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## REVIEW

# Obesity – A Risk Factor for Psoriasis and COVID-19<sup>☆</sup>



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**Abstract** Obesity is a major health problem whose well-known association with psoriasis has been amply described. The importance of obesity as a risk factor for poor prognosis in the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 infection has recently been demonstrated. This review examines a possible relationship between obesity, psoriasis, and COVID-19, analyzing the pathophysiological links and their practical implications. On the one hand, a higher body mass index increases the risk of psoriasis and is also a factor in metabolic syndrome, which is common in patients with psoriasis and has been implicated in reducing the effectiveness of psoriasis treatments. On the other hand, obesity is a risk factor for severe COVID-19 and mortality. Obesity also promotes a proinflammatory state in the lung, where it compromises respiratory mechanics.

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## Obesidad: factor de riesgo para psoriasis y COVID-19

**Resumen** La obesidad es un importante problema sanitario y su asociación a la psoriasis es bien conocida y ha sido ampliamente descrita. Recientemente, su relevancia en relación con la COVID-19, enfermedad causada por el betacoronavirus SARS-CoV-2, se ha puesto de manifiesto al demostrarse que es un factor de mal pronóstico para estos pacientes. En este trabajo se analiza la relación que puede existir entre obesidad, psoriasis y COVID-19, analizando los nexos

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fisiopatológicos comunes entre estas entidades y las implicaciones prácticas de esta asociación. Por un lado, el aumento del índice de masa corporal aumenta el riesgo de padecer psoriasis y, además, la obesidad es un factor implicado tanto en el síndrome metabólico, que también está incrementado en pacientes con psoriasis, como en una menor eficacia de los tratamientos. Por otro lado, la obesidad es un factor de riesgo para gravedad de la COVID-19 y para su mortalidad. Además, a nivel pulmonar promueve un estado proinflamatorio y tiene un efecto mecánico desfavorable.

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## Introduction

Obesity is a major health problem worldwide and one of the biggest public health challenges to emerge in recent decades.<sup>1</sup> It is associated with and a risk factor for a poor prognosis in many other diseases of various types, some with an inflammatory or infectious pathogenesis. The association of psoriasis with obesity is well known and has been widely reported in the literature.<sup>2</sup> Furthermore, following the recent emergence of COVID-19, a new disease caused by infection with the betacoronavirus SARS-CoV-2, the importance of obesity as a prognostic factor in patients with this infection has been demonstrated.<sup>3,4</sup> The aim of the present study was to analyze the possible involvement of obesity in psoriasis and in COVID-19 and the relationships between the three diseases, to explore common pathophysiological mechanisms, and to review the practical implications for their treatment in this context.

## Obesity and Psoriasis

Psoriasis is a chronic inflammatory disease that affects approximately 2% of the general population. Apart from the clinical spectrum of cutaneous symptoms, the altered immune system found in these patients also produces systemic alterations that provide a better understanding of the various comorbidities. Of particular relevance from a clinical standpoint are the comorbid heart conditions because these can reduce the life expectancy of patients with severe psoriasis.<sup>5,6</sup> Other important comorbidities of psoriasis are diabetes mellitus, hypertension, and dyslipidemia (all of which are components of metabolic syndrome) as well as non-alcoholic fatty liver and obesity.<sup>5</sup>

Obesity, a high body mass index (BMI), or high hip or waist circumference are all independent risk factors for psoriasis. An association has been observed between increments in BMI and increases in the risk of developing psoriatic disease.<sup>7</sup> A meta-analysis of 16 observational studies found an association between obesity and psoriasis,<sup>8</sup> and these findings were corroborated by the results of subsequent cross-sectional studies.<sup>9</sup> Obesity is one of the cluster of conditions that make up metabolic syndrome, which is also more prevalent in patients with psoriasis and correlates directly with the affected body surface area in this group.<sup>10</sup> However, of all the conditions included in metabolic syndrome, obesity is the component that has the strongest association with psoriasis.<sup>11</sup> The bidirectional nature of this association

between obesity and psoriasis was emphasized in a recent review article.<sup>12</sup> It has been observed that patients with a higher BMI are more likely to have psoriasis; similarly, obesity is associated with the incidence, prevalence, and severity of psoriasis.<sup>12</sup> Obesity is also associated with lower efficacy in patients on TNF- $\alpha$  inhibitors and is a predictor of risk of withdrawal from treatment for a number of biologic agents.<sup>12</sup> Finally, weight control can improve existing psoriasis and even reduce the risk of developing the disease.<sup>13</sup>

