Review

Fibromyalgia and metabolic syndrome: prevalence, potential shared pathophysiological mechanisms and non-pharmacological treatment strategies

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ABSTRACT

Fibromyalgia (FM) is a chronic pain syndrome defined by widespread musculoskeletal pain, fatigue and sleep disturbances, frequently accompanied by metabolic disturbances. Among these, metabolic syndrome (MetS), a cluster of abdominal obesity, hypertension, dyslipidaemia and impaired glucose regulation, stands out because of its strong association with cardiovascular disease and type 2 diabetes. Recent studies suggest that MetS and its individual components, particularly obesity, are highly prevalent in FM populations, raising important clinical and pathophysiological questions.

Both FM and MetS are associated with chronic low-grade inflammation, autonomic nervous system dysfunction, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, environmental factors, particularly early-life stress, may increase vulnerability by triggering persistent neuroendocrine and immune alterations. These overlapping pathways not only predispose to comorbidity but also contribute to increased symptom burden and therapeutic complexity. Systematic screening for MetS in patients with FM may improve cardiovascular risk stratification and inform more comprehensive treatment strategies. This narrative review summarises current evidence on the comorbidity of FM with MetS and its individual components, highlighting their shared pathophysiology. It also explores the therapeutic potential of non-pharmacological strategies, including structured exercise, dietary interventions, and microbiome-targeted approaches, that address common underlying mechanisms and hold promise for improving long-term outcomes.

Introduction

Fibromyalgia (FM) is a chronic syndrome characterised by widespread musculoskeletal pain, fatigue, and sleep disturbances, often accompanied by cognitive impairment, depression, and anxiety. Its etiopathogenesis remains unclear but likely involves a complex interplay of genetic, environmental and biological factors. Central sensitisation, an amplification of neuronal signalling within the central nervous system that heightens pain perception, has been proposed as a key mechanism (1).

FM frequently coexists with multiple comorbidities (2). A notable example is elevated body mass index (BMI), which is common among individuals with FM. Overweight and obesity are well-established risk factors for metabolic syndrome (MetS), conferring up to a fivefold higher risk compared with normal BMI (3, 4).

MetS is a multifactorial condition defined by a cluster of metabolic abnormalities. Although various diagnostic criteria have been proposed since the World Health Organization's (WHO) 1998 definition, no universal consensus exists (5). It is generally diagnosed when at least three of the following are present: abdominal obesity, elevated blood pressure, hypertriglyceridemia, hyperglycaemia, and reduced high-density lipoprotein (HDL) cholesterol.

MetS is a major public health concern due to its strong association with type 2 diabetes and cardiovascular disease (6, 7), two of the leading causes of morbidity and mortality worldwide. Beyond these well-established links, MetS has also been implicated in the pathogenesis of neurodegenerative disorders (8) and certain cancers (9), suggesting broader systemic consequences. Its

Table I. Fibromyalgia and metabolic syndrome.

Authors	Type of study	Study populations	Main results	Other results
Loevinger *et al*., 2007 (10)	Cross- sectional	109 FM women and 46 demographically similar healthy controls recruited through newspaper advertisements	women with FM had a 5.6-fold higher risk of MetS (Adult Treatment Panel III with glycosylated haemoglobin substituted for serum glucose) than controls	No relationship between MetS and pain severity or fatigue
Çakit *et al*., 2020 (11)	Cross-sectional	100 women with FM and 38 demographically similar healthy controls	women with FM had 3.76-fold higher risk of MetS (Adult Treatment Panel III-2001 criteria) than controls.	FM patients with MetS had greater symptom severity (p=0.004), higher pain scores (p=0.001), more tender points (p=0.039), lower total myalgic scores (p=0.029).
Atzeni *et al*., 2023 (12)	Cross-sectional	62 FM women and 4093 females recruited in a general population cohort	Prevalence of MetS in FM females 11.3 %, in general population 18.6% (p=0.139)	The absence of an increased MetS prevalence in FM patients is likely underestimated, as the NCEP ATP III criteria exclude individuals with treated hypertension or dyslipidaemia.

