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Original article

¹⁸F-Fluorodeoxyglucose positron emission tomography and serum cytokines and matrix metalloproteinases in the assessment of disease activity in Takayasu's arteritis



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ABSTRACT

Objective: To evaluate ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake on positron emission tomography–computed tomography (PET–CT) and serum levels of different cytokines and matrix metalloproteinases (MMPs) in patients with Takayasu arteritis (TA) and associations with disease activity.

Methods: Serum levels of tumor necrosis factor- α (TNF- α), interleukin (IL)-2, IL-6, IL-8, IL-12, IL-18, MMP-3 and MMP-9 were measured in 36 TA patients and 36 controls. Maximum standard uptake value (SUV_{max}) of ¹⁸F-FDG in arterial walls was determined by PET–CT scans. TA patients were classified as active disease, inactive disease and possible active disease.

Results: Serum IL-6 and MMP-3 levels were higher in TA patients than in controls ($p < 0.001$). Serum IL-6 was higher in patients with active disease and in patients with possible active disease than in inactive disease ($p < 0.0001$). Patients with active disease had higher serum TNF- α levels than patients with inactive disease ($p = 0.049$) while patients with possible active disease presented higher IL-18 levels than patients with inactive disease ($p = 0.046$). Patients with active disease had higher SUV_{max} values than those with inactive disease ($p = 0.042$). By receiver operating characteristic (ROC) curve SUV_{max} was predictive of active disease in TA and values ≥ 1.3 were associated with disease activity ($p = 0.039$). Serum TNF- α levels were higher in patients with SUV_{max} ≥ 1.3 than < 1.3 ($p = 0.045$) and controls ($p = 0.012$). Serum IL-6 levels were higher in patients with SUV_{max} ≥ 1.3 than in controls ($p < 0.001$). No differences regarding other biomarkers were found between TA patients and controls.

Conclusions: Higher serum IL-6 and TNF- α levels as well as higher ¹⁸F-FDG uptake in arterial wall are associated with active TA.

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Tomografia por emissão de pósitrons com 18F-fluordesoxiglicose e citocinas séricas e metaloproteinases da matriz na avaliação da atividade da doença na arterite de Takayasu

R E S U M O

Palavras-chave:

Citocinas

Metaloproteinases da matriz

Tomografia computadorizada

Arterite de Takayasu

Objetivo: Avaliar a captação de 18F-fluordesoxiglicose (18F-FDG) na tomografia por emissão de pósitrons-tomografia computadorizada (PET-CT) e os níveis séricos de diferentes citocinas e da metaloproteinases da matriz (MMP) em pacientes com arterite de Takayasu (AT) e associações com a atividade da doença.

Métodos: Foram mensurados os níveis séricos do fator de necrose tumoral- α (TNF- α), interleucina (IL)-2, IL-6, IL-8, IL-12, IL-18, MMP-3 e MMP-9 em 36 pacientes com AT e 36 controles. O valor padronizado de captação máximo (SUV_{max}) de 18F-FDG nas paredes arteriais foi determinado por exames de PET-CT. Os pacientes com AT foram classificados como tendo doença ativa, doença inativa e possível doença ativa.

Resultados: Os níveis séricos de IL-6 e MMP-3 foram mais altos em pacientes com AT do que nos controles ($p < 0,001$). Os níveis séricos de IL-6 eram mais elevados em pacientes com doença ativa e em pacientes com possível doença ativa do que naqueles com doença inativa ($p < 0,0001$). Os pacientes com doença ativa apresentaram níveis séricos mais elevados de TNF- α do que os pacientes com doença inativa ($p = 0,049$), enquanto os indivíduos com possível doença ativa apresentaram maiores níveis séricos de IL-18 do que os pacientes com doença inativa ($p = 0,046$). Aqueles com doença ativa apresentaram maiores valores de SUV_{max} do que aqueles com doença inativa ($p = 0,042$). De acordo com a curva ROC, o SUV_{max} era capaz de prever a doença ativa na AT e valores $\geq 1,3$ estavam associados à atividade da doença ($p = 0,039$). Os níveis séricos de TNF- α foram maiores em pacientes com SUV_{max} $\geq 1,3$ do que naqueles com valor $< 1,3$ ($p = 0,045$) e controles ($p = 0,012$). Os níveis séricos de IL-6 foram mais elevados em pacientes com SUV_{max} $\geq 1,3$ do que nos controles ($p < 0,001$). Não foram encontradas diferenças em relação a outros biomarcadores entre pacientes com AT e controles.

Conclusões: Níveis séricos elevados de IL-6 e TNF- α , bem como uma maior captação de 18F-FDG na parede arterial, estão associados a AT ativa.

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Introduction

Takayasu arteritis (TA) is a primary systemic vasculitis of unknown etiology that affects large arteries, mainly the aorta and its main branches and less frequently pulmonary and coronary arteries. The chronic granulomatous inflammation occurs in all layers of the vessel wall and may lead to stenosis, occlusion, dilation or aneurysm formation.^{1,2}

Cell-mediated autoimmunity plays a key role in the pathogenesis of TA. Immunohistochemical studies of the infiltrating cells in the aortic tissue have shown mainly gamma-delta T-cells, CD4+ and CD8+ T-cells, NK cells and macrophages.³ The presence of granulomatous inflammation in the internal elastic layer is the most characteristic pathologic finding of TA. The inflammatory process begins in the *vasa vasorum* and it is believed to be triggered by the activation of dendritic cells and dendritic cell/T-cell interaction in the vascular microenvironment of the adventitia of large arteries leading to the induction of a Th1 response.⁴

The detection of vascular inflammation in TA patients is a major challenge in clinical practice, since up to 60% of asymptomatic patients developed new angiographic lesions on sequential arteriographic evaluation, and 44% of patients

considered to be in remission by clinical evaluation showed histopathological evidence of active inflammation on surgical specimens.¹ Due to the evidence of progression of vascular damage in asymptomatic TA patients, additional evaluation is necessary to guide therapeutic decisions. Nevertheless, to date there is no reliable surrogate parameter to detect subclinical disease activity in TA patients. Potential biological markers of inflammation and tissue degradation, such as cytokines and metalloproteinases (MMPs) have been evaluated separately in different studies but some results have not been reproduced.⁵⁻⁷ Different imaging techniques have been used to assess the extent of arterial involvement in TA, among them ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography with computed tomography (PET-CT) scan can detect active arterial wall inflammation. Some studies have been promising⁸⁻¹⁰ whereas others have found conflicting results with the use of PET-CT scans to evaluate disease activity in TA.^{11,12}

The aims of this study were to evaluate the intensity of ¹⁸F-FDG uptake on PET-CT scans on arterial walls and quantify serum levels of interleukin-2 (IL-2), IL-6, IL-8, IL-12, IL-18, tumor necrosis factor- α (TNF- α), MMP-3 and MMP-9 in patients with TA and controls as well as to evaluate possible associations with disease activity in TA.

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