

## The Iceberg Nature of Fibromyalgia Burden: The Clinical and Economic Aspects

Rheumatology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

\*Department of Rheumatology, Iran University of Medical Sciences, Tehran, Iran

†Student Research Center, Guilan University of Medical Sciences, Rasht, Iran

‡Department of Allergy and Clinical Immunology, Iran University of Medical Sciences, Tehran, Iran

Banafsheh Ghavidel-Parsa, Ali Bidari\*, Alireza Amir Maafi<sup>†</sup>, and Babak Ghalebagh<sup>‡</sup>

This review has focused on important but less visible aspects of fibromyalgia (FM) with respect to the high impact of this disorder on patients and societies. FM is a common but challengeable illness. It is characterized by chronic widespread pain, which can be accompanied by other symptoms including fatigue, sleep disturbances, cognitive dysfunction, anxiety and depressive episodes. While our understanding of this debilitating disorder is limited, diagnosis and treatment of this condition is very difficult, even in the hands of experts. Due to the nature of disease, where patients experience invalidation by medical services, their families and societies regarding the recognition and management of disease, direct, indirect and immeasurable costs are considerable. These clinical and economic costs are comparable with other common diseases, such as diabetes, hypertension and osteoarthritis, but the latter usually receives much more attention from healthcare and non-healthcare resources. Present alarming data shows the grave and “iceberg-like” burden of FM despite the benign appearance of this disorder and highlights the urgent need both for greater awareness of the disease among medical services and societies, as well as for more research focused on easily used diagnostic methods and target specific treatment. (Korean J Pain 2015; 28: 169-176)

**Key Words:** Chronic pain; Cost of illness; Economics; Fibromyalgia; Musculoskeletal diseases; Pain.

### INTRODUCTION

Fibromyalgia (FM) is a chronic disorder that is characterized by chronic widespread pain and is generally accompanied by one or more concomitant symptoms, including fatigue, sleep disturbances, cognitive dysfunction, anxiety or/and depressive episodes, headache, abdominal pain or other somatic symptoms [1-3]. Up to 85% of patients with

FM are women, typically of childbearing age or older [4].

It is one of the most common conditions seen in the general population and outpatient rheumatology practice [3,5,6]. In primary rheumatology clinics, referrals for FM comprise 14-20% of new visits making FM the second to third most common reason for appointments [3,7]. However, clinic attendees might represent only the tip of the iceberg of people with FM. Indeed, prevalence esti-

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Correspondence to: Alireza Amir Maafi

Student Research Center Office, Research Deputy Building of Guilan University of Medical Sciences, Rasht 41446-65385, Iran

Tel: +98-937-6036481, Fax: +98-131-3228842, E-mail: alireza.am427@gmail.com

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mates of FM in the general population have ranged from approximately 1–11% to even more than 18% [2,8].

FM's definition and content has changed repeatedly in the 110 years of its existence. The most important change was the requirement for multiple tender points and extensive pain for diagnosis of this condition that arose in the 1980s (1990 American College of Rheumatology classification criteria). These are features that were not required previously. By 2010, a second shift revised the definition of FM, so it came into being in the form of the preliminary 2010 ACR criteria that excluded tender points, allowed less extensive pain, and placed reliance on patient-reported somatic symptoms and cognitive difficulties that had never been part of past definitions or content [3,9–14].

It seems the challenge for the diagnosis of FM will continue in the future until our knowledge about neurobiological mechanisms progresses.

On the other hand, FM is difficult to diagnose, and physician awareness of FM is relatively low despite the prevalence of the syndrome. Thus, it is not uncommon to see patients who have gone from doctor to doctor and who underwent multiple diagnostic tests, with a differential diagnosis that includes lupus erythematosus, rheumatoid arthritis, somatization and malingering [7,15].

FM was associated with high rates of many comorbid illnesses [16–19]. On average, FM claimants had claims for 4.2 distinct comorbid conditions per year [16,19,20]. Notable is that the high prevalence of various medical and psychiatric comorbidities is not necessarily suggestive of an etiological link between these conditions and FM. One explanation may be that these patients had frequent visits by medical providers. More frequent visits may lead to opportunistic case finding and hence a higher prevalence of diagnosed medical and psychiatric comorbidities. Another theory is the difficulty in making a diagnosis of FM. Patients might receive a variety of other diagnoses as possible explanations for the overlapping symptoms patients possess, or it may suggest that the clinicians of these patients were not satisfied that this condition fully explained their symptoms [11,12,16,19].