MetS: metabolic syndrome; FM: fibromyalgia.

prevalence has increased substantially, rising in the United States from 25.3% in 1988-1994 to 34.2% in 2007-2012 (10). This upward trend underscores the growing clinical relevance of MetS and the need to address its health impact. In this context, the present review synthesizes current evidence on the comorbidity between fibromyalgia (FM) and MetS, with attention to the contribution of individual MetS components, and examines non-pharmacological interventions aimed at targeting shared biological mechanisms to improve patient outcomes.

Fibromyalgia and metabolic syndrome

The first systematic investigation of the association between FM and MetS was conducted by Loevinger *et al*. (11). The study found that women with FM had a 5.6-fold higher risk of MetS (95% CI: 1.25-24.74) and elevated levels of all MetS components, including HbA1c, triglycerides, total and LDL cholesterol, blood pressure, and waist circumference, independent of age or BMI (Table I).

A subsequent cross-sectional study by Cakıt *et al*. (12) confirmed this association, reporting a 3.76-fold higher risk of MetS in FM patients relative to demographically matched controls. In that study, 24% of FM patients met the diagnostic criteria for MetS, compared to 7.9% of controls (p=0.047). Among individual MetS components, abdominal obesity (p=0.009), elevated blood pressure (p=0.046), and hypertriglyceridemia (p=0.03) were significantly more prevalent in FM patients than controls. No significant differences were observed for low HDL cholesterol or fasting hyperglycaemia.

In contrast to previous reports, Atzeni *et al*. (13) did not observe a higher prevalence of MetS in fibromyalgia patients compared to the general population, likely due to the use of NCEP ATP III criteria for MetS, which exclude patients with controlled hypertension or dyslipidaemia. Since many FM patients in that study were receiving antihypertensive and/or lipid-lowering therapy, the true prevalence of MetS may have been underestimated.

A potential confounder in evaluating the relationship between FM and MetS is the impact of medications commonly used to treat FM. A recent systematic review and network meta-analysis of randomised clinical trials comparing 30 antidepressants with placebo in acute monotherapy for various psychiatric disorders (14) provides important insights into their metabolic effects.

Among the antidepressants frequently prescribed for FM, the serotonin-noradrenaline reuptake inhibitor duloxetine and the tricyclic antidepressant amitriptyline are both associated with clinically meaningful increases in blood pressure. Compared with placebo, duloxetine is strongly linked to weight loss, whereas amitriptyline is associated with weight gain. Duloxetine has also been shown to significantly increase total cholesterol and glucose levels relative to placebo. In patients with fibromyalgia or chronic low back pain treated with duloxetine for up to 15 months, mean weight gain of up to 1.1 kg has been reported, in line with findings from 10 clinical trials in patients with major depressive disorder treated with duloxetine for up to 52 weeks (15). Pregabalin, an anticonvulsant commonly used to manage FM pain, is also associated with weight gain (16).

The comorbidity between FM and MetS may reflect shared biological mechanisms. Emerging evidence suggests that dysregulated inflammatory responses, marked by elevated levels of pro-inflammatory cytokines, play a central role in FM pathophysiology. Similarly, MetS has been associated with low-grade chronic inflammation in metabolic tissues, such as the liver, skeletal muscle, and pancreatic adipose tissue. This is accompanied by increased production of cytokines including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), and activation of inflammatory pathways such as c-JUN N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) (17).

Additional overlapping mechanisms include sympathetic nervous system

hyperactivity and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Elevated norepinephrine (NE) levels have been reported in patients with FM (18), along with features such as hypocortisolism or flattened diurnal cortisol rhythms (19). Loevinger's study (11) further reported increased NE excretion in FM patients, accompanied by low-to-normal levels of epinephrine and cortisol. These alterations were associated with a greater number of metabolic syndrome components, reinforcing the contribution of autonomic and HPA axis dysfunction to the comorbidity between FM and metabolic syndrome.

Environmental factors, such as childhood maltreatment (CM), may contribute to the development of both FM and MetS. A systematic review reported that physical and emotional CM, as well as cumulative maltreatment, increase the risk of MetS in adulthood (20). Similarly, childhood adversities are frequently reported by FM patients, with physical abuse showing the strongest association (21)

CM has lasting biological effects, including elevated inflammatory markers (C-reactive protein, IL-6, TNF-α) in response to daily stressors (22, 23), persistent HPA axis dysregulation, and heightened cortisol under stress (24). Whether these alterations mediate the CM-MetS link remains unclear. CM is also associated with smoking, sedentary behaviour, and alcohol use, behaviours that contribute to MetS (20).

