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EDITORIAL COMMENT

Psoriasis-Related Visceral Adiposity and Arterial Inflammation

A New Adiposity Disease Entity?*

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Psoriasis (PsO) is a chronic immune-mediated skin disease that may affect up to 3% of the adult population. In up to 40% of these patients, psoriatic arthritis may manifest, potentially causing joint damage and subsequent disability. In addition, PsO is often associated with obesity, cardiometabolic disease, diabetes mellitus or insulin resistance, dyslipidemia, and a 43% increased risk of cardiovascular disease (1). This may manifest into a 68% increased risk of myocardial infarction, 22% stroke, and 31% heart failure. Of note, this cardiovascular risk appears to be independent of comanifesting traditional cardiovascular risk factors, such as arterial hypertension, obesity, dyslipidemia, and diabetes mellitus, and has been suggested to be attributable to systemic inflammatory state of PsO (2).

The commonly used Framingham Risk Score to stratify coronary artery disease-related cardiovascular risk has been demonstrated to underestimate the true cardiovascular risk in patients with PsO (3). In some studies, medical treatment to control PsO with tumor necrosis factor-α inhibitor and/or methotrexate was associated with reduction in cardiovascular events and/or vascular inflammation in patients with PsO (4). Given the high risk of cardiovascular disease manifestation and its adverse outcome, identifying and treating these PsO patients at risk is of utmost importance. In this respect, imaging of subclinical atherosclerosis in PsO can be performed with ultrasound measurements of carotid intima media thickness and total plaque area, computed tomography (CT) measurements of coronary artery calcifications, and coronary computed tomography angiography to quantify coronary plaque burden and plaque composition. More recently, 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) has been widely recognized as a means to image arterial inflammation of the aorta and aortic branches that likely carry important diagnostic and prognostic information (5,6). ^{18}F-FDG-PET imaging demonstrated more severe arterial inflammation in patients with PsO compared with control patients and, notably, this inflammation was closely related to the extent of skin PsO and the presence of sacroiliitis (5,7).

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In this issue of *iJACC*, Rivers et al. (8) report novel observations using ^{18}F-FDG-PET/CT to link arterial inflammation to visceral adiposity in 77 patients with PsO. In addition, in a subset of 13 patients with PsO with severe skin disease, repeat ^{18}F-FDG-PET/CT after 1 year of PsO treatment demonstrated a decrease in visceral adiposity and arterial inflammation, putting forth visceral adiposity as an important biomarker related to arterial inflammation in PsO. These observations (8) therefore expand on a previous reported association between PsO and arterial inflammation (6,7) to a direct link between PsO-induced systemic arterial inflammation and visceral adiposity. The study included a cohort of 77 predominantly male (57%) PsO individuals with a mean age of 52 years and a low cardiovascular risk as determined by Framingham 10-year risk assessment. Of these study participants, 61 had mild-to-moderate and 16 had severe PsO manifestation. In those with severe PsO, body mass index (kg/m^2), waist-to-hip ratio, Framingham 10-year risk, and insulin resistance were significantly higher than in those with mild-to-moderate PsO,

