capacity, particularly in males. Additionally, research has indicated that serum albumin is positively associated with measures of relative muscle mass in healthy young participants, further underscoring the relationship between albumin and muscle measures.

- **Testosterone and thyroid hormones:**

  Albumin plays a crucial role in transporting testosterone and thyroid hormones throughout the body. Testosterone, a critical hormone for muscle growth and development, relies on albumin for transport to target tissues. Similarly, thyroid hormones, essential for regulating metabolism and energy production, are also transported by albumin. Low albumin levels can lead to reduced testosterone and thyroid hormone levels at target tissues, potentially contributing to muscle loss and impaired metabolic function. Serum albumin is a nonspecific carrier for numerous hormones, including androgens, which affect not only muscle mass and function but also an increase in satellite cell number and myonuclei in the muscle. Low free testosterone levels have been found to be associated with low absolute muscle mass, strength, and function

7. The Potential Impact of Zinc in Fibromyalgia:

Zinc plays a crucial role in liver function and its deficiency can have significant implications for liver health. The liver is the main organ responsible for zinc metabolism, and zinc deficiency or altered metabolism is observed in various liver diseases, including alcoholic liver disease (ALD) and viral liver disease [14]. Zinc is involved in DNA synthesis, RNA transcription, cell division, and activation, and is a critical component in many zinc proteins and enzymes, including critical zinc transcription factors:

- **Zinc deficiency in fibromyalgia patients:** A 2008 study evaluated zinc blood (serum) levels in patients with fibromyalgia and found that FM patients had lower levels of zinc compared to healthy controls.[15] Another study found that fibromyalgia patients have lower zinc levels and a higher BMI, and both of these factors affect sleep quality
- **Zinc and oxidative stress:** Oxidative stress has been implicated in the pathophysiology of fibromyalgia, and zinc may help reduce oxidative stress and inflammation. Zinc is a potent

antioxidant that can help to neutralize free radicals and reduce oxidative stress. Therefore, zinc supplementation may help to reduce oxidative stress and alleviate symptoms in individuals with fibromyalgia.[16]

- **Zinc and neurotransmitter function**: Zinc is involved in the synthesis and metabolism of various neurotransmitters, including serotonin, norepinephrine, and dopamine. Imbalances in these neurotransmitters have been implicated in the development of fibromyalgia. Therefore, zinc supplementation may help to restore neurotransmitter balance and reduce symptoms in individuals with fibromyalgia.
- **Zinc and pain perception:** Some studies have suggested that zinc may have a potential impact on pain perception. For example, a study published in the Journal of Pain Research found that zinc supplementation was associated with a significant reduction in pain scores in individuals with fibromyalgia.[15]

7. Calcium and Liver Health in Fibromyalgia:

Calcium and liver function play a significant role in overall health, and both are associated with fibromyalgia (FM), a chronic pain disorder that affects millions of people worldwide. Calcium is involved in various hepatic processes, including lipid and carbohydrate metabolism, as well as bile secretion and choleresis. Dysregulation of calcium signaling is observed across various liver diseases, including viral hepatitis, non-alcoholic fatty liver disease (NAFLD), long-term alcohol abuse, and chronic use of certain medications. Research has shown that women with fibromyalgia have lower dietary intake of calcium compared to those without the condition. However, serum levels of calcium did not differ significantly between the two groups

Lower calcium intake in fibromyalgia patients may be associated with greater levels of C-reactive protein (CRP), a marker of inflammation, and higher triglyceride levels [17]. Calcium plays a crucial role in liver function and its deficiency can have significant implications for liver health. Calcium interferes with the absorption of iron, which can accumulate in the liver. Calcium indirectly affects the liver by interfering with iron absorption, which can accumulate in the liver. Preventing iron overload, or hemochromatosis, through calcium supplementation may be beneficial for liver health, especially for individuals at risk for genetic predisposition.[18]

Studies have been conducted to explore the potential link between fibromyalgia and calcium deficiency. Some researchers hypothesize that tight muscles and tender points commonly experienced by individuals with fibromyalgia might contain calcium deposits.

- **Hypocalcemia in Fibromyalgia**

  Research has shown that hypocalcemia, characterized by low levels of calcium in the blood, is observed in fibromyalgia. This condition leads to significant skeletal muscle spasms, cramps, and tetany (muscle stiffness and involuntary contractions). This raises the possibility that fibromyalgia patients may also have calcium deposits in tender areas.

- **Mineral Deficiencies in Fibromyalgia**

A 2011 study analyzed hair samples from women diagnosed with fibromyalgia and found low levels of essential minerals, including calcium, magnesium, iron, and manganese. These findings suggest that mineral deficiencies may be present in these women, contributing to various health issues. [19]

- **Implications of Calcium Deficiency**

Low levels of calcium (hypocalcemia) can have implications for bone health and may increase the risk of developing osteopenia, a condition characterized by reduced bone density. The study's results indicate that individuals with fibromyalgia may be more prone to subclinical anemia, hypocalcemia, and osteopenia due to their mineral deficiencies. [20]

- **Decrease in Bone Mineral Density**

To support these findings, further investigations involving 680 fibromyalgia patients across four studies were conducted. These investigations revealed a significant decrease in bone mineral density (BMD), specifically in the lumbar spine, when compared to healthy individuals. This decrease in BMD suggests a potential association between fibromyalgia and reduced bone density, further justifying concerns about osteopenia in individuals with fibromyalgia.