Fibromyalgia and the components of metabolic yndrome

Fibromyalgia and overweight or obesity

A growing body of evidence supports an association between excess body weight and FM, though the directionality and mechanisms remain unclear (Table II). A community-based twin registry study by Wright *et al*. (25) reported that overweight (BMI 25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) twins were more likely to experience chronic pain syndromes, including FM, compared to normal-weight twins. Similarly, an Internet-based survey of 2,596 individuals with FM found that 27% were overweight and 43% obese (26).

In clinical cohorts, Neumann *et al*. (27) reported comparable rates (28% overweight, 45% obese), with higher BMI linked to greater pain, poorer function, and reduced quality of life. Other studies also observed that excess weight was associated with more severe FM symptoms (27-29), higher depression scores (29, 30), and impaired sleep quality (31, 32). More recent data support these findings: an Italian web-based registry of 2,339 FM patients reported that 51.8% were overweight or obese, with excess weight associated with greater symptom severity and functional impairment (33). Likewise, in a sample of 110 FM patients, 67.3% who were overweight/obese reported higher physical and psychological symptom burden than normal-weight patients (32).

Conversely, some studies did not find a direct relationship between BMI and FM symptoms. Okifuji *et al*. (34) reported that obese FM patients had lower fitness levels and higher inflammatory and stress markers, but BMI was not associated with self-reported symptom severity. Other studies similarly found no significant associations between BMI and FM symptoms (28, 31).

A systematic review and meta-analysis of 41 studies (15 included in quantitative synthesis) found a high prevalence of obesity in FM, ranging from 43% in the USA to 32% in Europe, with the lowest rates in Asia (22.1%), reflecting global obesity patterns (35). Most studies reported only weak associations between obesity and FM-related outcomes, including pain severity, tender point count, stiffness, fatigue, physical dysfunction, poor sleep quality, and reduced quality of life (36).

In obese populations, FM prevalence reaches 37% (36) and 51% (37), far exceeding the ~4% observed in the general population, suggesting that obesity may increase the risk of developing FM.

Preliminary evidence indicates that weight reduction may alleviate FM symptoms. A low-calorie diet has been associated with significant improvements in pain (p=.022), symptom severity (p=.004), and depression (p<.001) (38). In a small trial, a very low-calorie ketogenic diet in 18 obese women with FM led to symptom improvements across multiple domains, with benefits persisting even after carbohydrate reintroduction, suggesting possible ketosis-specific effects beyond weight loss (39).

Surgical interventions may also be beneficial. In one study, laparoscopic Roux-en-Y gastric bypass resulted in significant reductions in median pain scores and tender point counts (both p=.001) (40). However, the small sample size (n=10) and retrospective design limit the strength of these findings.

Several shared clinical features may contribute to the elevated co-occurrence of FM and obesity, including reduced physical activity (41), sleep disturbances (42) and chronic fatigue. Obesity may exacerbate daytime sleepiness in FM patients (43), while poor sleep quality is itself a risk factor for obesity (44), suggesting a bidirectional relationship. Both conditions are also associated with low-grade systemic inflammation and hypothalamic-pituitary-adrenal (HPA) axis dysregulation. Although depression is prevalent in both FM and obesity, its mediating role remains unclear. Of note, one study (45) reported a link between BMI and hypomania-related symptoms, particularly overactivity, a behavioural trait frequently observed in FM (46, 47).

A critical point is the impact of drugs commonly used to treat FM on weight gain. An analysis of 10 clinical study showed that the use of duloxetine in major depression produce a weight loss after short-term treatment, followed by modest weight gain and possibly dose-related on longer-term treatment.

In conclusion, overweight and obesity are common in fibromyalgia and may increase disease risk. Although the link with symptom severity is modest, weight-loss interventions show promise for symptom relief, supporting weight management as a potential component of FM care.

Fibromyalgia and insulin resistance

Insulin resistance (IR) is a metabolic disorder in which skeletal muscle, liver and adipose tissue respond poorly to insulin, leading to reduced glucose uptake, compensatory hyperinsulinemia

Table II. Fibromyalgia and obesity.