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outlining a link between disease severity of PsO, increase in body weight, and metabolic alterations. On univariate analysis, visceral adiposity was significantly associated with Framingham 10-year risk, insulin resistance, body mass index, waist-to-hip ratio, PsO severity as reflected by PsO area and severity index, and, notably, arterial inflammation determined by FDG-PET. Further, PsO disease activity significantly correlated with the volume of visceral adiposity ($\beta = 0.33$; $p = 0.004$) but not with subcutaneous adiposity ($\beta = 0.09$; $p = 0.43$). In addition, both subcutaneous and visceral adiposity were positively associated with arterial inflammation, but the association between arterial inflammation and adiposity was more pronounced for visceral adiposity ($\beta = 0.37$, $p = 0.001$ and $\beta = 0.71$, $p < 0.001$, respectively). This is also reflected by the multivariate analysis that revealed visceral but not subcutaneous adiposity to be an independent predictor of arterial inflammation ($\beta = 0.55$, $p = 0.001$ and $\beta = 0.15$, $p = 0.11$). To evaluate whether visceral adiposity yielded incremental value beyond anthropomorphic measures in association with arterial inflammation, a nested modeling was performed that confirmed the independent link between visceral adiposity and arterial inflammation. Thus, it appears indeed that PsO-mediated visceral adiposity releases mediators or so-called adipocytokines that are likely to account, at least in part, for the observed inflammation of the aorta. A previous study in patients with PsO (9) described an increased risk of these patients developing obesity with cardiometabolic alterations, leading to inflamed atherosclerosis with an increased likelihood of cardiovascular event manifestation. Conversely, it is still a matter of ongoing debate whether obesity alone or only in conjunction with traditional cardiovascular risk factors, such as arterial hypertension, dyslipidemia, low high-density lipoprotein levels, and pre-diabetic state, may indeed initiate the atherosclerotic process. Someone could argue that coexisting traditional cardiovascular risk factors may account for the subclinical manifestation of atherosclerosis and that PsO-related visceral adiposity may enhance the inflammatory process in the arterial wall, contributing to a further progression of coronary atherosclerosis and plaque "vulnerability" with subsequent plaque rupture and its atherothrombotic sequelae. As in the current study, the extent and severity of the atherosclerotic process of the aorta was not assessed, and the relationship between the observed arterial inflammation and the presence of atherosclerosis in the aorta or coronary vessels remain uncertain. The results of the current investigation, however, emphasize that visceral adipose tissue is a metabolic key player in fueling arterial inflammation that likely contributes to progression of atherosclerosis and vulnerable plaque formation in PsO (5,10). Inflammation of the visceral adipose tissue per se may release various adipocytokines, such as leptin, adiponectin, ghrelin, and endocannabinoids, altering coronary vasomotor dysfunction commonly seen as a functional precursor of the coronary artery disease process (11,12). For example, adiponectin and ghrelin are known to mediate endothelium-dependent and, thus, nitric oxide–mediated vasodilation, whereas chronic elevations of endocannabinoids in the plasma lead to a dysfunction of endothelium-dependent and endothelium-independent vasomotor function (11,13). Regarding leptin, there is much evidence of its prothrombotic and pro-inflammatory effects mediated via stimulation of the release of tumor necrosis factor-α and an array of cytokines from the adipose tissue that may favor vasomotor dysfunction. Conversely, other studies have suggested increase in leptin plasma levels contribute to the maintenance of vasomotor function (12). In this respect, it is important to bear in mind that the effects of adipocytokines or endocannabinoids on the endothelium may vary or they may even be discordant dependent on acute or chronic elevations of these mediators in the plasma that may lead to post-receptor changes in enzyme cascade activation. For example, insulin in the circulation may induce divergent vasomotor responses strictly on the presence or absence of insulin resistance of the organs and vascular arterial wall (13). In a normal insulin-sensitive state of the vascular endothelium, insulin prevalently activates mitogen-activated protein kinase that again causes an endothelium-mediated vasodilation via release of nitric oxide in the subintimal space. Conversely, the insulin-resistant state, such as in pre-diabetes or diabetes, is predominantly geared toward the phosphoinositide 3-kinase/Akt pathway, causing an abnormal absence of vascular dilation and/or even a vasoconstriction, outperforming mitogen-activated protein kinase–related vasodilation. Such a concept may also apply for the discordant observations of leptin plasma levels altering vasomotor function in the peripheral and coronary circulation (12). There is also increasing evidence that a certain balance or disbalance between adipocytokines and endocannabinoids may be seen as critical determinant of arterial function (13). Because the current study did not assess specifically the effects of a variety of adipocytokines and endocannabinoids, it remains uncertain what constellation of these mediators from the visceral adipose tissue may account for the observed

arterial inflammation in PsO individuals. Such information is vital for further understanding of this novel kind of PsO-related adipositas disease entity and how it differs from classical obesity and morbid obesity. These important observations by Rivers et al. (8) may also apply to other rheumatologic diseases, such as lupus erythematosus or scleroderma, and need further investigation. Importantly, the authors (8) have also demonstrated that immune-suppressive treatment of PsO in 16 patients with initial severe stages of PsO over a 1-year follow-up period was associated with a decrease in both visceral adiposity and arterial inflammation, providing direct evidence of a causal relationship between visceral adiposity and arterial inflammation. Given the strong link between systemic inflammation and cardiovascular events (1), immune-suppressive treatment has indeed emerged as a potential effective means to further improve the cardiovascular outcome in these patients, apart from beneficial effects for the skin and joint disease (14). Thus, the central role of anti-inflammatory medication in improving cardiovascular outcome not only in patients with chronic inflammatory conditions, such as PsO, but also in classical cardiovascular risk individuals is emphasized by the randomized clinical trial CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), which demonstrated that suppression of inflammation by targeting the interleukin-1β innate immunity pathway with canakinumab can indeed reduce the incidence of cardiovascular events, without affecting mortality because of an increase in infectious disease and sepsis (15).

The observations of the current study conducted by Rivers et al. (8) are unique because they provide first evidence suggesting that visceral adiposity is a novel critical player in fueling arterial inflammation in psoriasis that is likely to account for an increased prevalence of an inflammatory atherosclerotic process and increased cardiovascular risk. Albeit that immune-suppressive treatment may be geared to identifying and characterizing arterial inflammation, such as demonstrated by FDG-PET, in patients with chronic inflammatory disease such as PsO, further large-scale clinical trials with immune-suppressive treatment need to be conducted to explore its potential and, importantly, safety profile.

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