adjusted for overweight/obesity and including both UA and CRP levels also showed a significant association between UA (OR = 1.94, 95%CI = 1.25 - 3.01, p = 0.0029), CRP (OR = 1.53, 95%CI = 1.12 - 2.09, p = 0.007) and MetS.

We did not observe a link between UA, CRP, or ESR and any chronic musculoskeletal pain site or diseases described in this study (data not shown). None of the participants had clinical features of gout, ankylosis spondylitis, rheumatoid arthritis, or other autoimmune rheumatic disease.

Discussion

We observed an increased rate of chronic musculoskeletal pain at any anatomic site in patients with MetS compared with individuals without MetS, particularly in weight-bearing sites, such as the lower back, hips, knees, ankles and feet. The factors that were adjusted for overweight/obesity showed significant associations between MetS, LBP and KOA; however, the association between chronic MSK-related pain at any site, PF and fibromyalgia was no longer significant. Furthermore, no association was observed between any laboratory parameters and MSK disease. Nevertheless, a positive correlation was observed between UA, CRP levels, and MetS before and after adjustment for overweigh/obesity.

Goodson., *et al*. (2013) [18] reported an association between chronic pain and MetS (OR = 1.42, 95%CI = 1.24 - 1.62), adjusted for age and sex, and multivariate analysis identified age, sex, smoking, dyslipidemia, obesity, and waist-hip ratio as independently associated with chronic pain. In our study, the association between MetS and chronic musculoskeletal pain became non-significant after adjustment for overweight/obesity. In this regard, studies have demonstrated that obesity has implications in several MSK diseases, such as soft tissue conditions, OA and inflammatory arthritis [19]. After adjustment for age, sex, educational and physical activity levels and depressive symptoms, a Brazilian study showed that obesity and abdominal obesity were associated with musculoskeletal pain at any anatomic site and multisite musculoskeletal pain, with a dose-response relationship observed with increased levels of obesity [20]. Moreover, there is evidence of a higher prevalence of chronic musculoskeletal diseases affecting the lower limb at one or more locations in overweight (OR = 1.6, 95%CI = 1.3 - 1.9) and obese (OR = 2.5, 95%CI = 1.9 - 3.2) individuals [21].

Obesity has also been associated with tendinopathy, particularly Achilles tendinopathy and PF, in which increased weight is associated with increased load on these tendons during standing and walking [22,23]. One study showed that plantar fascia and Achilles tendon thickness were significantly increased on ultrasound in patients with diabetes compared with individuals with normal glycemic levels and normal weight. They also found a correlation between BMI and plantar fascia thickness (r = 0.749, p < 0.0001) [24]. These observations support our findings in relation to PF, since we showed that the significance of the association between PF and MetS disappeared after adjustment for overweight/obesity.

One study described an OR of 5.56 (95%CI = 1.25 - 24.74) for women with fibromyalgia [26] who met the 1990 ACR criteria [25] for MetS compared with healthy controls with a similar BMI. They also described a statistically significant association between all factors associated with MetS in patients with fibromyalgia when compared with controls [26]. On the other hand, our study showed a higher rate of fibromyalgia in patients with MetS; however, the association was not significant when values for overweight/obese subjects were included in the logistic regression. Indeed, it has been shown that fibromyalgia is associated with obesity and low-level physical activity in women [27] as well as high levels of leptin, with a positive correlation with BMI [28].

Regarding hip pain, a recent study on 119 patients with MetS and 235 controls demonstrated that hip OA defined by magnetic resonance imaging (MRI) was not associated with MetS [29]. Also, a systematic review concluded that the influence of obesity on the development of hip OA is moderate, and the association is stronger in studies in which the diagnosis is based on both clinical symptoms and radiological criteria than in those based only on X-ray results [30]. Additionally, chronic, work-related, restricted hip pain is associated with obesity in men (OR = 3.15, 95%CI = 2.07 - 4.83) and women (OR = 3.25, 95%CI = 2.42 - 4.38) compared to the general population [31]. In our study, hip pain was more frequent in patients with MetS; however, due to the small sample size, it was not possible to adjust the analysis for BMI. Interestingly, in a study with subjects with mean BMI = 51 (8.0) kg/m^2 before bariatric surgery, significant symptomatic improvement of chronic pain after surgery and weight loss was not observed for hip pain; however, it was observed for knee, ankle, and foot pain, as well as for fibromyalgia [11].

There are multiple reports on the association between increased BMI and incidence and progression of KOA defined by imaging criteria with or without clinical symptoms [19]. It was reported that mechanical overloading causes collagen network damage and proteoglycan loss of the articular cartilage. The cartilage

matrix breakdown products lead to inflammation and transcription of nuclear factor-κB and mitogen-activated protein kinases [32]. Nevertheless, obesity-related metabolic factors, particularly levels of adipokines, such as leptin, adiponectin and resistin, are recognized to be more important factors than mechanical overload in the development of KOA. These adipokines could influence OA by direct local joint degradation or through control of the local inflammatory process [33]. Leptin has been associated with the degree of cartilage degeneration and a synergic relationship with proinflammatory cytokines [34].

