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The application of molecular imaging to advance translational research in chronic inflammation

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Abstract

Over the past several decades, molecular imaging techniques to assess cellular processes *in vivo* have been integral in advancing our understanding of disease pathogenesis. ^{18}F-fluorodeoxyglucose (18-FDG) positron emission tomography (PET) imaging in particular has shaped the field of atherosclerosis research by highlighting the importance of underlying inflammatory processes that are responsible for driving disease progression. The ability to assess physiology using molecular imaging, combining it with anatomic delineation using cardiac coronary angiography (CCTA) and magnetic resonance imaging (MRI) and lab-based techniques, provides a powerful combination to advance both research and ultimately clinical care. In this review, we demonstrate how molecular imaging studies, specifically using 18-FDG PET, have revealed that early vascular disease is a systemic process with multiple, concurrent biological mechanisms using inflammatory diseases as a basis to understand early atherosclerotic mechanisms in humans.

Keywords

Atherosclerosis; Inflammation; ^{18}F- fluorodeoxyglucose (18-FDG); Immunology

Introduction

The use of radiolabeled imaging probes in molecular imaging offers the unique ability to assess molecular processes, evaluate organ function and probe underlying disease pathogenesis.[1] Molecular imaging techniques are highly relevant in atherosclerosis, especially for early disease detection and understanding inflammation-driven disease progression related to coronary plaque disease activity.[1] From early observations that increased deoxyglucose is trapped by macrophages in tumor cells[2, 3] to determination that macrophage density is increased in atherosclerotic plaques,[4, 5] ^{18}F- fluorodeoxyglucose (18-FDG) positron emission tomography (PET) was established as a useful methodology

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to investigate inflammatory plaques in both animal and human models.[5–8] More recently, a second tracer, ^{18}F- sodium fluoride (^{18}F-NaF) PET, was employed for microcalcification imaging within coronary plaques to identify high risk coronary plaque disease activity and to detect the presence of ruptured plaques, which along with 18-FDG PET, may allow for identification of early- stage atherosclerosis.[9–11] Such efforts in molecular imaging have advanced our understanding of the biology of atherosclerosis and aided in the design of translational studies to elucidate the effects of targeted interventions in inflammatory diseases. The purpose of this review is to highlight how the use of 18-FDG molecular imaging has shaped our understanding of atherosclerosis as an inflammatory disease, demonstrated multi-system effects of chronic inflammation and refined translational studies to dissect disease pathogenesis by combining immune cell- based laboratory studies and imaging-based clinical studies in humans.

Inflammation in the pathogenesis of atherosclerosis

Despite a wide range of contemporary treatment strategies, cardiovascular disease (CVD) remains the leading cause of death in the United States, with coronary artery disease (CAD) being the most common CVD and affecting an estimated 18.2 million American adults.[12] Both clinical and pre-clinical studies demonstrate the importance of inflammation in the development and progression of atherosclerosis. Rather than a passive process of lipoprotein buildup, atherosclerosis pathogenesis is dynamic and complex with significant contributions from inflammation and immune effectors.[13, 14] This immune response is initially triggered by cholesterol accumulation in the vessel wall.[13] Local cellular response involving leukocyte adhesion molecules and chemokine expression further attract monocytes and mononuclear phagocytes resulting in low-grade, chronic inflammation and acceleration of atherosclerosis.[14, 15] Activated T cells in plaques recruited via chemokine receptors illustrate the significant role of adaptive immunity.[13, 14] Further differentiation of naive T- helper cells into separate T-helper phenotypes with immune- activating or protective effects[13] demonstrates that immune regulation is nuanced and requires further careful investigation to understand specific cellular subsets, their etiology and function for development of potential therapeutic targets. The important role of immunology in early vascular disease including vascular inflammation has been previously reviewed in detail.[16]

Overview of 18-FDG PET imaging in vascular disease

Given their highly sensitive and non-invasive qualities, molecular imaging techniques are well- suited to advance our understanding of atherosclerosis, especially in the context of chronic inflammation. Owing to rich pre-clinical studies as well as contemporary molecular imaging techniques, the inflammatory process is recognized as central to atherosclerosis development[16] from initial fatty streak formation to late plaque erosion and eventual rupture leading to myocardial infarction.[17] Macrophages localized within atherosclerotic plaque consume glucose as an important respiratory substrate,[18] and therefore take up detectable amounts of 18-FDG, allowing 18-FDG PET imaging to provide a non-invasive assessment of the inflammatory components of vascular disease activity (Figure 1). Given increased macrophage density in ruptured plaques as well as high levels of glucose transporter and

hexokinase expression in activated macrophages,[19] 18-FDG PET imaging is a valuable tool to monitor atherosclerosis disease progression.

Initial diagnostic efforts in vascular inflammation focused on 18-FDG uptake within the carotid arteries. Rudd et. al observed an increase in 18-FDG uptake within culprit carotid lesions in patients with transient ischemic attack compared to plaques in asymptomatic patients.[20] Utilization of this modality was then extended to imaging the aorta and peripheral arteries, allowing 18-FDG phenotyping of multiple vascular beds, an especially valuable tool for characterizing the systemic nature of inflammatory vascular disease.[21–23] In particular, aortic vascular 18-FDG uptake was shown to be a reliable surrogate biomarker for stratifying patients at increased risk for CVD[24] by identifying atherosclerotic plaque with high-risk morphological features,[25,26] and predicting future cardiovascular events.[24] Moreover, aortic vascular 18-FDG uptake correlated with coronary plaque burden as assessed by cardiac computed tomography angiography (CCTA) both in human immunodeficiency virus (HIV)[26] and psoriasis.[27] These findings suggest that elevated vascular uptake of 18-FDG, especially in the aortic arch, complements anatomic imaging techniques which delineate coronary plaque composition suggesting the importance of 18-FDG uptake in the aorta in identifying patients at high risk for coronary artery disease.

