Prevention of Fibromyalgia: Is It Possible?

Yonatan Shneor Patt MD[1,2,3] and Howard Amital MD MHA[1,2,3]

[1]Zabludowicz Center for Autoimmune Diseases and [2]Internal Medicine B, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT Fibromyalgia is one of the most significant causes of chronic widespread musculoskeletal pain, heavily burdening both individual patients and the healthcare system. Hence, reducing the prevalence of the disorder is of paramount importance. Unfortunately, the etiology and the exact risk factors leading to the development of fibromyalgia are not clearly known, making its prevention difficult and challenging. Nevertheless, there are numerous risk markers that are associated with an increased probability of the disease, such as obesity, psychological and physical stress, exposure to traumatic life events, certain infectious disorders, and co-morbid rheumatic and psychiatric disorders. It is reasonable to assume that targeting preventable risk markers may suppress consequent emergence of fibromyalgia, but studies investigating primary prevention on fibromyalgia are scarce. In this review, we examined several studies that discuss proven methods to prevent fibromyalgia, including maintenance of a normal body mass index, regular physical exercise, and psychological techniques such as cognitive behavioral therapy.

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KEY WORDS: body mass index (BMI), cognitive behavioral therapy (CBT), fibromyalgia, physical exercise, prevention

Fibromyalgia is the most common cause of chronic non-articular widespread musculoskeletal (MSK) pain, often accompanied by fatigue, cognitive disturbance, psychiatric manifestations, and multiple somatic symptoms [1]. The reported prevalence of fibromyalgia varies depending on the diagnostic criteria used to define the condition and the geographic location in which it was diagnosed [2]. The Minnesota population survey found that 7.7% of women and 4.9% of men fulfilled American College of Radiology (ACR) 2010 criteria for fibromyalgia [3].

Fibromyalgia is a medical condition of paramount importance given its impact both at the level of the individual patient (functional capacity, quality of life) and at the level of the healthcare system (payment burden). A comprehensive review presents several studies that elaborate on the effect of fibromyalgia [4]. For example, Burckhardt et al. [5] reported that 60% of women with fibromyalgia were working at the time of diagnosis, but only 41% remained in their position one year later. In another study based on U.S. health insurance data of 33,176 fibromyalgia patients, the total annual healthcare costs per fibromyalgia patients were approximately three times higher than control patients [6]. In addition, in the Israeli population, healthcare services were used at a significantly higher rate among fibromyalgia patients, including visiting rheumatology (odds ratio [OR] 11.36, $P < 0.001$), pain (OR 36.8, $P < 0.001$), and primary care clinics (OR 3.82, $P < 0.001$). Patients with fibromyalgia visited emergency departments more often (2.39, $P < 0.001$) compared to the general population and were more often hospitalized in internal medicine wards (1.57, $P < 0.001$) [7]. Hence, a critical goal when tackling fibromyalgia is its prevention as well as reducing its harmful influence on patients and the healthcare system as well.

Preventive health measures have been traditionally grouped into several stages including primary, secondary, and tertiary prevention [8]. Primary prevention aims to prevent disease before it occurs in a susceptible population. The secondary prevention goal is the early detection and treating of asymptomatic patients with a subclinical form of the disease, while tertiary prevention involves the prevention of complications in people who have already developed the disease as well as the reduction of its severity. So far, there are multiple reviews about tertiary prevention and management of fibromyalgia.

To date, fibromyalgia diagnosis is still based on clinical findings. Common proposed diagnostic criteria are based on different combinations of signs and symptoms all underlining the hallmark of the fibromyalgia syndrome: widespread pain and tenderness. However, the newer set of criteria all include accompanying elements of the syndrome such as fatigue, unrefreshing sleep, and cognitive impairment. Currently, we do not have any sensitive and specific tools to guide us in the early detection of disease progression in asymptomatic individuals [9]. As fibromyalgia cannot be defined in the absence of active symptoms it is currently not possible to differentiate primary prevention from secondary prevention.