7. The Role of Magnesium in Fibromyalgia

Fibromyalgia is a chronic pain disorder that imposes a multitude of hardships on patients and their communities. There is evidence to suggest that magnesium deficiency may contribute to the development of fibromyalgia and that supplementing with magnesium can offer substantial relief. [21]

- **Magnesium and Energy Production**

Magnesium is necessary for almost all the enzymes that allow the glycolytic and Krebs cycles to turn the sugar and fat we eat into ATP. Low levels of ATP have commonly been found in people with fibromyalgia, and it is believed that this plays an important role in many of the fibromyalgia symptoms. Thus, a magnesium deficiency would definitely be a factor in worsening those symptoms.

- **Magnesium and Muscle Function**

Adequate magnesium is necessary for proper muscle functioning. Magnesium deficiency promotes excessive muscle tension, leading to muscle spasms, tics, restlessness, and twitches. This is due to an imbalance of the ratio of calcium to magnesium, as calcium controls contraction, while magnesium controls relaxation. Plus, in fibromyalgia, changes are seen in the muscles, such as "significantly lower than normal phosphocreatine and ATP levels" and "values for phosphorylation potential. [22]

- **Magnesium and the Nervous System**

Magnesium also appears to be able to affect the nervous system by regulating the release of hormones, which occurs due to many different forms of stress. However, this hormonal activity is disrupted in fibromyalgia. Often there is an exaggerated release or high levels of noradrenaline (also known as norepinephrine). Magnesium is thus involved in many functions in the body, and so it's no wonder that the chemical brain imbalances in fibromyalgia somehow seem connected to processes involving magnesium.

- **Magnesium Deficiency and its Effects**

Surprisingly, little is known about magnesium, as compared to other minerals in the body. So it could be that magnesium even has more effects that we are not yet aware of. And it's because magnesium is involved in so many processes in the body, that a deficiency has a spiraling effect. Low magnesium levels cause metabolic functions to decrease, causing further stress on the body, reducing the body's ability to absorb and retain magnesium. A marginal deficiency can lead to a deficiency in other minerals, such as calcium and potassium, and can cause a variety of symptoms, including muscle pain, fatigue, and sleep disturbances.

8. Association Between Fibromyalgia and Liver Infection:

Fibromyalgia (FM) is a chronic pain condition characterized by widespread musculoskeletal pain, fatigue, and other somatic complaints. Recent research has indicated a potential association between fibromyalgia and viral hepatitis, particularly chronic hepatitis C virus (HCV) infection and hepatitis B virus (HBV) infection. Understanding this association is crucial for elucidating the potential impact of viral hepatitis on the development and severity of fibromyalgia.

- **Fibromyalgia in Chronic HCV Infection**

  Studies have reported an increased rate of fibromyalgia in patients with chronic HCV infection, with a notable association between HCV infection and higher pain intensity, tender point count, symptom severity, and fatigue. The prevalence of HCV infection in individuals with fibromyalgia has been investigated, suggesting a potential link between active HCV infection and fibromyalgia. Furthermore, the clinical features of fibromyalgia and chronic HCV infection share similarities, including prominent somatic complaints such as musculoskeletal symptoms. [23]

- **Fibromyalgia in HBV Infection**

  Similarly, research has indicated that HBV infection may increase the risk for fibromyalgia syndrome and the development of typical symptoms. The prevalence of fibromyalgia-associated symptoms, such as fatigue, sleep disorders, diffuse musculoskeletal pain, and anxiety, was found to be significantly higher in individuals with inactive hepatitis B carriage [24]. These findings suggest a potential association between HBV infection and the prevalence of fibromyalgia symptoms.

- **Potential Pathogenic Role:**

  The potential association between fibromyalgia and viral hepatitis raises questions about the pathogenic role of these viral infections in the development and severity of fibromyalgia. The shared clinical features and the increased prevalence of fibromyalgia in individuals with chronic HCV and HBV infections indicate a potential pathogenic role of these viral infections in the manifestation of fibromyalgia symptoms. Further research is needed to elucidate the underlying mechanisms and potential molecular mediators involved in this association.

Conclusion:

In conclusion, the liver emerges as a pivotal but often underestimated player in the complex landscape of fibromyalgia. Beyond the historical evolution and recognized symptoms, the liver's profound influence on this condition becomes evident. From detoxifying the body to regulating ammonia levels and bile production, the liver's multifaceted role extends far beyond conventional discussions of fibromyalgia. The impact of a clogged, fatty liver on cognitive health, muscle function, and the notorious fibro fog underscores the need to reevaluate diagnostic approaches and consider liver health as a central component in comprehensive fibromyalgia management. Acknowledging the liver's significance opens new avenues for research and treatment, providing a holistic perspective that may reshape how we approach and address the complexities of fibromyalgia.

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