Not only is 18-FDG uptake a reliable diagnostic marker, it also varies in response to treatment, allowing for both disease diagnosis and treatment monitoring. Prior studies demonstrating attenuation of plaque inflammation in the thoracic aorta, carotid arteries and coronary arteries after statin threapy[28–30] and lifestyle modification[31] suggest that 18-FDG PET is a consistent method to monitor the effects of drug interventions on vascular disease through quantification of changes in early inflammatory disease burden which may precede changes in plaque morphology.[32,22,23] Additionally, because inflammatory pathways and traditional lipid pathways both contribute to the pathogenesis of atherosclerosis, molecular imaging to assess inflammation may be useful to identify residual risk in patients already optimized on statin therapy.

18-FDG PET application in chronic inflammatory diseases

The important contribution of chronic inflammation to CVD has been observed in patients with chronic inflammatory diseases. Compared to the general population, chronic inflammatory diseases have been associated with about a two-fold increased risk of developing CVD.[33] Importantly, application of traditional risk assessment tools to patients with chronic inflammatory diseases such as psoriasis and rheumatoid arthritis has been shown to underpredict clinical events,[34–38] prompting recommendations that chronic inflammatory disease be considered a risk- enhancing factor.[39] Hence, capturing subclinical CVD using imaging in this population may improve risk prediction beyond traditional risk assessment, especially in intermediate- risk individuals.[40] Indeed, 18-FDG PET studies in psoriasis, rheumatoid arthritis and human immunodeficiency virus (HIV) have shown heightened premature atherosclerosis and vascular 18-FDG uptake compared to healthy populations, thus offering a potential explanation for the increased risk of major adverse cardiac events observed in large epidemiological studies.[34, 37] For example, in those with rheumatoid and psoriatic arthritis, joint inflammation severity as assessed by joint

18-FDG uptake correlated with vascular 18-FDG uptake.[33, 41] In individuals with HIV infection, 18-FDG uptake in lymph nodes correlated with both nodal HIV activity and coronary atherosclerosis including high-risk coronary plaque.[26, 42] Finally, 18-FDG uptake evaluation also improves long-term cardiovascular event prediction.[24, 43] Taken together, these findings suggest a potential role for 18-FDG in molecular imaging-based evaluation of atherosclerosis in those with chronic inflammatory conditions whose cardiovascular risk may be under appreciated by conventional risk assessment.

18-FDG PET application in stress- mediated cardiovascular disease

Because maladaptive physiologic responses occur in multiple organ systems in chronic inflammatory diseases, simultaneous assessment of inflammation in several tissues better enables assessment of overall risk. Chronic psychosocial stress, independent of traditional cardiovascular risk factors, has been increasingly recognized as a potent contributor to the development of adverse cardiovascular outcomes ranging from hypertension to diabetes mellitus and CAD.[44, 4546] Although the exact mechanisms are poorly understood, complex neuro- immune- arterial axis involving dysregulation of the hypothalamic-pituitary- adrenocortical (HPA) axis, stress-induced immune dysregulation characterized by increased leukopoiesis from the bone marrow, and cytokine release propagating downstream endothelial and vascular dysfunction have all been proposed as mechanisms linking stress to CVD.[45, 47] Because the limbic system and specifically the amygdala regulates the HPA axis,[48, 49] the recent application of 18-FDG in quantifying perceived stress as represented by increased amygdalar 18-FDG uptake permits assessment of heighted neural biological activity to understand perceived stress on CV risk (Figure 2).[45] Increased 18-FDG uptake in the amygdala, suggesting a higher stress response, was associated with worsening vascular 18-FDG uptake and greater risk for subsequent CV events.[50] 18-FDG uptake in the amygdala was also related to noise pollution exposure, which associated with vascular inflammation and major adverse cardiac events.[51] Additional 18-FDG assessment within the bone- marrow provides information on leukopoietic activity (Figure 3) which was shown to be related to heighted amygdalar activation, vascular inflammation and increased future CVD events.[50, 52]

An example of 18-FDG PET application to advance translational science

Given that atherosclerosis development is accelerated in chronic inflammatory diseases, psoriasis, a chronic inflammatory, immune-mediated skin disease serves as a model to study the inflammatory contributions of vascular disease, especially since it impacts lipid handling and affects several key tisssues involved in early atherogenesis including skin, joints, liver, blood vessels (Figure 4). Psoriasis affects 2–3% of the adult US population and heightens the risk of developing early-onset atherosclerosis related to a variety of pathways leading to vascular dysfunction.[35, 53, 54] Furthermore, patients with psoriasis have elevated high sensitivity C-reactive protein (hs-CRP) levels, heightened inflammatory biomarkers such as GlycA, and increased inflammatory cytokines in circulation.[55, 56] 18-FDG PET imaging is valuable in understanding the systemic nature of chronic inflammation by demonstrating that patients with psoriasis have increased skin inflammation as evidenced by increased uptake of 18-FDG in the skin (Figure 5), joints and liver compared to those without