PREVENTION OF FIBROMYALGIA IS CRUCIAL IN REDUCING THE HEAVY BURDEN IT PLACES ON INDIVIDUAL PATIENTS AND THE HEALTHCARE SYSTEM

ETIOLOGIES: RISK FACTORS

Prevention, in general, requires understanding the etiology of the disease, but unfortunately the causes leading to the emergence of fibromyalgia are multifactorial [3]. Burt [10] defined risk markers as attributes or exposures that are associated with an increased probability of the disease.

In a literature review, Tan et al. [9] presented numerous risk markers, including genetic factors, female sex, preterm birth, being overweight or obese, sleep problems, previous functional pain disorders such as migraines, primary rheumatic disorders such as rheumatoid arthritis and systemic lupus erythematous, various infections, and iron deficiency in early life. Regarding psychological and stressful event factors, post-traumatic stress disorder (PTSD), anxiety and depression, low socioeconomic status, and physical and sexual abuse in childhood and adulthood have been mentions as risk factors [11]. Physical trauma such as cervical whip lash injuries occurring in motor vehicle collisions are listed as well [12].

Blokh and colleagues [13] compared 14,296 fibromyalgia patients to 71,324 healthy patients based on the databases of Clalit Health Services, the largest health maintenance organization in Israel. Body mass index (BMI) was proven to be higher among the fibromyalgia group (29.1 vs. 28.0, $P < 0.001$), and with each increment of 1 BMI unit, the probability of developing the syndrome increased by 2.7% ($P < 0.001$). An additional interesting finding showed significant association between smoking and lower socioeconomic status and a higher prevalence of fibromyalgia. Moreover, another study found that excessive weight was negatively related to quality of life and pain in women with fibromyalgia [14].

IMPROVING HEALTHCARE PROVIDERS' KNOWLEDGE AND UNDERSTANDING OF FIBROMYALGIA CAN LEAD TO BETTER PREVENTION STRATEGIES AND MORE EFFECTIVE MANAGEMENT OF THE DISORDER

To the best of our knowledge, there are no theories that explain an exact causal relationship between a high BMI and fibromyalgia. However, both obesity and fibromyalgia share some etiologic factors that may explain a relationship. Elevated serum levels of proinflammatory cytokines have been observed in both patients with fibromyalgia and obesity. In addition, dysregulation of hypothalamus-pituitary-adrenal axis with relative increase in norepinephrine secretion, and accordingly, increased sympathetic tonus was detected among patients with fibromyalgia and obesity. Furthermore, it is possible that high subcutaneous fat results in higher pain sensitivity, and it has been hypothesized that there are more pain receptors in fat tissue [15].

Chronic local or regional musculoskeletal pain (CRP) is another reported major risk factor, which may progress into chronic widespread pain (CWP) in general and to fibromyalgia in particular. Larsson and co-authors [16] conducted a systematic review to identify the risk factors associated with developing CWP following chronic regional pain. Based on the examined studies, they reported that transition from CRP to CWP occurred in 18% of the 9662 patients at follow-up. Their study found five risk factors including female sex, older age, family history of pain, depressed mood, and several pain sites at baseline.

In a retrospective study, the outcome of chronic low back pain syndrome was investigated in a group of 53 patients. Of this group 25% developed fibromyalgia. Predictive parameters for the chance of turning into fibromyalgia were female sex and postural disorders such as scoliosis [17]. In another study, Buskila and associates [18] examined 102 patients with neck injury compared to 59 patients with leg fractures and assessed the probability of developing fibromyalgia. Following the incident, the neck injury group had a much higher risk of developing fibromyalgia than the leg fracture group (21.6% vs. 1.7%, $P = 0.001$). They suggested several theories to explain these findings, including that biomechanical or physical disturbances play a role in the pathogenesis of fibromyalgia. Regarding the special association of fibromyalgia with neck injury, they suggest a theory of interaction between cervical spine and nocturnal pain or sleep disturbance, which is also associated with developing central pain sensitization.