Authors	Type of study	Study populations	Main results or rates of overweight/obesity	Other results
Wright *et al*., 2010 (22)	Twin registry	Data collected from 3,471 twins	overweight and obese twins reported more pain- syndromes, including FM, than normal-weight twins	All relationships were diminished after adjustment for depression, indicating that depression may contribute to the association between higher BMI and pain symptoms.
Bennet *et al*., 2007 (23)	Internet-based survey	2,596 individuals with self-reported FM	27% overweight and 43% obese	The prevalence of obesity was notably higher than the 21% reported for females in the 2004 National Health Interview Survey
Neumann *et al*., 2008 (24)	Cross-sectional	random sample of 100 females with FM from a database of 550 FM individuals	28% overweight and 45% were obese	BMI was negatively correlated with quality of life (p=0.044) and tenderness threshold (p=0.021) and positively correlated with physical dysfunction (p=0.047) and TP count (p=0.011).
Okifuji *et al*., 2009 (31)	Cross-sectional	38 patients with FM	21% overweight and 50% obese	Higher BMI is linked to elevated inflammatory markers (IL-6, CRP), stress indicators (cortisol, epinephrine), and poorer fitness (shorter treadmill distance, higher max heart rate), but not to self-reported FM symptoms
Okifuji *et al*., 2010 (28)	Cross-sectional	215 patients with FM	30% overweight and 47% obese	Obesity was related significantly to greater pain sensitivity to TP palpation, reduced physical strength, disturbed sleep
Kim *et al*., 2012 (27)	Cross-sectional	888 patients with FM	26.8% overweight and 44.8% obese	Greater BMI had greater fibromyalgia-related symptoms, worse scores in the FIQ subscales of physical function work missed, job ability, pain, stiffness, depression and poorer SF-36 scores in physical functioning pain general health perceptions, role emotional and physical component
Gota *et al*., 2015 (26)		305 consecutive patients with FM 224 (73.2%) had data to calculate BMI	9.9%, overweight; 43.8%, obese.	Higher BMI is linked to greater disability, depression, comorbidities, and reduced aerobic capacity, but shows no association with FM symptoms or FIQ scores
Correa-Rodriguez *et al*., 2019 (25)	cross-sectional	73 FM women and 73 controls, matched on weight	38.4% overweight and 31.5% obese	BMI was significantly associated with disease severity assessed by FIQ-R.
Atzeni *et al*., 2021 (30)	web-based registry	2,339 FM patients with FM	51.8% were overweight or obese	overweight/obesity in FM patients is associated with increased symptom severity and impaired function.
Mathkhor & Ibraheem, 2023 (29)	Cross-sectional study	110 (10 males and 100 females) patients with FM	67.27% overweight or obese	FM with excess weight reported had higher rates of pain, TP, morning stiffness, sleep disturbances, headaches, fatigue, anxiety, depression (p<0.05 for all comparisons)

BMI: body mass index; TP: tender points; FIQ Fibromyalgia Impact Questionnaire; FIQ-R: revised Fibromyalgia Impact Questionnaire; SF-36: Short Form 36 health survey.

and increased risk of type 2 diabetes (48). In both clinical and research settings, IR is commonly assessed using surrogate markers, such as the homeostatic model assessment of insulin esistance (HOMA-IR), and glycated haemoglobin (HbA1c) levels.

Growing evidence links IR to FM. Elevated glucose and insulin increase pain sensitivity in both healthy individuals (49) and FM patients. Retrospective studies comparing HbA1c values from thirty-three patients with FM with the mean HbA1c levels of two control populations show a strong association between FM and insulin resistance (IR), independent of demographic factors (50). Forty female patients with FM also display higher glucose levels on oral glucose tolerance tests compared with thirty age- and sex-matched

healthy controls, although BMI and smoking partially explain these findings (51).

A more recent study (52) strengthened the evidence for an association between FM and IR, demonstrating that seventy females with FM exhibited significantly higher levels of IR than seventy age-matched healthy females across several metabolic indices. Furthermore, IR positively correlated with both disease duration and symptom severity.

Importantly, FM patients unresponsive to pain-reducing effects of serotonin-noradrenaline reuptake inhibitors (SNRIs) often show greater IR, higher BMI, and more psychiatric comorbidities, suggesting that metabolic dysfunction influences both symptoms and treatment outcomes (53).