## Obesity and COVID-19

There is a growing body of evidence supporting the hypothesis that obesity is a risk factor for greater severity and mortality in patients with COVID-19.<sup>3,14</sup> The authors of a study of patients in China affected by COVID-19 matched obese (defined as a BMI > 25 in this Asian population) and nonobese patients by sex and age. The group of obese patients was characterized by higher levels of c-reactive protein, lower lymphocyte counts, and a higher proportion of severe disease; the obese patients also required longer stays in hospital.<sup>3</sup> In the logistic regression analyses, a 1-unit increment in BMI was associated with a 12% increase in risk of severe COVID-19 (OR 1.12; 95% CI, 1.01-1.23). Even after adjusting for age, sex, smoking status, diabetes, and dyslipidemia, the association between obesity and greater COVID severity remained significant, with an adjusted odds ratio of 3.00 (95% CI, 1.22-.38).<sup>3</sup>

Several hypotheses have been advanced to explain this damaging bidirectional relationship, although none has yet been confirmed. On the one hand, obesity is a risk factor for type 2 diabetes, hypertension, kidney disease, and heart disease, as well as having an unfavorable mechanical effect on lung function.<sup>15</sup> Furthermore, obesity induces a proinflammatory state that leads to greater susceptibility to a number of respiratory viruses.<sup>16</sup> This state has been shown to support a more diverse viral quasispecies in obese patients with influenza virus infections, favoring potentially pathogenic viral variants capable of inducing greater tissue damage.<sup>17</sup> However, it is not yet known whether this mechanism occurs in SARS-CoV-2 infections. Obesity may also increase the duration of the period during which a patient can infect others, similar to what occurs with other viruses, influenza A for example.<sup>18</sup> Finally, obesity also favors endothelial dysfunction through proinflammatory factors.

With respect to the possible relationship between obesity and infection with MERS-CoV or SARS-CoV-2, a meta-analysis

of the results of 14 studies identified in a systematic review found that obesity was present in 12% to 19% of patients affected by MERS-CoV; however, the hypothesis that obesity could contribute to a poor prognosis in this setting was not confirmed.<sup>19</sup>

Moreover, not only do obese patients develop more severe disease once infected, it has also been postulated that they may be more susceptible to infection. In a study comparing obese and nonobese patients with chronic obstructive pulmonary disease (COPD), increased expression of angiotensin converting enzyme 2 (ACE2) in the bronchial epithelium was observed in the obese patients (demonstrated by comparison of RNA levels), a factor that would make them more predisposed to SARS-CoV-2 infection.<sup>20</sup> Furthermore, ACE2 expression is higher in adipose tissue than in the pulmonary epithelium; however, no differences in ACE2 expression have been observed between adipocytes from patients with normal weight and adipocytes from obese patients.<sup>21</sup> It is possible, however, that viruses of the coronavirus family, and in particular SARS-CoV-2, may accumulate in adipose tissue, which may serve as a reservoir, as has been shown to occur in the case of human adenovirus Ad-36, influenza A virus, and human immunodeficiency virus.<sup>4,21,22</sup>

## Pathophysiological Features Common to COVID-19 and the Comorbidities of Psoriasis

Psoriasis and its comorbidities have many inflammatory pathways in common: CDKAL1 and apolipoprotein E are common factors in both psoriasis and cardiometabolic diseases<sup>23</sup>; interleukin (IL) 17A and CCL20 are a point of connection linking psoriasis and atherosclerotic plaques, and drugs that inhibit that pathway may have a cardioprotective effect.<sup>24</sup>