Since FM is a common disorder with diverse manifestations, under-diagnosis causes excessive testing and inappropriate treatment. The delay in diagnosis causes an economic burden on the healthcare system and frustration for patients and their families [11,21–24].

Medical care of FM and comorbidities are not only

quite difficult, time consuming and costly, but this disorder also tends to be intractable. There is no reliable tool to predict treatment response in individual patients, and clinical routine largely relies on trial and error [2]. Furthermore, the majority of patients have unmet needs other than widespread pain, including mood disorders, cognitive abnormality, sexual dysfunction and a lack of sociomedical acceptance – aspects that have a deep effect on their quality of life.

Consequently, it is not surprising that the high impact of fibromyalgia on the quality of life of these subjects leads to poor health at home and work, loss of productivity due to absenteeism, presenteeism, unemployment, and disability. Consequently, this puts a strain on involved health-care and non-healthcare resources [21,25,26].

Recent studies evaluated fibromyalgia-related direct and indirect costs [16,19,21,25–30]. Direct costs include medical and pharmacy costs, while indirect costs include the cost of disability and productivity loss, absenteeism, presenteeism, changes in employment status, and unpaid informal care. FM patients make 10 to 18 primary care appointments per year and are hospitalized on average once every 3 years [16,19,20,30]. Patients also reported missing 0.4 to 3.0 days from work and being unable to complete 3.6 to 35.4 hours of unpaid informal work due to FM, including child care, housework, yard work, or other daily activities [30].

The mean annual cost per patient ranged US \$2,274 to \$9,573 or even more in various studies depended on the severity of symptoms and route of cost calculation [19,30,31].

Notably, indirect costs account for the majority of FM-related costs at all severity levels. More than three-quarters of total FM-related costs were attributable to lost productivity and disability [30,31].

Although various studies tried to calculate the direct and indirect cost of disease, it seems that estimation of real cost is very difficult and under-assessed. Patients with FM often require additional resources, such as unpaid assistance from family or paid caregivers and for help with independent daily activities [21,30]. Sick time at home and productivity when at work were not fully measured. Failure to properly account for comorbid conditions is another reason for the underestimation of the real costs of the disease [19].

Overall, it seems the clinical and economic burden of

the disease on societies is high so that FM is on the same level as other chronic diseases, such as diabetes or hypertension. Although, the latter usually receives much more attention from the healthcare and non-healthcare systems [32,33]. The aim of this review is to find and highlight the hidden but alarming data about the difficulty of the diagnosis and management of FM. This paper has also tried to show the importance of this “iceberg like condition” regarding the high burden on patient and society with respect to life and economic impacts.

### DIFFICULTY FROM DIAGNOSIS TO TREATMENT

FM, often disputed and challenged, has emerged as a clinical syndrome with a clear cluster of symptoms and comorbidities [12].

Moreover, considerable overlap exists in the symptoms between FM and other ‘central pain’ or ‘functional somatic’ syndromes, such as irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, chronic pelvic pain, and temporomandibular joint disorder, as well as a number of psychiatric disorders, such as depression and anxiety [2,34,35].

While FM was originally defined by the ACR 1990 classification criteria based on chronic widespread pain and tender points, the cluster of symptoms which defines FM goes beyond chronic widespread pain and tenderness [3]. The existence of polysymptomatic distress, or symptoms beyond body pain, constitutes a “minor” diagnostic criterion of the preliminary ACR 2010 diagnostic criteria [10].