Mechanistically, IR may exacerbate FM through oxidative stress and mitochondrial dysfunction. Chronic hyperglycaemia and hyperinsulinemia increase reactive oxygen and nitrogen species, damaging cellular components (54) and impairing mitochondrial function (55). Mitochondrial dysfunction has been documented in both muscle and neural tissues of patients with FM, where it appears more pronounced than in healthy controls and correlates with symptom severity (56, 57).

IR may further contribute to the cognitive symptoms of FM, as higher HOMA-IR scores have been associated with an increased risk of memory impairment (58). Supporting this, neuroimaging studies have identified subtle abnormalities in the temporal lobe, a region critical for memory and executive function, in individuals with IR-related cognitive dysfunction (59).

In summary, IR is increasingly recognized as a common comorbidity in FM and may contribute to pain, cognitive dysfunction, and poor treatment response. Targeting IR could therefore represent a therapeutic strategy in FM management.

Fibromyalgia and diabetes mellitus

A large population-based study in Israel, which analysed electronic health records from 14,296 FM patients and 71,324 matched controls, found that diabetes mellitus (DM) was significantly more prevalent in FM patients than in controls (19.8% *vs*. 17.4%, $p<0.001$) (60).

Most studies, however, have examined FM prevalence among DM populations, consistently reporting higher rates than in the general population. For example, FM was diagnosed in 17% of DM patients compared with 2% of controls ($p=0.008$), with tender point counts correlating positively with HbA1c levels ($r=0.72$, $p=0.027$) (61). In Turkish and Sudanese cohorts, FM prevalence in DM reached 18% and 21%, respectively, with affected patients showing higher BMI, more tender points, and greater musculoskeletal pain (62, 63). Notably, peripheral neuropathy was present in 61.9% of DM patients with FM compared to only 2.5% without FM (63). Other studies reported higher FM prevalence in diabetic women than controls (23.3% *vs*. 10.6%) (64) and up to 27.3% in Arab women with type 2 DM (65).

Further evidence from India reinforces this association. An analysis of 31,464 individuals aged ≥60 years found that diabetes was strongly linked to musculoskeletal disorders, particularly when combined with obesity (66). This likely reflects metabolic and structural alterations in skeletal muscle driven by obesity, insulin resistance, and mitochondrial dysfunction, including impaired mitochondrial calcium uptake (67, 68). Consistently, musculoskeletal pain is reported more frequently in DM patients than in the general population (68).

Overall, while FM prevalence in DM populations has been reported as high as 27%, emerging evidence also indicates increased DM rates among individuals with FM. The limited number of studies in FM populations underscores the need for well-designed longitudinal research to clarify the directionality and mechanisms underlying this association.

Fibromyalgia and serum lipid profile

Emerging evidence suggests a link between FM and altered lipid metabolism. Early studies associated hyperlipidaemia with musculoskeletal conditions (69), such as migratory polyarthritis (also seen in familial hypercholesterolemia) (70), oligoarthritis and Achilles tendon pain or tendinitis.

Case-control studies show mixed results. Some found FM patients had higher total and LDL cholesterol but no differences in triglycerides, HDL, or VLDL (71), while others reported no significant lipid differences except for higher triglycerides in overweight FM patients compared with controls (72). A larger study strengthens the association: in 183 FM patients, over half had elevated total cholesterol and LDL cholesterol. In this cohort, specific lipid parameters were significantly associated with FM clinical features: total cholesterol levels correlated with the number of tender points ($p<0.005$), Fibromyalgia Impact Questionnaire (FIQ) score, pain severity, disease duration, (all $p<0.05$). Triglyceride levels were also associated with visual analogue scale (VAS) pain scores, FIQ total score, pain intensity (all $p<0.05$), and fatigue ($p<0.005$) (73).

A recent population-based study of 8,608 individuals linked functional somatic disorders (including FM) with higher triglycerides and non-HDL cholesterol and lower HDL cholesterol, but no consistent changes in total cholesterol (74).

Beyond traditional lipid measures (LDL, VLDL cholesterol, triglycerides), emerging data indicate that alterations in other lipid classes, such as phospholipids and sphingolipids, which are key components of cell membranes, may contribute to cardiovascular disease (CVD) pathogenesis. Dysregulation of these lipids has been linked to inflammation, oxidative stress, endothelial dysfunction, and atherosclerosis (75). Notably, incorporating plasma lipidomic profiles into cardiovascular risk models has improved predictive accuracy of traditional risk factors in diabetic patients (76).