psoriasis (Figure 6). An important early observation was that aortic vascular inflammation as measured by 18-FDG PET was associated with skin disease severity independent of traditional cardiovascular risk factors (Figure 7) providing important evidence of external inflammation relating to internal inflammation. Those patients with more severe skin disease also had increased aortic wall thickness as measured by cardiac magnetic resonance imaging (CMR)[57] (Figure 8) which was significantly associated with increased 18-FDG PET uptake in the aorta, suggesting that vascular inflammation by FDG captures early atherosclerotic disease.[57] Most importantly was the fact that aortic vascular inflammation associated with non-calcified coronary plaque burden by CCTA, providing strong evidence that aortic vascular inflammation serves as a reliable surrogate marker of high-risk coronary plaque (Figure 9). [27, 35, 58, 59] Another important contribution facilitated by 18-FDG was proof of concept that treatment and withdrawl of inflammation impacted vascular disease. For example, when psoriasis was treated with biologic therapies, there was a 6% reduction in aortic vascular 18-FDG uptake after 1 year of therapy (Figure 10), a finding comparable to the effect of a low dose statin.[60] This study's findings provided preliminary evidence that psoriasis inflammation and its treatment can be used to test whether changing systemic inflammation in humans modifies coronary atherosclerosis.[9, 10, 61, 62]

In addition to being used for assessment of vascular inflammation, 18-FDG PET also enables simultaneous assessment of the neuro- immune- arterial axis as a mechanism for stress induced CVD as previously mentioned. Patient with psoriasis demonstrated higher 18-FDG amygdalar uptake, increased bone marrow 18-FDG uptake and higher coronary disease burden on CCTA.[63] A reduction in skin disease severity by treating psoriasis resulted in a reduction in amygdalar 18-FDG uptake, bone- marrow FDG uptake, and aortic vascular inflammation.[64] Recently, amygdalar activity assessed by18-FDG was shown to associate with an allostatic load score (physiologic effects of stress on cardiovascular, metabolic and inflammatory indices),[65] underscoring the need to further investigate the effects of stress-induced physiological dysregulation on CVD.

Bone marrow 18-FDG uptake and understanding myeloid cells

The observation of a reduction of bone marrow 18-FDG uptake following primary skin disease therapy in psoriasis spawned a series of lab- based experiments. These studies provide an illustratation of how biologic understanding can be augmented by synergistic use of lab-based experiments and image-based studies. Myeloid cells are critical mediators of CVD with both macrophages and neutrophils detected in coronary plaques and present at the onset of plaque development. In psoriasis, neutrophils are abundant in circulation and maintain an activated state. [55] Furthermore, the pathogenic neutrophil subset, low-density neutrophils, are elevated in psoriasis and associate with early onset CAD and the severity of skin disease.[66] Murine studies of atherosclerosis have highlighted biological pathways interlinking myeloid cells and lipid homeostasis, which are shown to converge in the bone marrow.[67] Cholesterol accumulation in the bone marrow upregulates myelopoiesis, resulting in accelerated release of myeloid cells into the blood stream, exacerbating atherosclerotic plaque development. In psoriasis, 18-FDG uptake in the bone marrow is a surrogate for increased bone marrow activity as previously discussed. When bone marrow 18-FDG uptake was examined against the total frequency of low-density neutrophils, classical monocytes

and platelets in circulation, there was a strong relationship between these indices by flow cytometry and 18-FDG uptake in the bone marrow.[68] This total myeloid score, termed the atherogenic myeloid score, associated with psoriasis severity, bone marrow 18-FDG uptake as well as non-calcified coronary burden in psoriasis.[68] These studies provide evidence as to how PET molecular imaging can be coupled with lab-based investigations to accelerate understanding of biologic relationships. The studies also support further investigation using molecular imaging to enhance translational research in humans utilizing this multi-disclipinary approach.

Limitations of 18-FDG PET Imaging

The ability to diagnose inflammatory vascular disease, monitor therapeutic intervention, provide cardiovascular risk stratification[69, 70] and guide lab- based efforts makes 18-FDG PET imaging application promising for clinical translational investigation. However, studies using 18-FDG PET must be considered in light of several biologic and technical limitations. Although there is a strong correlation between macrophage density and 18-FDG uptake in endarterectomy specimens,[8, 25] non- macrophage cells have also been observed to take up 18- FDG,[71] leading to uncertainty about whether macrophages are the only cell type within vessel walls to take up 18-FDG. Indeed, activated smooth muscle cells within the blood vessel wall also take up 18-FDG.[72] Additionally, spatial resolution limitations of <4mm, combined with the small caliber of the coronary arteries, make identification of the exact location of coronary plaque challenging, although application of this technique has been successfully applied to larger, peripheral arteries.[11] Furthermore, areas of 18-FDG uptake do not directly correlate with coronary calcification on CT, suggesting that the detected metabolic activity assessed as vascular inflammation by 18- FDG detects more ‘active’ and inflamed plaque compared to more mature, calcified disease observed late in atherosclerosis.[11, 73] Because 18- FDG is more likely to be detected in younger patients with less calcification, 18- FDG uptake may represent earlier, predominantly inflammatory components of disease development and progression[11] however dedicated prospective studies are needed to better understand the significance of this.