Despite the ongoing tools available for screening, diagnosing and monitoring of this condition, there is no trusty agreement between experts for diagnosis and/or screening routes. These controversies may be related to ambiguous pathophysiology of FM, despite recent research focusing on the neurobiological mechanisms of this disorder [2,15]. Currently, there is no specific diagnostic laboratory test or biomarker available for the diagnosis of FM and diagnosis was made largely by clinical judgment. The diagnosis of FM must be established in most cases by primary care physicians who are unfamiliar with this syndrome [36]. So, in addition to the absence of uniform consensus about FM diagnostic criteria among experts, the low awareness among general physicians and even differ-

ent specialists about the diagnosis and principles of treatment of this disease is disappointing [23,36–39].

A study of 172 family physicians demonstrated that physicians were not familiar with the diagnostic criteria for FM, although 96% thought that they were. They were able to identify the symptoms of the disorder, but were not able to establish the diagnosis. Only 55% of them knew that the syndrome is characterized by diffuse musculoskeletal disorders. This study also concluded continuing education could improve awareness and knowledge of the disorder [23].

Results from Choy et al. study expanded our insight into patients’ journey to diagnosis. At the time of this survey, patients had been experiencing FM symptoms for an average of 6.5 years. Based on their own recollection, patients experienced symptoms for an average of 11 months before presenting them to a physician. Aside from the time lag between first symptoms and presentation to a physician, patients recalled first presenting their FM symptoms to a doctor within an average of 2.3 years and presenting to 3.7 physicians before receiving a diagnosis [36].

Patients with FM are often referred to multiple specialists and have numerous investigations before the diagnosis is established [24,36,40]. It seems confusing that multiple symptoms compounded by limited consultation time may be an important factor for delaying in diagnosis. Also, many physicians are not aware of the ACR criteria. A small percentage of those who are aware of the ACR criteria; the ACR Criteria are not used in routine clinical practice likely due to some burden on the examiner and thoughtful interview of patients [36,40].

Delay in diagnosis can contribute to patient frustration, as White et al. [28] and Annemans et al. [22] showed that a diagnosis of FM improves satisfaction and subsequently reduces healthcare costs including referrals and investigations.

From the point of view of treatment, in general, FM tends to be intractable, although symptom improvement is achieved in some cases. The number of drugs evaluated for the treatment of FM has notably increased over the past decade. More than 40 substances have been investigated to date, with a high variation in effectiveness and side effects [2]. But treatment of this syndrome is disappointing. Three drugs have been approved by the FDA for the treatment of pain in FM: pregabalin, which binds to a voltage-dependent, presynaptic calcium channel, and

duloxetine and milnacipran, which selectively inhibit reuptake of serotonin and norepinephrine, respectively. Although these pharmacological substances are well characterized with respect to their mechanisms of action and binding sites, the exact location in the CNS remains to be fully elucidated, both from an anatomical perspective and with respect to receptor subtypes [2,20,41].

At the time of this review, FM management has focused on symptom relief and pain modification, as well as treatment for comorbid conditions [2,38,41]. Therefore, it should not come as a surprise that until revealing the unifying concept of the neurobiological mechanism of FM and emerging of new target specific therapy, treatment of the disease largely relies on trial and error.

It has been demonstrated that even after labeling FM diagnosis, patients have recurrent office visits and do not perceive their prescription medications as completely effective and express some dissatisfaction with current pharmacological and non-pharmacologic treatments [24,40]. Hughes et al. reported that, among 2,260 UK patients newly diagnosed with FM, there were 25 office visits, and 11 prescriptions per patient in the year prior to diagnosis, and levels of healthcare utilization generally increased following diagnosis. This result was confirmed by Perrot et al. who presented that considerable healthcare utilization even after diagnosis indicated an unmet need for FM patients [24,40]. As such, management of FM remains an ineffective and costly challenge for patient and physician.

### INVALIDATION AND LOW QUALITY OF LIFE

There are too many symptoms in this disorder, the symptoms appear too severe and too unusual, and the patients appear as being healthy when compared with patients with other pain disorders [11,12]. Due to the subjective nature of symptoms and lack of physical or laboratory features in fibromyalgia, patients may be faced with disbelief and distrust about the legitimacy of their illness in family and/or social interactions. This condition was recently described as ‘invalidation’ [42]. Invalidation is a new concept in rheumatologic disorders and fibromyalgia and it seems to be having a high impact on patients and societies, but research on various aspects of it in fibromyalgia is scarce.