In FM, lipidomic analyses reveal altered levels of lysophosphatidylcholine (LPC), lysophosphatidylethanolamine (LPE), phosphatidylcholine (PC), and sphingomyelin (SM) compared with controls (77, 78). These alterations have been associated with mitochon-

drial dysfunction, systemic inflammation, and oxidative stress, mechanisms thought to underlie FM pathophysiology.

In summary, FM is associated with dyslipidaemia, particularly elevated LDL and triglycerides, and with broader lipidomic changes linked to inflammation and mitochondrial dysfunction. Whether these abnormalities are causal or secondary remains unclear, highlighting the need for longitudinal and mechanistic studies.

Fibromyalgia and hypertension

Hypertension is one of the most widespread global health issues. Between August 2021 and August 2023, its prevalence among U.S. adults reached 47.7%, with higher rates observed in men (50.8%) than in women (44.6%). Prevalence increased markedly with age, rising from 23.4% in adults aged 18-39 to 71.6% in those aged 60 and older (79).

Several studies have explored the relationship between FM and hypertension, with mixed findings. In a large comparative analysis of four rheumatic diseases (FM, rheumatoid arthritis, systemic lupus erythematosus, and noninflammatory rheumatic disorders) Wolfe *et al*. (80) found that FM patients had the highest overall comorbidity burden, largely driven by psychiatric disorders. The sex- and age-adjusted prevalence of lifetime and current hypertension in FM was 27% and 18.8%, respectively, figures broadly similar to those reported in the general population. With a different study design, Haviland *et al*. (81) conducted a large-scale analysis of hospital discharge records using ICD-9 codes from the U.S. Nationwide Inpatient Sample (1999-2007). Although FM was rarely the primary reason for hospitalisation, it frequently appeared as a secondary diagnosis in patients admitted for essential hypertension (34.8%), lipid metabolism disorders (17.8%), coronary artery disease (16.3%), diabetes mellitus (14.8%) and mental health conditions (14%).

Conversely, an Italian case-control study by Atzeni *et al*. (13) suggests a stronger association between FM and hypertension, reporting a significantly higher prevalence of hypertension in women with FM (51.6%) compared to the general female population (37.8%, p=0.025). FM patients were also more likely to use antihypertensive medications (p<0.001), further supporting an association between FM and increased cardiovascular risk.

However, not all data supports a positive correlation. In a cohort of 180 women with FM, Bernatsky *et al*. (82) self -reported hypertension or other vascular comorbidities was detected in only 10% of participants, substantially lower than national averages.

Similarly, in a cross-sectional study comparing 436 women with FM to 217 healthy controls, Acosta-Manzano *et al*. (83) found that, after adjusting for potential confounders, systolic blood pressure was significantly lower in FM patients (p=0.028).

In conclusion, while some studies report a similar or even lower prevalence of hypertension in FM patients compared to the general population, others suggest a significantly increased burden. Discrepancies may stem from methodological differences, sample characteristics, and the influence of confounders such as medication use, physical activity, and autonomic dysfunction. Nevertheless, the high overall comorbidity burden observed in FM, including potential cardiovascular risk, highlights the importance of routine screening for hypertension and tailored risk management in this population. Notably, studies demonstrating a significant comorbidity between FM and MetS have consistently identified hypertension as one of the most prevalent MetS components in FM patients.