Another proposed risk factor for fibromyalgia is complex regional pain syndrome (CRPS). Despite the lack of data, authors presented three cases with typical CRPS evolving to full-blown fibromyalgia. Regarding the mechanism, they suggested that dorsal root ganglion (DRG) injury after trauma in CRPS may produce proinflammatory mediators and drive the immune response to more rostral and caudal sites. DRG metabolic changes can lead to small nerve fiber degeneration and accordingly may theoretically explain the development of CWP and fibromyalgia [19].

Moreover, not only CRP but also acute or subacute localized MSK pain may progress to fibromyalgia. Nijs et al. [20] designed a theoretical framework for manual therapy in patients with acute localized pain. One of their key recommendations was to limit the time course of afferent stimulation of peripheral nociceptors in acute MSK pain. Accordingly, they proposed trying to facilitate tissue healing and focal pain recovery within a period of approximately 3 months. Their claim was that an ongoing source of pain may lead to progression of peripheral sensitization towards establishment of central sensitization. Central sensitization is a seminal theory that proposes that people with fibromyalgia have a lower threshold for pain due to increased reactivity of pain-sensitive nerve cells in the spinal cord and brain [21]. However, their proposition was based only on a theoretical framework rather than on evidence from other studies.

A large cross-sectional study of 2051 Brazilian active civil servants examined the association between occupational stress and CWP, a key feature and characteristic symptom of fibromyalgia. Job stress was assessed using the Effort-Reward Imbalance questionnaire, and chronic MSK pain was categorized into any

Table 1. Known risk factors for fibromyalgia and prevention strategies

Preventable risk factors	
Overweight and obesity [9,13] Physical and psychological trauma (PTSD) [9,11,12] Acute and subacute pain [20] Chronic regional pain [16,18] Anxiety, depression [9] Smoking history [13] Low socioeconomic status [13] Occupational stress [22] Sleep problems [9] Complex regional pain syndrome [19] Functional pain disorders [9] Previous infections [9] Iron deficiency in early life [9] Rheumatologic disorders [9]	
Prevention strategies	**Type of study**
Maintenance of normal body weight [24]	Prospective
Regular physical exercise [24,25]	Prospective, cross-sectional
Regional pain recovery within a short period of time (approximately 3 months) [20]	Literature review
Cognitive behavioral therapy for patients who are identified as high-risk for chronic widespread pain [26,27]	Randomized controlled trial, literature review

site pain, multisite pain, and generalized pain. A strong association was found between lower reward, greater overcommitment, and higher effort at work with increasing the odds of MSK pain at any site, and particularly to multisite generalized pain [22].

HOW CAN WE PREVENT FIBROMYALGIA?

Applying primary prevention of fibromyalgia may require reducing the burden of the preventable risk factors in the general population [Table 1]. This modification may be accomplished partially through changing lifestyle (diet and exercise); psychological and pharmacological solutions for depression, anxiety, and PTSD; preventing physical trauma; treating acute and chronic regional pain; lowering stress at work; and providing social workers and national insurance assistance and immunization against viruses and bacteria [23]. Studies investigating primary prevention effects on fibromyalgia in the general population are scarce. In this review we will also refer to the entity of CWP as well, given the similarities between these two syndromes.

Mork and colleagues [24] performed a longitudinal study with an 11-year follow-up based on a population of 15,990 female patients without fibromyalgia or other physical impairments at baseline. They investigated the association between both exercise time and BMI level and the future development of fibromyalgia. During this period, 380 cases of fibromyalgia were reported. BMI was proven to be an independent risk factor for fibromyalgia. Overweight or obese women had a 60–70% higher risk of developing fibromyalgia compared to women with a normal BMI. Regarding physical exercise, only weak evidence of a dose-response association was found ($P = 0.13$). However, when they examined the combined effect of exercise and BMI, they observed that the risk of fibromyalgia was more than twofold higher for overweight or obese women who were either inactive or exercised less than one hour per week, compared to women with normal BMI who exercise more than one hour per week.