In many cases, both invalidation and the comorbidities associated with fibromyalgia impair the patient’s quality of

life to a significant extent, culminating in loss of employment and/or withdrawal from social life [43]. Indeed, “discounting”, one of invalidation dimensions, correlates strongly with poor social and physical functioning as well as impaired mental health in fibromyalgia. It was also revealed that negative social interactions (discounting) might have stronger effects on health than positive social interactions (lack of understanding) [44]. So, aside from having a negative effect on mental well-being, invalidation could impact physical health and social functioning as well. It also decreases social support and increases social rejection [42]. Finally, in response to social rejection, patients may hide their symptoms and isolate themselves from society, which is likely to influence their healthcare, and in turn, their relationship with spouses, colleagues and medical care providers [45].

Furthermore, it was studied recently that invalidation can alter disease impact on health status and symptom severity in fibromyalgia patients. So, the more invalidation experienced by the patients leads to a higher score on the Revised Fibromyalgia Impact Questionnaire [an instrument for evaluation of fibromyalgia impact on life], indicating a greater disease impact and the greater symptom severity [46,47].

Consequently, the existence of fibromyalgia cluster symptoms, comorbidities, difficulties in diagnosis and management, and patient experience of invalidation lead to poor quality of life; so that for almost any symptom characteristic or comorbid illness, the subjects with fibromyalgia have SF-36 or SF-12 scores that are more abnormal than those of control groups [48,49]. Only patients with end-stage renal failure have a lower quality of life; and patients having other pain disorders have been identified to have better scores of quality of life than fibromyalgia [10,48].

### HIGH LEVEL OF COMORBIDITIES

As mentioned above, fibromyalgia was associated with high rates of many comorbid illnesses. These high rates may be related to the fact that fibromyalgia claimants appraise their health as including more medical symptoms, and they value each symptom with greater importance than patients with other rheumatic conditions [50]. Consequently, fibromyalgia patients report more frequently to medical services and have a higher chance for detection

of disorders which are either related or unrelated to their first complaints.

The comorbid conditions may be characterized as existing upon a continuum of painful conditions, sharing key symptoms or simply co-occurring with FM [16,17]. It was showed that one of the most commonly comorbid category is “other diseases of the musculoskeletal and connective tissue,” where 45% of FM claimants had at least one claim [16].

Some disorders such as hypertension, respiratory and other chest disorders, back disorders, abdominal pain, irritable bowel disorder, depression and other mental diseases and neoplasms were reported in fibromyalgia more frequently than other conditions [16,19,20].

Now it is clear that the *bête noire* of fibromyalgia, one of the most common comorbidity in fibromyalgia, is a psychological illness. Indeed, fibromyalgia patients experience psychiatric comorbidities in 30–60% [2]; this rate increases when the rate of lifetime psychiatric disorders (commonly depression and anxiety) is considered. As often debated, mood disorders may aggravate and complicate the management of fibromyalgia, but the nature of the causal relationship between these two conditions is unclear [2,11].

Several analyses revealed the high levels of comorbidities and resource utilization of fibromyalgia claimants [19–21,24,25,27,29–33]. Commonly visited specialists such as radiologists and mental health practitioners, rheumatologists and internists may further reflect unsatisfactory diagnosis and medical care for both physicians and patient. The cost of patient management in all levels of care is high because of the extensive work-up and disappointing treatment [19,21].

### HIDDEN COST OF DISEASE

While all the components of total annual direct and indirect costs (i.e., medical utilization, receipt of prescription drugs, work loss, disease disability) are substantial, it estimates that less than 6% of these costs were attributable to fibromyalgia-specific claims [19]. The studies highlight the wide range of illnesses and services that affect fibromyalgia claimants beyond a specific diagnosis of fibromyalgia [11,12,16,19–22].

The estimated costs of fibromyalgia presented in recent studies most likely still underestimate the true burden of fibromyalgia on society. For example, sick time at home

and productivity when at work were not fully measured. Only that part of work loss due to illness that was associated with disability or medical care was taken into account. Additionally, the payments for disability reported in several studies reflect only a fraction of the employer’s total opportunity cost for workforce disruptions due to disability [29,30].