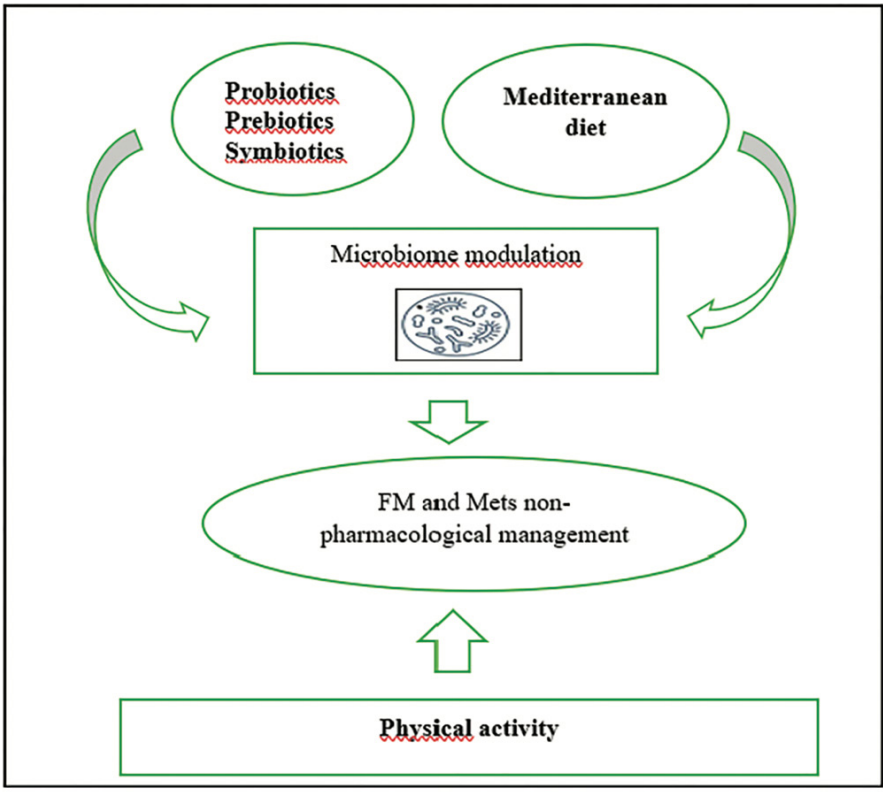

Fig. 1. Non-pharmacological management of FM and MetS.
FM: fibromyalgia; MetS: metabolic syndrome.

Potential non-pharmacological therapeutic approach to fibromyalgia and metabolic syndrome comorbidity

Pharmacological treatments for FM (*e.g*., antidepressants, gabapentinoids, muscle relaxants, analgesics) often provide incomplete symptom relief, particularly when used as monotherapy (84). Consequently, non-pharmacological strategies play a pivotal role, either as adjuncts or alternatives to pharmacotherapy.

Similarly, management of MetS com-

bines pharmacological agents targeting hyperglycaemia, dyslipidaemia and hypertension with non-pharmacological interventions, primarily physical activity and dietary modification (Fig. 1).

Aerobic and mind-body exercise

Numerous studies support the efficacy of supervised aerobic and resistance training in FM. These interventions are associated with reductions in pain intensity and improvements in both physical and psychological functioning, ultimately enhancing quality of life (85-87). A recent functional MRI study demonstrated that a 3-week exercise program led to clinically meaningful improvements in FM symptoms and motor function, correlating with changes in functional connectivity in brain regions implicated in the development of chronic pain (88).

Aerobic exercise, characterised by activities such as walking, swimming, running and cycling, enhances insulin sensitivity, reduces triglyceride levels and lowers blood pressure (89). Systematic reviews and meta-analyses confirm that aerobic training improves multiple components of MetS, both in the general population (90) and in specific subgroups such as older adults with diabetes and MetS (91) or individuals with MetS without diabetes (92).

Mind-body exercises, such as yoga, Tai Chi, and Qigong, combine slow movements with breathing and mental focus (93). A Cochrane review concluded that such practices lead to significant improvements in physical function, pain and mood in FM patients compared to usual care (94). A meta-analysis of six randomised controlled trials found that Tai Chi significantly improved pain, fatigue, sleep quality, depression and overall quality of life in FM over 12-16 weeks (95).

Additionally, mind-body practices have demonstrated metabolic benefits. Meta-analyses further support their efficacy in lowering BMI, blood pressure, fasting glucose, and lipid levels in individuals with MetS (96), with Qigong specifically improving waist circumference, blood pressure, triglycerides, total cholesterol, and HDL cholesterol (97).

Since exercise therapies are effective for both FM and MetS individually, it is reasonable to assume that they may also be beneficial when the two syndromes occur comorbidly.

Gut microbiome

Emerging human and animal evidence suggests that the gut microbiome plays a key role in the pathophysiology of both FM and MetS. Dysbiosis increases intestinal permeability, allowing bacterial endotoxins such as lipopolysaccharide (LPS) to enter the circulation. Elevated anti-LPS antibodies reflect this process and may drive chronic immune activation and systemic inflammation, contributing to persistent widespread pain (98).