Clinical translational perspective

The power of molecular imaging lies in its ability to improve the understanding of disease pathophysiology at the molecular and cellular levels within an *in vivo* system. We have illustrated how studies using 18-FDG PET imaging techniques have helped to establish the role of inflammation in atherosclerotic disease development and progression and further serve as a reliable non- invasive method for monitoring effectiveness of disease treatment. Furthermore, 18-FDG PET imaging measures vascular inflammation, detects early vessel wall abnormalities and assesses bone marrow activity and stress-related neural activity. Given continued technical advances, including improvements in scanner technology and incorporation of magnetic resonance imaging, future studies targeting a broader array of subclinical molecular processes will enable better understanding of biology to broaden discovery across the spectrum of cardiovascular diseases to improve diagnosis, treatment and prevention of disease in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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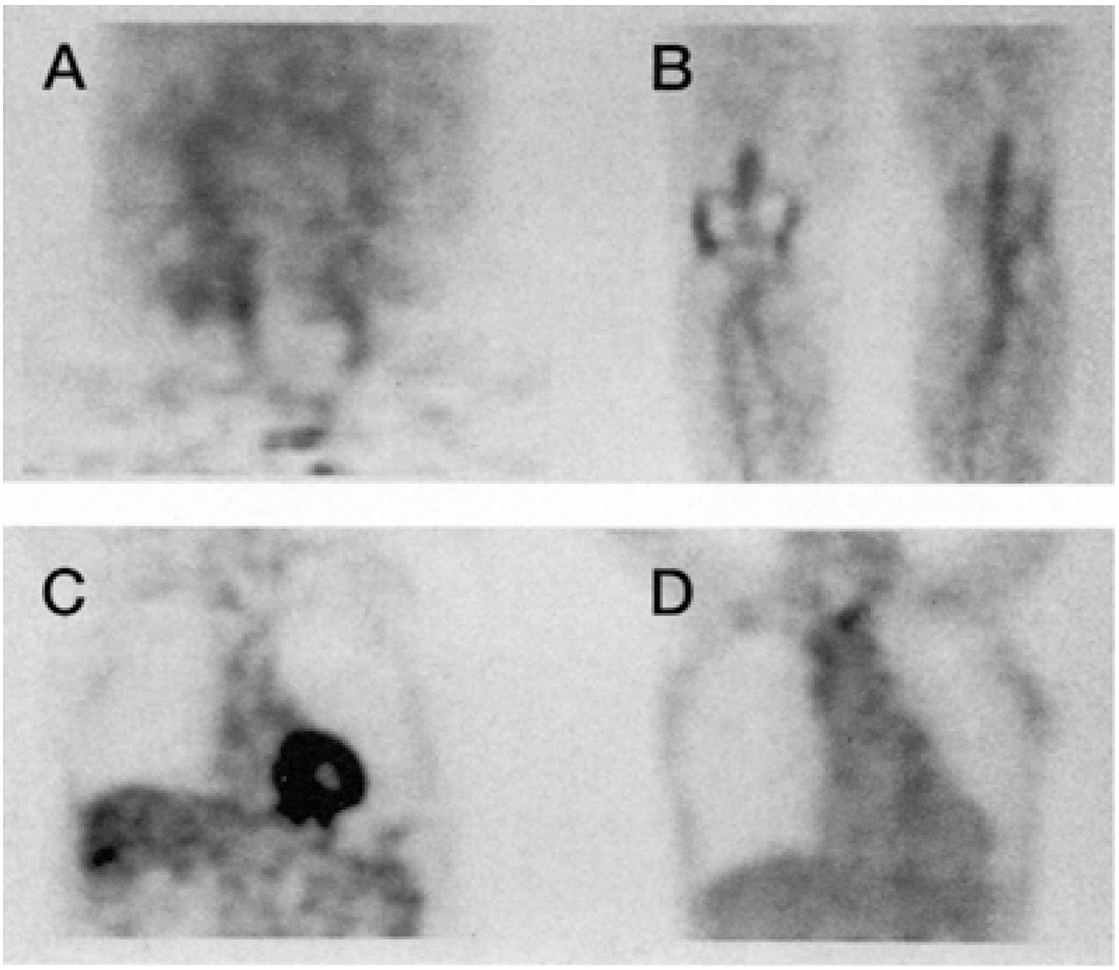

Figure 1:

18-FDG PET imaging for the evaluation of inflammatory activity of large and medium-sized arteries.

Representative PET images demonstrating 18-FDG uptake in the iliac and femoral arteries (A); popliteal arteries (B); abdominal aortic (C); aortic arch (D); in patient with psoriasis. The mean TBR was 1.26 (0.17) for the suprarenal abdominal aorta, 1.20 (0.16) for infrarenal abdominal aortic, and 1.30 (0.22) for the aortic arch.