A case-control study described a significantly higher prevalence of KOA in 60 individuals with MetS (83.3%) than in controls, with a statistically similar BMI (73.3%), p = 0.034 [35]. In our study, we were not able to balance the groups in terms of BMI; however, the adjustment for overweight/obesity reduced, but did not eliminate, the significance of the association between KOA and MetS. A study using MRI demonstrated an association between medial knee compartment cartilage volume loss and MetS, and low HDL-C after adjustment for central obesity and BMI [36]. However, the Framingham OA study with 991 individuals reported that after adjustment for BMI, the association between KOA and all factors associated with MetS, except hypertension, became non-significant [37]. On the other hand, a study using a cohort of 16,362 participants aged ≥ 55 years without diabetes at baseline and controlled for confounders reported that the presence of hip/knee OA was a significant independent predictor of diabetes incidence [38].

The association between obesity and LBP is controversial and there is a lack of a clear dose relationship between LBP and BMI [19,39]; however, obesity is associated with the transition from acute to chronic occupational back pain [40]. One study with 1395 individuals demonstrated a higher prevalence of LBP in women with MetS than in controls (OR = 1.5, 95%CI = 1.0 - 2.5), but not in men [41]. Also, it has been reported that MetS is associated with disability due to LBP among care workers after adjustment for age, sex, job demands, intensity and duration of pain, social support, and fear of movement [42]. In a Brazilian study, LBP was associated with overweight (OR = 1.18, 95%CI = 1.02 - 1.36) and obesity (OR = 1.26, 95%CI = 1.05 - 1.53), as well as hypertension (OR = 1.42, 95% CI = 1.23 - 1.65) and high cholesterol (OR = 1.6, 95%CI = 1.34 - 1.920) when adjusted for age and education [43]. Our results showed a significant statistical relationship between LBP and MetS only after adjustment for overweight/obesity, suggesting an interaction between MetS and overweight/obesity.

Associations between UA and MetS have been consistently described in the literature [44]. A case-control study demonstrated higher levels of UA in individuals with MetS than in controls (5.70 ± 1.62 vs. 4.97 ± 1,30 mg/dL, respectively, p = 0.001), and after adjustment for age, sex, and BMI, the association of UA and MetS was still significant (OR = 2.11 [95%CI = 1.30 - 3.41, p = 0.002) [45]. The increased renal absorption of UA at the proximal renal tubules secondary to hyperinsulinemia is reportedly associated with high UA levels in MetS [46]. It has also been shown that individuals with hyperuricemia (UA > 7 mg/dL) have an increased risk of developing insulin resistance [hazard ratio (HR) = 1.36, 95%CI = 1.23 - 1.51] and prediabetes (HR = 1.25, 95%CI = 1.04 - 1.52) [47]. However, we did not find an association between UA and MSK pain, or any other specific disease included in our study. Afzal., *et al.* (2003) [48] compared two groups of 36 patients each, with and without chronic, nonspecific musculoskeletal pain, and reported that the experimental group had higher levels of UA compared with controls (p = 0.05), and female patients had a significantly lower UA excretion (p < 0.001). One study described the association of UA and KOA in women [49] and another study found an association between higher UA levels with the presence of synovitis on MRI (OR = 1.017, 95%CI = 1.007 - 1.028) and soft tissue swelling (OR = 1.008, 95%CI = 1.00 - 1.016) in individuals with KOA [50]. There is also an interesting report on the correlation between UA levels and joint space narrowing in non-gout patients with KOA, suggesting that UA could be a biomarker for OA progression [51].

The association of CRP and MetS has been demonstrated after adjustment for BMI [52] and this association is cumulative by increasing the number of factors linked with MetS [53]. Some researchers have described a relationship between radiographic OA and increased CRP; however, higher levels were observed in obese patients with OA, as well as obese patients without OA, than in non-obese patients. They concluded that the high correlation with obesity limited the use of CRP as a marker for OA [54]. Few studies have addressed the link between CRP and non-specific LBP, and none showed an association between CRP and chronic LBP, only with acute pain [55].

The cross-sectional design and the small sample size of this study limited our ability to detect causal relationships between chronic musculoskeletal pain and MetS. These limitations also contributed to our inability to control other possible confounding factors, such as occupational physical demands. Another limitation is the fact that the study was conducted in a single institution, therefore generalized conclusions cannot be drown from our results.

Conclusion

In conclusion, this study adds to the growing body of evidence that MetS is linked to musculoskeletal complications and higher levels of CRP and UA. Differently from the majority of the studies that observed associations of MetS with individual musculoskeletal disease, we considered the relative frequency of musculoskeletal pain at different anatomic sites in patients with MetS. Thus, this paper described that patients with MetS have more chronic pain localized in the lower limb joints. Also, the factors that were adjusted for overweight/obesity showed significant associations between MetS, LBP, and KOA supporting that both mechanical overload and systemic factors contribute to these associations. Although the cross-sectional design and the small sample size of this study limited our ability to detect causal relationships between chronic musculoskeletal pain and MetS, the pain in these joints could impair walking, leading to a reduction in physical activity and exercise, and contribute to a cycle of weight gain and deterioration of MetS condition and musculoskeletal health [7]. Nevertheless, further prospective studies are needed to elucidate if CRP and/or UA could be associated with the progression of musculoskeletal conditions, other than gout, associated with MetS, which may provide insights into management options that addresses both, musculoskeletal diseases and MetS.

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Conflict of Interest

All the authors declare that they have no conflict of interest for this manuscript.

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