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REVIEW ARTICLE

Psoriasis strikes back! Epicardial adipose tissue: Another contributor to the higher cardiovascular risk in psoriasis

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Abstract For many years psoriasis was considered an inflammatory condition restricted to the skin. However, nowadays it is considered an immune-mediated, systemic inflammatory condition associated with numerous medical comorbidities, particularly cardiometabolic diseases, and overall cardiovascular mortality. Several studies have suggested that psoriasis may be an independent risk factor for atherosclerosis, indicating that psoriasis itself poses an intrinsic risk for cardiovascular disease, probably due to the disease's inflammatory burden. However, other causes beyond systemic inflammation and traditional cardiovascular risk factors may be implicated in cardiovascular disease in psoriasis. Recently, epicardial adipose tissue, an emerging cardiovascular risk factor, has been shown to be increased in psoriasis patients and to be associated with subclinical atherosclerosis, providing another possible link between psoriasis and atherosclerosis. The reason for the increase in epicardial adipose tissue in patients with psoriasis is unknown, but it is probably multifactorial, with genetic, immune-mediated and behavioral factors having a role.

Thus, along with the increased prevalence of cardiometabolic risk factors and systemic inflammation in psoriasis, epicardial adipose tissue is probably another important contributor to the higher cardiovascular risk observed in psoriasis.

PALAVRAS-CHAVE
Aterosclerose;
Doença cardiovascular;
Gordura epicárdica;

Psoríase contra-ataca! Gordura epicárdica: outro importante contribuidor para o aumento do risco de doença cardiovascular na psoríase

Resumo A psoríase foi considerada durante muitos anos uma doença inflamatória exclusivamente cutânea. No entanto, hoje em dia, a psoríase é considerada uma doença inflamatória

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sistémica, imuno-mediada, associada a diversas comorbilidades, em particular cardiometabólicas, e a um aumento da mortalidade cardiovascular. Vários estudos apontam que a psoríase, por si só, apresenta um risco intrínseco de doença cardiovascular, provavelmente relacionado com a inflamação sistémica, representando um fator de risco independente de aterosclerose. Contudo, outras causas para além da inflamação sistémica e dos fatores de risco cardiovasculares tradicionais poderão estar implicados no desenvolvimento de doença cardiovascular na psoríase. Recentemente, a gordura epicárdica, demonstrou estar aumentada em doentes com psoríase, e associar-se a aterosclerose subclínica, providenciando outra possível explicação para a ligação entre a psoríase e aterosclerose. A razão pela qual a gordura epicárdica se encontra aumentada em doentes com psoríase é ainda desconhecida, mas será provavelmente multifatorial, com fatores genéticos, imunológicos, e comportamentais a desempenharem um papel.

Assim, juntamente com o aumento da prevalência de fatores de risco cardiovasculares tradicionais e a inflamação sistémica psoriática, a gordura epicárdica é provavelmente outro importante contribuidor para o maior risco cardiovascular observado nos doentes com psoríase.

A long time ago, in a Medicine far, far away, psoriasis was considered an inflammatory condition restricted to the skin. With increasing knowledge of the immunopathogenesis of psoriasis, it became clear that the disease's inflammatory action went beyond the skin, affecting the individual systemically. A new view of psoriasis was then formulated: the condition formerly viewed as exclusively dermatologic is now considered an immune-mediated, systemic inflammatory disease associated with numerous medical comorbidities.[1,2] Patients with psoriasis present an increased prevalence of cardiometabolic diseases and overall cardiovascular mortality,[3,4] and epidemiologic studies have demonstrated higher prevalence and incidence of cardiovascular risk factors, such as diabetes, dyslipidemia, hypertension and obesity, in these patients.[4] However, these factors are not on their own sufficient to explain the increased risk of cardiovascular disease in psoriasis. The inflammatory pathophysiology of atherosclerosis is mechanistically similar to psoriasis, as atherosclerosis and psoriasis share several cytokines and inflammatory mediators.[1] Various studies have suggested that psoriasis may be an independent risk factor for atherosclerosis, due to the disease's inflammatory burden, showing that psoriasis itself poses an intrinsic risk for cardiovascular disease.[5]

However, just when it was thought that the association between psoriasis and cardiovascular disease was explained, psoriasis has produced a surprise once again. It appears that causes other than systemic inflammation and traditional cardiovascular risk factors may be implicated in cardiovascular disease in psoriasis.