TBR: tissue- to- background ratio

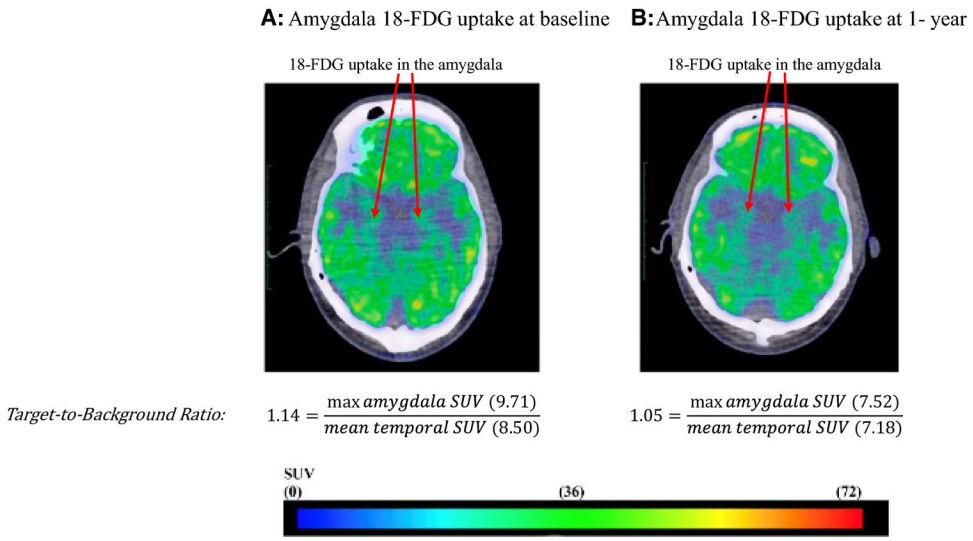

Figure 2:

18-FDG PET/CT imaging for the evaluation of neural biological activity of the amygdala. Representative fused PET/CT images from a patient with psoriasis who had reduction in psoriatic skin disease activity at baseline (A) and one year (B) showing decreased 18-FDG activity in the amygdala.

SUV: standard uptake value

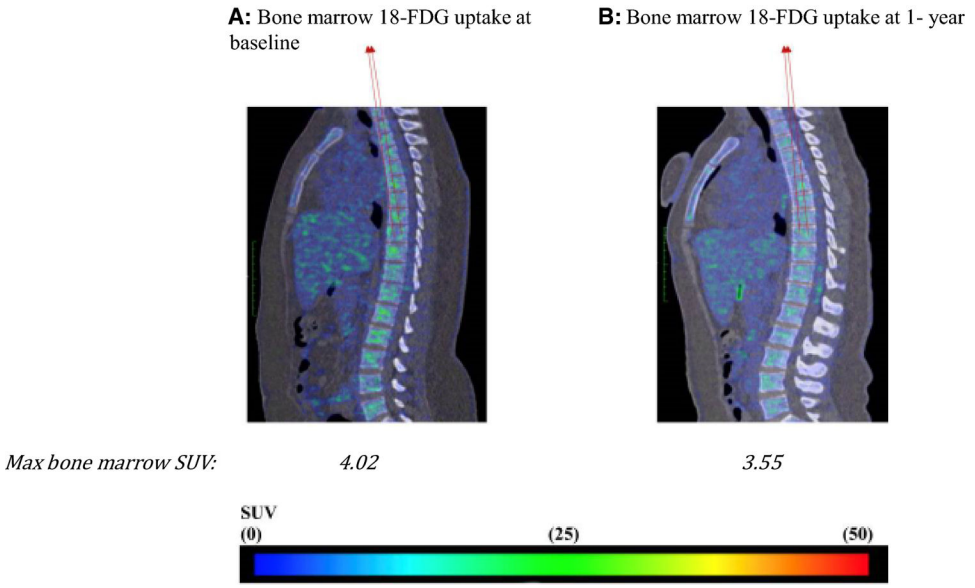

Figure 3:

18-FDG PET/CT imaging for the evaluation of leukopoietic bone marrow activity. Representative fused sagittal PET/CT images from a patient with psoriasis who had reduction in psoriatic skin disease activity at baseline (A) and one year (B) showing decreased 18- FDG activity in T1-L5 vertebrae.