The systemic inflammation associated with psoriasis also promotes inflammation of adipose tissue, an effect that may favor cardiometabolic disease,<sup>25</sup> predisposing patients to obesity and insulin resistance. Obesity is also associated with systemic inflammation due to the release of adipokines, including adiponectin, resistin, visfatin, C-reactive protein, and chemerin, which release macrophages and T cells that infiltrate adipose tissue and can further promote the inflammation associated with psoriasis.<sup>26</sup> These adipokines, together with CXCL8 and CCL2, also play a role in the progression of atherosclerosis, influencing endothelial function and producing endothelitis.<sup>27–29</sup> In fact, endothelial vascular damage resulting in apoptosis, a finding reported in the autopsies of patients who have died from severe COVID-19, is considered to be a key factor in lung microvascular dysfunction, leading to pulmonary permeability, alveolar edema, and ultimately hypoxia.<sup>30</sup> At the same time, secretion of proinflammatory cytokines increases the expression of adhesion molecules, promoting endothelial activation and impairing microvascular flow and tissue perfusion.<sup>31</sup> The acronym MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) has recently been suggested as a name for these pathological changes observed in COVID-19.<sup>32</sup>

Even more specifically, epicardial adipose tissue inflammation has been considered responsible for a distinctive pattern in the cardiovascular disorders most prevalent

in patients with psoriasis, such as accelerated coronary atherosclerosis, atrial myopathy leading to atrial fibrillation and thromboembolic stroke and, finally, ventricular myopathy leading to heart failure with a preserved ejection fraction.<sup>33</sup> COVID-19 also produces cardiovascular manifestations, primarily acute myocardial infarction but also ventricular systolic dysfunction and arrhythmias. The pathogenic mechanism for these combines both direct and indirect viral damage caused by the inflammatory response syndrome and the adverse cardiovascular effects of some of the drug combinations used to treat these patients.<sup>34</sup> Even within its mechanisms of acute vascular damage, COVID-19 shares pericardial inflammation with psoriasis.<sup>35</sup> Furthermore, while the specific relationship between psoriasis and COVID-19 has not been assessed, it is known that the presence of hypertension and diabetes—more frequent in patients with psoriasis—increases the risk of cardiovascular problems.<sup>34</sup>

Another aspect of interest is the generation of neutrophil extracellular traps (NETs) or NETosis, a defense mechanism involved in psoriasis and also found in atherosclerosis. NETs are based on the formation of cytosolic proteins, which contain autoantigens, induce the activation of macrophages and the Th17 pathway, and trigger immune cell recruitment.<sup>36–38</sup> More recently, NETs have been involved in the pathogenicity of COVID-19,<sup>39</sup> explaining the presence of neutrophils and subcorneal pustules in recently reported skin biopsies.<sup>40</sup> It is not, however, the only cytokine common to psoriasis and COVID-19; for example, disease severity in psoriasis appears to be increased by high levels of IL-6,<sup>41</sup> another cytokine that plays a key role in the inflammatory storm recently observed in patients affected by COVID-19.<sup>42</sup>

In short, there are still numerous gaps in our understanding of the pathogenesis of vascular damage and pericardial inflammation in COVID-19. No studies have been undertaken to assess the various implications of obesity and infection with SARS-CoV-2 on these proinflammatory pathways, beyond associating the presence of obesity with more severe disease.<sup>4</sup> However, our review of the literature has enabled us to identify pathogenic pathways that appear to be common to both diseases.

## Practical Aspects of Weight Loss Strategies in the Context of COVID-19 and Psoriasis

While much remains to be clarified regarding the underlying pathogenic pathways, the preceding review clearly shows that obesity is a risk factor for both COVID-19 and psoriasis.

In view of this relationship between obesity, psoriasis, and COVID-19, a number of practical implications need to be considered.

The first of these is the potential increase in the number of obese patients as a result of the lockdown measures imposed to minimize the spread of the coronavirus. Overweight people, like everyone else, have been confined to home, a situation that has made them more vulnerable to excess food consumption and a sedentary lifestyle, predisposing them to additional weight gain.<sup>43</sup>

Consequently, weight control strategies are particularly important in the current context since weight loss has been shown to improve psoriasis and even prevent its onset.<sup>13</sup>

In this scenario, various weight loss strategies can be considered, including a low-calorie diet, which is a useful option in patients with psoriasis<sup>44</sup> but may represent a challenge under lockdown conditions, especially given the psychological stress generated by the pandemic.<sup>45</sup> The impact of surgical weight loss interventions in psoriasis has also been evaluated and the following is a brief discussion of the topic.<sup>44</sup> The consideration that obese patients are at increased risk of COVID-19 infection has led to a recommendation that bariatric surgery should be avoided in these patients during the pandemic, a proposal that has led to complaints from associations representing these patients.<sup>46</sup>