MAINTAINING A HEALTHY BODY WEIGHT, A BALANCED DIET AND REGULAR PHYSICAL EXERCISE PROGRAM CAN REDUCE THE RISK OF DEVELOPING FIBROMYALGIA

In another study, Arnson and co-authors [25] examined 55 Israeli male patients with combat-related PTSD. Each patient was asked about his regular exercise habits and completed questionnaires to measure disease severity, quality of life, and disability. Moreover, a tenderness assessment was performed manually by a senior rheumatologist to verify fibromyalgia in these patients. It was found that the extent of widespread pain measured by tender points count decreased with increasing physical activity. The authors concluded that physical exercise in PTSD patients may protect from development of fibromyalgia.

In these two studies [24,25], the authors examined a population without a diagnosis of fibromyalgia and found that normal BMI and physical exercise served as primary prevention from developing fibromyalgia. Regarding physical exercise, its potential effect may relate to the enhancement of the endogenous pain inhibitory capacity, often named exercise-induced analgesia. These studies may indicate that exercise not only provides temporary pain relief, but also may defend against MSK symptoms eventually progressing to fibromyalgia.

Kendall et al. [26] demonstrated an approach to the prevention of CWP by using a closely associated model of low back pain. They claimed that integrating psychological factors in the early management of a pain problem may be essential for preventing transition from acute to chronic low back pain. They suggested using screening questionnaires to identify patients with a high-risk profile and deal with them appropriately by adopting cognitive and behavioral therapy (CBT). However, this statement seems to be controversial in the literature.

A large randomized controlled study was conducted to determine whether CBT may be beneficial in a healthy population that had been identified as being at high risk for development of CWP. The risk was determined based on reporting somatic symptoms, sleep problems, and aspects of illness behavior. Participants received a short course of telephoned CBT compared to the control group who were treated with usual care. At 12 months there was no difference in the primary outcome, that is, onset of CWP. Nonetheless, the randomized group were more likely to report better quality of life and they had lower scores of WPI and SSS, indexes for the diagnosis of fibromyalgia [27].

Another study was initiated to examine the risk and protective factors for transition from CRP (low back pain) to CWP, including psychological factors such as coping resources and resilience. The authors recruited 746 patients experiencing localized chronic low back pain and evaluated them across 12 months using questionnaires. In one year, the incidence for the onset of CWP among these patients was 23.8%, and the identified risk factors included female sex, long duration of pain and a high rate of psychosomatic symptoms. However, the protective factors of resilience and coping resources had no significant impact on the transition from CRP to CWP [28]. They claimed that resilience and coping do not prevent pain generalization, which was already at a chronic stage, but they might play a role in early stages, as Kendall et al. suggested [26].

HEALTHCARE PROVIDERS NEED TO DISCARD THE STIGMATIZATION OF FIBROMYALGIA PATIENTS, WHICH CAN LEAD TO BETTER PATIENT OUTCOMES AND EFFECTIVE PREVENTION STRATEGIES

THE ROLE AND THE CHANGES REQUIRED BY THE MEDICAL COMMUNITY

Supporting patients with fibromyalgia is often challenging and sometimes disappointing. This is even more difficult given that many medical communities share a certain degree of hostility directed against fibromyalgia as a concept, which is often directed against the patients themselves [29]. This approach is understood from the fact that the management of such patients may be frustrating and difficult. Often such challenges are interpreted as threats to the content and mix of a secondary clinic. Many caregivers feel that they have inadequate skills managing patients with fibromyalgia and a lack formal medical education and training regarding the fibromyalgia construct. Furthermore, these feelings and concepts of the medical staff are sometimes manifested as unwelcoming behaviors toward the patients by labeling them as malingers or as secondary gain seekers.