Epicardial adipose tissue (EAT), a subtype of visceral adipose tissue located between the epicardial layer surrounding the heart and the myocardium, has gained recent clinical attention. EAT is currently considered an active metabolic and inflammatory tissue, with the ability to produce and release various proatherosclerotic and proinflammatory hormones and cytokines, including IL-1 beta, IL-6, TNF-alpha, leptin, plasminogen activator inhibitor-1, and monocyte chemoattractant protein-1.[6] Its close relation to the coronary tree has been suggested as potentially relevant for the development of coronary artery disease (CAD) by endocrine mechanisms, and particularly by local inflammation and paracrine mechanisms. EAT has been independently associated with CAD, and in the Multi-Ethnic Study of Atherosclerosis it was shown to be predictive of incident cardiovascular events independently of conventional risk factors and body mass index.[7] Moreover, EAT has been implicated in the development of insulin resistance, diabetes and metabolic syndrome.[8]

Recently, using imaging methods such as transthoracic echocardiography and multidetector computed tomography, EAT has been shown to be increased in psoriatic patients and to be associated with subclinical atherosclerosis, providing another possible link between psoriasis and atherosclerosis.[9–12] Interestingly, in one study with 100 severe psoriasis patients and 202 controls, EAT volume was found to be increased in psoriatic patients independently of abdominal visceral fat, a reliable marker of excess visceral adiposity, indicating that there may be some psoriasis-related mechanisms contributing to this increased EAT volume.[9]

The reason for the increase in EAT in patients with psoriasis is unknown, but it is probably the result of multifactorial interaction. The association may be partly explained at a genetic level, due to shared genetic and immune-mediated mechanisms. It has recently been shown that psoriasis patients carrying the minor allele (G) of the IL-6 rs2069840 (C>G) polymorphism have increased EAT volume independently of age, gender and abdominal visceral fat. This effect appeared to be enhanced in homozygosity for the G allele (GG), as these patients had increased EAT volume compared to those carrying the C allele (CC+CG).[13] The mechanisms by which IL-6 gene polymorphisms influence EAT or overall adiposity are unknown. It is possible that some IL-6 genotypes are associated with lower energy expenditure, providing a possible explanation for an association between certain polymorphisms and long-term weight gain and obesity.[14] If the G allele of the IL-6 rs2069840 polymorphism is associated with lower energy expenditure, these subjects might be expected to have more adiposity for the

same level of physical activity and calories ingested compared with persons without the G allele. Additionally, there is increasing evidence for the influence of proinflammatory cytokines, particularly IL-6, on excess adiposity.[15] IL-6 has been shown to have a role in the pathogenesis of psoriasis, as it is involved in the immunologic cascade that leads to the disease, including the development of Th17 cells from naïve T cells, and the IL-23-induced skin inflammation that cannot occur without its presence.[16] It also has a biologic role in the modulation of body fat and obesity, being secreted by adipose tissue, and is involved in atherogenesis.[17] Thus, polymorphisms associated with higher expression of IL-6 may partly explain the association between psoriasis and increased EAT volume. Although the IL-6 rs2069840 polymorphism has not been extensively studied, it has been shown to be associated with higher IL-6 plasma levels.[18]

On the other hand, the reason for increased EAT independently of overall adiposity may be more difficult to explain. However, a recent study showed that epicardial adipocytes differ substantially from visceral adipocytes, expressing higher levels of IL-6 (8.13-fold, $p<0.05$) and IL-8 (3.25-fold, $p<0.05$) and lower levels of the atheroprotective adiponectin compared with visceral preadipocytes.[19] Thus, it is possible that certain gene polymorphisms present in patients with psoriasis may be associated with localized increases in adipose tissue.

Finally, another possible cause is behavioral. Aerobic exercise training has been shown to be associated with significant reductions in EAT thickness. Psoriatic patients exhibit decreased levels of physical activity, possibly for both psychological and physiological reasons, as the stigmatization and social avoidance usually seen in patients with psoriasis might make adherence to physical activity problematic.[20]

Regarding the clinical applications of these findings, EAT measurement may be used as a simple marker to identify psoriatic patients with higher cardiovascular risk. There are several imaging modalities for measuring EAT.[21] Although magnetic resonance imaging and computed tomography are currently considered gold standard, echocardiographic measurement of EAT is feasible, reproducible and less expensive and may be a simple and practical tool in clinical practice and research for cardiovascular risk stratification of psoriatic patients.

To summarize, epidemiologic studies have demonstrated that morbidity and mortality in psoriasis are mainly due to cardiovascular disease. Current evidence indicates that along with the increased prevalence of cardiometabolic risk factors and systemic inflammation in psoriasis, EAT is probably another important contributor to the higher cardiovascular risk observed in these patients, with particular importance due to the local effect on the myocardial vasculature. For this reason, it can be said that EAT may be another ''Death Star'' in psoriasis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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