SUV: standard uptake value

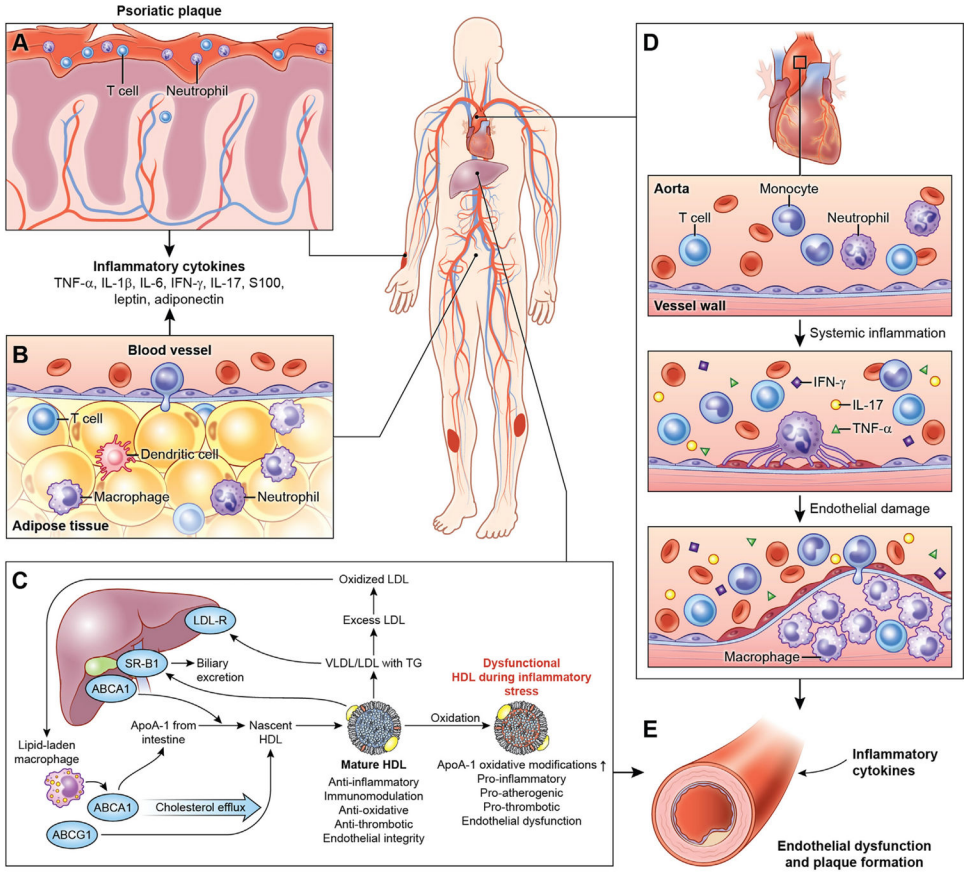

Figure 4:

Psoriasis as a model to study inflammatory contributions of vascular disease.

Psoriasis is a chronic systemic inflammatory disease associated with increased circulating pro-inflammatory cytokines and immune effectors (A), adipose tissue dysfunction (B), lipid profile derangement (C), cellular components, cholesterol crystals and lipoprotein accelerating atherosclerosis (D) and endothelial dysfunction (E).

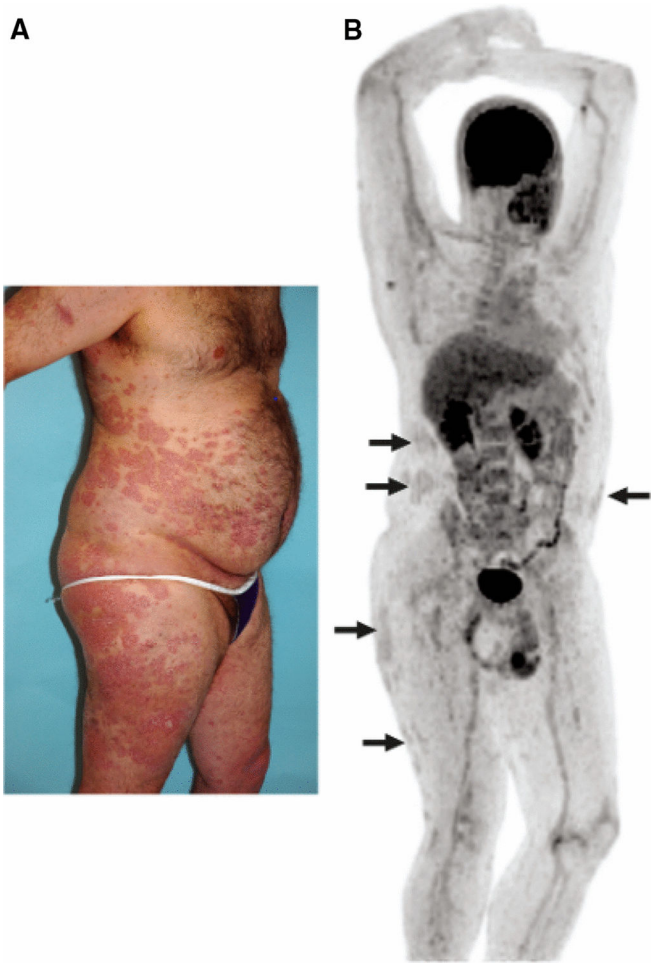

Figure 5:

18-FDG PET imaging for the evaluation of skin inflammation in psoriasis.

Focal areas of extensive skin inflammation related to plaque psoriasis (A) corresponds to similar distribution of areas of 18-FDG uptake on PET (B).

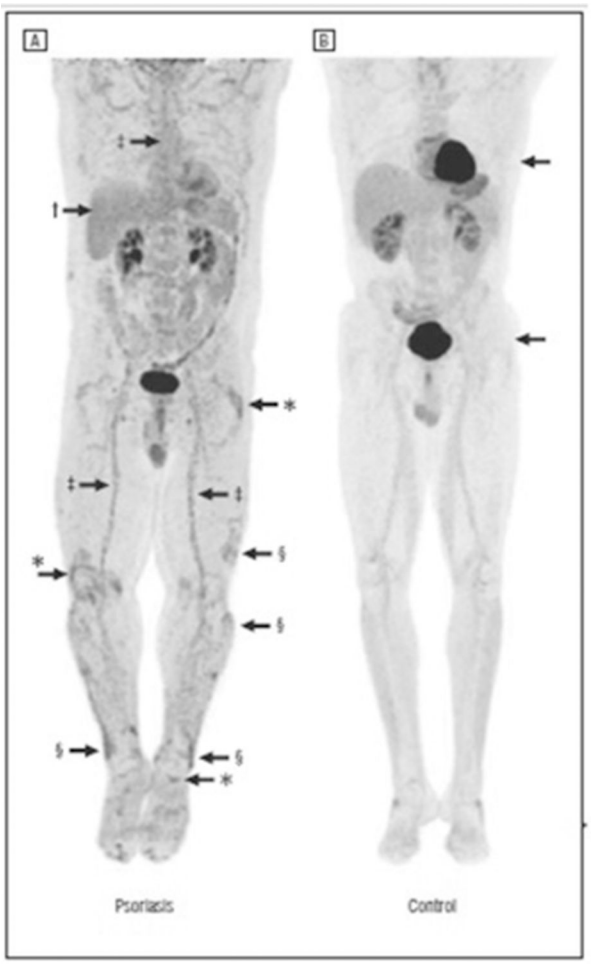

Figure 6:

18-FDG PET imaging demonstrates increased systemic inflammation in psoriasis compared to control.