Several studies support the role of dysbiosis in FM (99). Malatji et al. (100) identified altered urinary microbial metabolites in FM patients, while Minerbi *et al*. (101, 102) reported gut microbiota changes correlating with FM severity and alterations in bile acid–metabolizing bacteria. Machine learning models using these microbial signatures accurately distinguished FM patients from controls.

Clos-García *et al*. (103) further identified two distinct microbiota clusters, with FM-associated profiles showing reduced diversity and depletion of short-chain fatty acid (SCFA)–producing bacteria (*e.g*., Bifidobacterium, Eubacterium, Lachnospiraceae). A Mendelian randomization study also suggested a causal role for specific gut genera, with Coprococcus2, Eggerthella, and Lactobacillus increasing FM risk, while Family XIII UCG-001 and Olsenella were protective (104).

Similarly, the gut microbiome is increasingly recognized as a key modulator of metabolic homeostasis in MetS. A hallmark feature of MetS-associated dysbiosis is a reduction in SCFA-producing genera such as *Faecalibacterium*, *Alistipes*, *Oscillibacter*, *Roseburia*, and *Pseudoflavonifractor* (105). SCFAs, particularly butyrate, are known to support intestinal barrier integrity and regulate glucose and lipid metabolism (106).

Another relevant microbial mechanism in MetS involves impaired bacterial deconjugation of primary bile acids. This results in elevated fecal levels of cholate and chenodeoxycholate, which have been linked to insulin resistance (107).

Additionally, elevated microbial-derived branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, have been associated with insulin resistance, type 2 DM, and obesity (108).

In summary, converging evidence implicates the gut microbiome as a shared mechanistic link between FM and MetS, through SCFA depletion, bile acid dysregulation, and endotoxin-mediated inflammation.

Microbiota-targeted therapies

Early evidence indicates that microbiota-modulating strategies, including probiotics (live microorganisms with health benefits), prebiotics (fibres that stimulate beneficial bacteria), and synbiotics (their combination), may improve outcomes in both FM and Met.

In FM, small clinical studies report improvements in pain, sleep, mood, anxiety (109),<<<<<<and cognition (110), though one trial found no significant effect (111). Research remains limited by small sample sizes, heterogeneous strains, and variable dosages, making conclusions tentative.

In MetS, probiotics have been associated with reductions in triglycerides and diastolic blood pressure (112), while synbiotics improved BMI, fasting glucose, and insulin resistance (113). Meta-analyses show probiotics and synbiotics reduce total cholesterol (114) and, more broadly, lower BMI and waist circumference in individuals with MetS (115), though effects on other metabolic outcomes are inconsistent.

Overall, probiotic and synbiotic interventions show promise for symptom relief in FM and metabolic improvements in MetS.

Diet

Diet is a major modulator of gut microbiota composition and function, influencing microbial diversity, metabolite production, and host-microbe interactions (116). While dietary changes can

lead to measurable microbial shifts, the human microbiome also displays a degree of temporal stability, particularly over short to moderate timescales (117).

The Mediterranean Diet (MedDiet), characterised by high intake of extra virgin olive oil, legumes, whole grains, nuts, fruits, vegetables, and fish, with moderate wine consumption, has been linked to reduced risks of mortality, cardiovascular disease, cancer, neurodegeneration, and type 2 DM (118).

In FM, adherence to the MedDiet has been associated with improvements in pain, fatigue, sleep, and cognitive symptoms (119). In MetS, a meta-analysis of 50 studies confirmed its effectiveness in preventing and managing hypertension, dyslipidemia, and insulin resistance (120).

By enhancing microbial diversity and reducing inflammation and oxidative stress, the MedDiet offers a promising strategy for FM–MetS comorbidity.

Conclusions

The overlap between fibromyalgia and metabolic syndrome is clinically relevant and likely driven by shared mechanisms, including chronic inflammation, HPA axis dysfunction, and environmental factors. Non-pharmacological strategies, such as structured exercise, microbiota-targeted therapies, and anti-inflammatory diets like the Mediterranean diet, show promise, but evidence in patients with both FM and MetS remains limited. Future research should focus on clarifying causal pathways, and developing personalised, metabolically informed treatment approaches. A multidisciplinary, integrative strategy may offer the best opportunity to improve outcomes and quality of life in this population.

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