A long-lasting discrimination of patients with fibromyalgia by the Israeli National Security (Bituach Leumi) was ended and corrected by a successful campaign of ASAF, the fibromyalgia patients association providing some hope for a welcoming approach to these patients in the future.

To treat patients with fibromyalgia and perhaps prevent its emergence, the medical community needs to discard the demonization of such patients and to stop the fibromyalgia phobia that many professionals developed throughout the years. Such a change in the atmosphere will lead to better handling of patients with fibromyalgia and will pave the way for achieving improved clinical and social outcomes.

CONCLUSIONS

Primary and secondary prevention of fibromyalgia are crucial given the heavy burden of this disorder on the healthcare system. However, the literature dealing with this issue is inadequate and further research is warranted to assess the value of preventive measures. Moreover, improving the medical community's knowledge and acquaintance with the fibromyalgia construct may lead to better understating and collaboration between patients and health care providers.

Correspondence

Dr. H. Amital
Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2652
Fax: (972-3) 535-4796
Email: howard.amital@sheba.health.gov.il

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I think there is only one quality worse than hardness of heart, and that is softness of head.

Theodore Roosevelt (1858–1919), American politician, statesman, soldier, conservationist, naturalist, historian, and writer who served as the 26th president of the United States

Capsule

Spike and nsp6 are key determinants of SARS-CoV-2 Omicron BA.1 attenuation

Chen et al. generated chimeric recombinant SARS-CoV-2 encoding the *S* gene of Omicron (BA.1 lineage) in the backbone of an ancestral SARS-CoV-2 isolate and compared this virus with the naturally circulating Omicron variant. The Omicron S-bearing virus robustly escaped vaccine-induced humoral immunity, mainly owing to mutations in the receptor-binding motif; however, unlike naturally occurring Omicron, it efficiently replicated in cell lines and primary-like distal lung cells. Similarly, in K18-hACE2 mice, although virus bearing Omicron S caused less severe disease than the ancestral virus, its virulence was not attenuated to the level of Omicron. Further investigation showed that mutating non-structural protein 6 (nsp6) in addition to the S protein was sufficient to recapitulate the attenuated phenotype of Omicron. This result indicates that although the vaccine escape of Omicron is driven by mutations in S, the pathogenicity of Omicron is determined by mutations both in and outside of the S protein.

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Eitan Israeli

Capsule

Real-world COVID-19 vaccine effectiveness against the Omicron BA.2 variant in a SARS-CoV-2 infection-naive population

The SARS-CoV-2 Omicron variant has demonstrated enhanced transmissibility and escape of vaccine-derived immunity. Although first-generation vaccines remain effective against severe disease and death, robust evidence on vaccine effectiveness (VE) against all Omicron infections, irrespective of symptoms, remains sparse. **Lau** et al. used a community-wide serosurvey with 5310 subjects to estimate how vaccination histories modulated risk of infection in infection-naive Hong Kong during a large wave of Omicron BA.2 epidemic in January–July 2022. The authors estimated that Omicron infected 45% (41–48%) of the local population. Three and four doses of BNT162b2 or CoronaVac were effective against Omicron infection 7 days after vaccination (VE of 48% [95% credible interval 34–64%] and 69% [46–98%] for three and four doses of BNT162b2, respectively; VE of 30% [1–66%] and 56% [6–97%] for three and four doses of CoronaVac, respectively). At 100 days after immunization, VE waned to 26% (7–41%) and 35% (10–71%) for three and four doses of BNT162b2, and to 6% (0–29%) and 11% (0–54%) for three and four doses of CoronaVac. The rapid waning of VE against infection conferred by first-generation vaccines and an increasingly complex viral evolutionary landscape highlights the necessity for rapidly deploying updated vaccines followed by vigilant monitoring of VE.

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Eitan Israeli