Other likely sources of workplace costs include reduced productivity, administrative and training expenses for replacement workers, and days missed for sick time [19,29]. Evaluation of fibromyalgia costs is limited to a few studies received recently; in these ones it was reported that for every dollar spent on fibromyalgia-specific healthcare costs for employees (i.e., medical plus prescription), the employer spends \$57 to \$143 on additional direct and indirect costs [19]. In other words, failure to properly account for the broader consequences of fibromyalgia in terms of comorbid conditions would result in a significant under-assessment of the cost of disease. On the other hand, the invalidation experience and poor quality of life could impair patients’ relationships and daily living quality and/or work effectiveness that consequently increase immeasurable socio-economic burden.

Thus, hidden costs of disability and comorbidities greatly increase the true burden of fibromyalgia [27,31]. Regardless of the clinical understanding of disease, when a claim for fibromyalgia is present, considerable costs are involved [19].

### HIGH IN ECONOMIC BURDEN BUT LOW IN ATTENTION

Partially due to chronic nature of the disease, fibromyalgia patients are high consumers of healthcare services in societies. Although present data suggests that the cost before diagnosis may be even higher than the cost after diagnosis, it showed that one would expect a confident diagnosis to reduce the incidence of further diagnostic tests and referrals. Even so, a diagnosis, by itself, would not be expected to reduce symptoms and/or disability and the need for medical care [21,22,24].

The majority of fibromyalgia related costs are attributable to lost productivity (absenteeism, presenteeism, unemployment) and disability, which ranged from 75–88% of total costs. This level of social burden is higher than what is caused by other disorders. White et al. [29] reported that

FM patients missed significantly more days of work in one year compared with non-FM patients. Boonen et al. [25] also found similar results with high absenteeism and work loss compared with other groups.

It is estimated the mean annual measurable cost per patient ranged US \$2,274 to \$9,573 or even more than approximately \$13,000 in various studies depended on severity of symptoms and rout of cost calculation, In addition, it is important to note that hidden impact and costs of the disease can hardly be assessed; and if high immeasurable cost is taken into account, the real economic impact of this complex disorder it may be appreciated [19,24,30,31].

The burden of illness in fibromyalgia is substantial and comparable to some other chronic disease such as osteoarthritis, rheumatoid arthritis (RA), diabetes and hypertension [29,32,33]. Fibromyalgia patients incur direct costs approximately equal to RA patients and have more visits to emergency physicians, physicians, and physical therapy than RA patients [33]. These patients are often referred to for additional specialist consultations and undergo more diagnostic tests, but usually receive much less attention from the healthcare system than other chronic diseases. It was identified that some physicians do not want to see fibromyalgia patients, and the medical and lay literature contains many descriptions of the antagonism between physicians and ‘difficult’ patients with this condition [51]. Patients’ invalidation experience from medical systems, family and societies could create vicious cycle that lead to more and more impact to patients and societies and consequently considerable clinical and economic burden.

## CONCLUSIONS

This review has focused on important but less visible aspects of fibromyalgia with respect to the high impact of this disorder on patients and societies. It has emphasized that in spite of the benign appearance of this syndrome, which is known as a painful condition without injury to any organ of body, it has exhibited another grave “iceberg-like” feature with marked disability and challenges for patients and medical care providers. Challenges with fibromyalgia patients begin from making a diagnosis to manage this disorder, poor assessment of quality of life and experiencing invalidation from people involved with patients. The journey of diagnosis and management of these patients

leads to high individual and social burden through health-care and non-healthcare pathways. Indeed, it was shown that direct, indirect and immeasurable costs of fibromyalgia are considerable.

This alarming data highlights the urgent need for greater awareness of disease among medical services and societies. Case finding by alert general physicians and specialist could help avoid exhausting investigations and prescriptions and could consequently eliminate additional stress on patients and physicians due to labeled “unknown disease”. On the other hand, increased disease awareness among families and societies could lead to a better understanding of patients and then cost reduction. Furthermore, the present data emphasizes the need for future research focused on neurobiological mechanisms, more accurate routes for diagnosis and to target specific treatment of this illness.

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