Multifocal areas of increased 18-FDG uptake on PET are observed in a patient with psoriasis (A) compared to control patient (B). 18-FDG uptake is noted within the myocardium (top arrow) within the range of normal variation and also in the kidneys and bladder (bottom arrow), where 18-FDG is excreted. *FDG uptake in the right knee joint (standardized uptake value [SUV], 3.0) and distal right quadriceps tendon, left trochanteric bursa, and left ankle in asymptomatic patient with psoriasis. †Moderately diffusely increased FDG uptake throughout the liver (SUV, 1.64) consistent with increased hepatic inflammation. ‡Diffuse FDG uptake in the aortic wall (SUV, 1.29–1.72) and in the femoral arterial tree, consistent with vascular inflammation. §Focal areas of FDG uptake in skin consistent with inflammation in thick plaques in lower extremities. SUV: standard uptake value

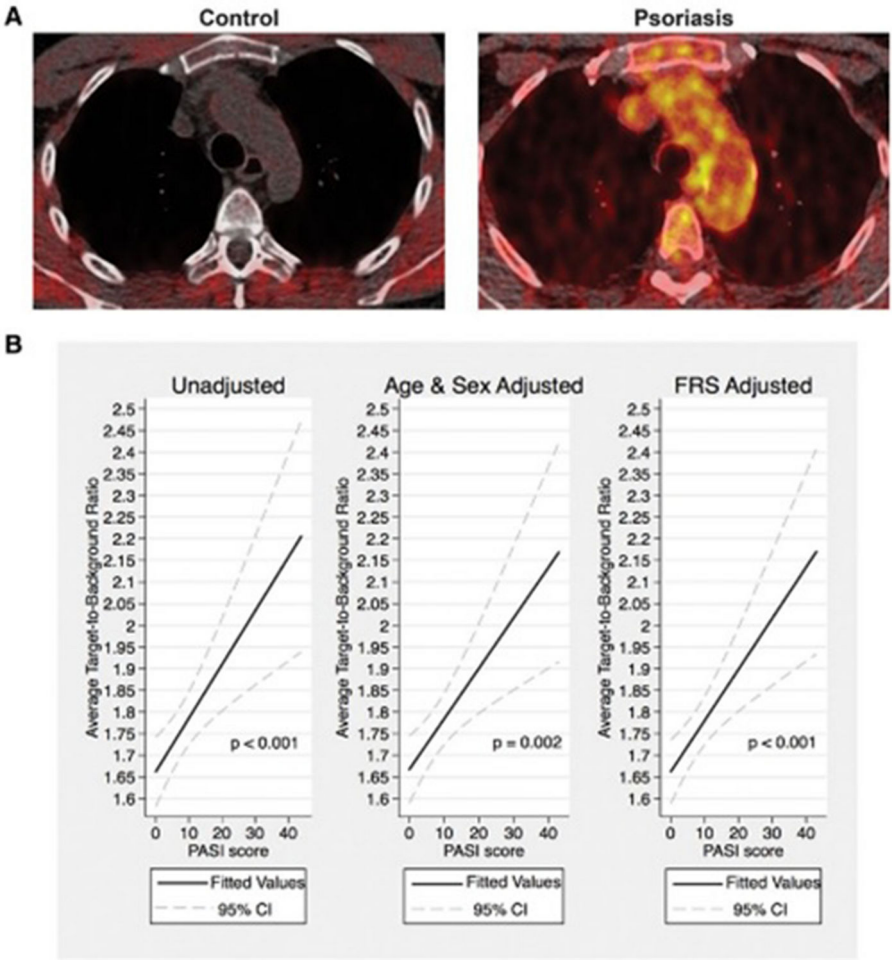

Figure 7:

Vascular inflammation is associated with skin disease severity in psoriasis.

Tomographic fused 18-FDG PET/ CT image of the aortic arch from a patient with severe skin disease and control patient (A). Regression plots for multivariable regression analysis of vascular inflammation as measured by target-to-background (TBR) with skin disease severity as measured by psoriasis area and severity (PASI) score. CI indicates confidence interval; and FRS indicates Framingham risk score.

The median TBR was 1.6±0.1 for controls and 1.8±0.3 (p<.001). CI indicates confidence interval; and FRS indicates Framingham risk score.

TBR: tissue- to- background ratio

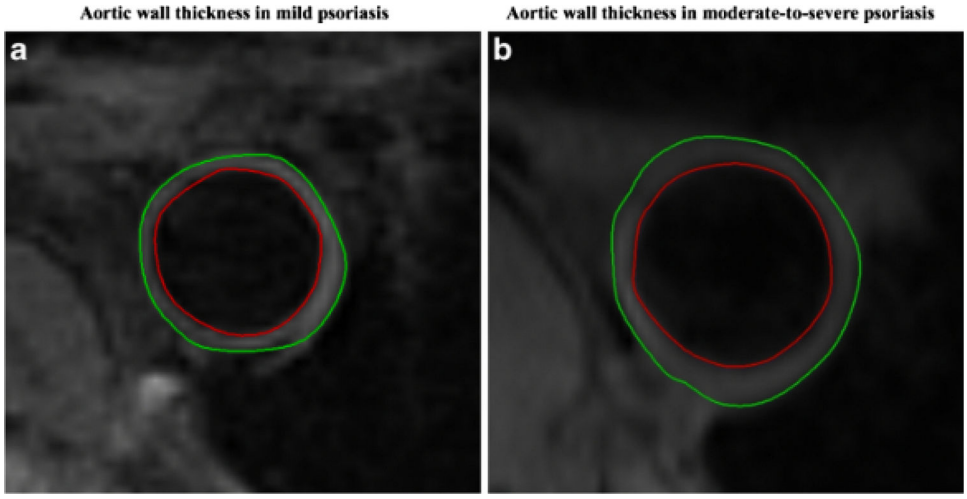

Figure 8:

Aortic wall thickness is associated with skin disease severity in psoriasis.

Transverse magnetic resonance imaging slices of a patient with mild psoriasis (A) at the level of the descending aorta depicting lower aortic wall thickness when compared with patient with moderate to severe psoriasis (B). The green and the red contours represent the outer and inner border of the aortic wall respectively.

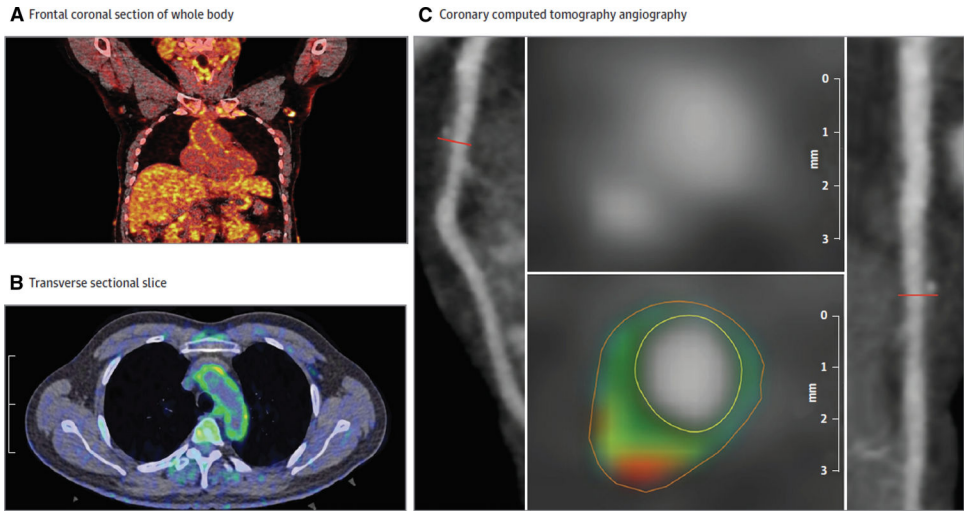

Figure 9:

Aortic vascular inflammation by 18-FDG PET/CT and coronary artery characterization by cardiac computed tomography angiography (CCTA).

Frontal coronal section of whole- body 18- FDG PET/CT demonstrating 18- FDG uptake in the aortic wall (A). Transverse section of 18-FDG PET/CT demonstrating vascular inflammation in the aortic wall (B). A panel of reconstructed images from the CCTA demonstrating path of left anterior descending coronary artery (left), depicting noncalcified coronary burden and transverse section of the left descending coronary artery (right). The planar reconstruction (middle) reveals low- attenuation lipid- rich plaque (green and red). The mean TBR was 1.70 [0.26].

TBR: tissue- to- background ratio

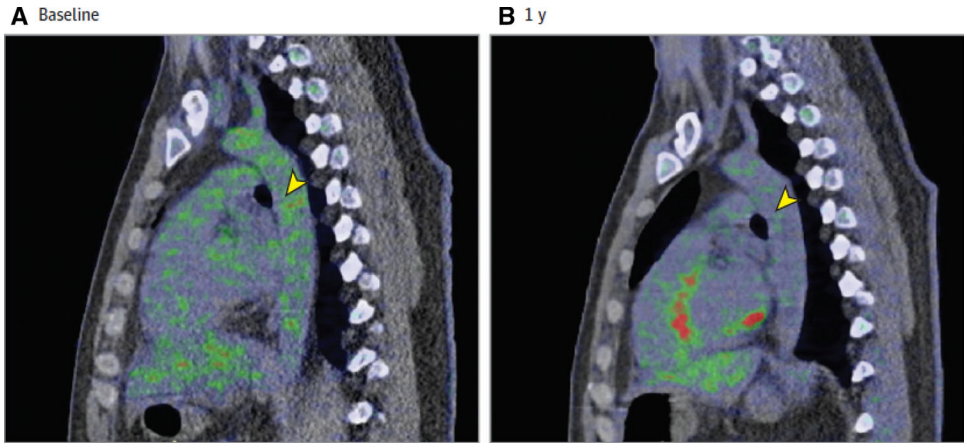

Figure 10:

Treatment with biologic therapy for psoriasis is associated with reduction in aortic vascular inflammation.

The images show a sagittal section of the level of the mid aorta at baseline (A) and at 1 year after treatment with biologic therapy for psoriasis (B). 18-FDG uptake in the aorta is higher at baseline compared to 1 year after treatment (yellow arrowheads). The mean TBR at baseline was 1.91 [0.29] vs 1.79 [0.22] at 1 year follow up ($p<0.001$).

TBR: tissue- to- background ratio