At the same time, a decline in purchasing power is associated with an increase in the consumption of cheaper but more unhealthy foods; consequently, an economic recession can lead to an increase in the prevalence of obesity, particularly in the most economically disadvantaged sections of the population.<sup>47</sup>

To return to the specific topic of obese patients with psoriasis, weight reduction improves the skin disease<sup>48</sup> in this setting and maintaining weight loss in the long term also produces additional beneficial effects. With respect to the relationship between biologic therapies and weight control, some studies have suggested that TNF inhibitors tend to cause weight gain, apremilast may favor weight loss, and no effect on weight has been observed with IL-17, p40, and IL-23 inhibitors.<sup>12,49</sup> With respect to response to therapy, TNF inhibitors are the group of drugs in which obesity is associated with the greatest loss of efficacy, and IL-17 inhibitors are the drugs that best maintain their effectiveness in patients with a high BMI, although the response to secukinumab is better in patients who weigh less than 90 kilograms than in overweight patients.<sup>12</sup> In the case of ixekizumab and brodalumab, the clinical response is more independent of body weight. Also with regard to treatments, in this case not specific to psoriasis, it is interesting to note that some authors have reported cases of improvement in the control of psoriasis with the use of certain antidiabetic drugs.<sup>50</sup>

Bariatric surgery is the most effective intervention for achieving weight loss, with reductions of up to 26% of baseline weight in the short term.<sup>51</sup> Although there is only limited evidence in the literature on the use of bariatric surgery as a way to improve psoriasis or psoriatic arthritis, a meta-analysis of 2 cohorts observed that bariatric surgery can reduce the risk of developing psoriasis.<sup>48</sup> Two studies based on data from national registries were undertaken to identify incident psoriasis and psoriatic arthritis in obese patients who underwent weight loss interventions (gastric bypass, vertical gastroplasty, or gastric banding) and to compare the outcomes with those of obese patients who declined such interventions: Egeberg et al.<sup>13</sup> studied data from the Danish registry over a 16-year period; and Maglio et al.<sup>52</sup> analyzed data from the Swedish registry.<sup>52</sup> The Danish study found statistically significant differences in the case of gastric bypass but not gastric banding, perhaps because of the greater ability of the former to produce weight loss or, as the authors postulated, due to the direct anti-inflammatory effects achieved by altering the microbiome or releasing certain hormones, such as glucagon-like peptide.<sup>48</sup> The authors of the Swedish study observed no

differences between the results obtained with the different types of interventions.<sup>52</sup>

## Conclusions

Obesity is an independent risk factor for psoriasis, related to incidence and prevalence as well as disease severity. Furthermore, it is the factor most strongly associated with metabolic syndrome and is associated with an increased risk of withdrawal from treatment for various biologic therapies and reduced efficacy in the case of certain biologic agents.

As well as its negative impact on disease severity and response to treatment in patients with psoriasis, obesity is also a negative prognostic factor in SARS-CoV-2 infection. It has also been postulated that excess weight may increase susceptibility to infection with SARS-CoV-2 or prolong the time during which patients can infect others, although neither of these hypotheses have been demonstrated. Although psoriasis and obesity, and even SARS-CoV-2 infection, share common pathogenic pathways and cytokines and both psoriasis and COVID-19 promote systemic inflammation that can lead to endothelial vascular damage, further studies are needed to elucidate how these 3 diseases interact. Finally, apart from encouraging the patients who consult us to take steps to become more healthy, encouraging them to eat a healthy diet and incorporate aerobic exercise routines into their lives at least 5 days a week,<sup>53</sup> we should also consider the possible interest of exploring the option of bariatric surgery, not only because of its effects on psoriasis but also because it reduces the patient's baseline risk with respect to SARS-CoV-2 infection.

## Conflicts of interest

The authors declare that they have no conflicts of interest related to this article. Dr. Llamas-Velasco has received fees as a consultant and/or speaker from and/or has participated in studies or clinical trials sponsored by the following pharmaceutical companies: AbbVie, Almirall, Amgen, Biogen, Celgene, Galderma, Janssen, Leo, Lilly, Novartis, UCB.

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