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EDITORIAL COMMENT

Diabetes and Vascular ^{18}F-Fluorodeoxyglucose Positron Emission Tomography Uptake

Another Step Toward Understanding Inflammation in Atherosclerosis*

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Atherosclerosis remains the leading cause of death in North America and Europe. During the natural course of atherosclerosis, inflammation plays a major role in the development of complex plaque lesions containing activated macrophages, foam cells, T lymphocytes, mast cells, and a necrotic lipid-rich core (1). When such a plaque becomes unstable due to uncontrolled inflammation and thinning of the matrix-rich fibrous cap, it can suddenly rupture, triggering thrombotic vessel occlusion leading to the clinical expression of a stroke or a myocardial infarction. Type 2 diabetes mellitus is a complex disease, with disturbances in glucose and lipid metabolism and systemic inflammation. It is an established risk for atherosclerosis and increases the prevalence of stroke and cardiovascular disease (CVD).

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Over the last decade, imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has emerged as a powerful technique to measure local vascular inflammation due to atherosclerosis (2,3), offering molecular information, which is not available by anatomic imaging such as x-ray angiography, computed tomography, and magnetic resonance imaging. Uptake of ^{18}F-FDG-PET is thought to represent macrophage activity in inflamed intimal atherosclerotic plaques (4), with a possible response of macrophage to hypoxia (5). The ^{18}F-FDG-PET uptake is transiently observed in the early phase of atherosclerosis and regresses when plaque calcification occurs in more stable lesions (6,7). Studies investigating the association of ^{18}F-FDG-PET uptake and cardiovascular risk factors have shown correlations with older age, male sex, and hypercholesterolemia (8); Framingham risk score (9); diabetes mellitus (9,10); body mass index, insulin resistance, and C-reactive protein (11); and matrix metalloproteinases and plaque high-risk morphological features (12).

In this issue of the *Journal*, Bucerius et al. (13) evaluated the impact of type 2 diabetes on carotid ^{18}F-FDG-PET uptake in a large population of 134 patients with documented or suspected cardiovascular disease, among which 43 patients had documented type 2 diabetes. They measured the maximum standardized uptake value ($_{mean}$SUV) averaged over all slices of both common carotid arteries, the target-to-background ratio ($_{mean}$TBR) obtained by normalizing SUV by jugular veins' blood pool activity and the single hottest slice (SHS) defined as maximum carotid TBR. They proposed to linearly normalize these indices by fasting blood glucose in analogy to oncologic PET (14). They found a significant independent correlation between these glucose-corrected indices of ^{18}F-FDG-PET uptake and the presence of diabetes, although these associations were not observed with non–glucose-corrected indices.

Hyperglycemia is thought to decrease ^{18}F-FDG-PET uptake in tumors by a direct competition mechanism (15). Although glycolytic activity is heterogeneous and glucose utilization varies among tumors, blood glucose correction is recommended in oncological PET studies (14). In fact, whether to correct for fasting blood glucose is a matter of glucose utilization rate (MR_{gluc}) in the tissue being considered (16). For instance, if MR_{gluc} is proportional to blood glucose such as in skeletal muscle, non–glucose-corrected SUV leads to a more stable parameter independent of blood glucose variations. On the contrary, when glucose transport or metabolic process in tissue is highly saturated or regulated such as in most tumors, MR_{gluc} remains constant, while the uptake constant is inversely proportional to blood glucose and a linear correction of SUV by blood glucose is meaningful (16).

However, no data are yet available in vivo on MR_{gluc} in macrophage-induced inflammation, and more basic studies are needed to better understand ^{18}F-FDG-PET uptake. In the literature, other blood glucose correction methods exist for SUV (17,18). Serial dynamic PET acquisitions under glucose clamping conditions may help characterize differences between tumors and inflammation regarding ^{18}F-FDG-PET uptake, and understanding which blood glucose correction to apply, if required. In spite of this uncertainty, the study by Bucerius et al. (13) is adding additional knowledge on the effect of diabetes on carotid ^{18}F-FDG-PET uptake. There have been only a few studies investigating the ^{18}F-FDG-PET uptake in relation to diabetes (9,10), in which significantly higher ^{18}F-FDG-PET uptake was found in diabetic patients as compared to nondiabetic ones. Additionally, Bucerius et al. (13) found positive

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correlations with body mass index, alcohol intake, and an unexpected inverse correlation with positive family history of CVD.

Carotid plaque imaging with ^{18}F-FDG-PET is at the forefront of cardiology: its value lies in its correlation with clinical symptoms and outcome, and its ability for therapy monitoring. Indeed, direct in vivo visualization of the diseased process in atherosclerosis may help identify patients at high risk for cardiovascular events not presently identified by clinical or laboratory examinations. Moreover, trials using this technology to monitor therapeutic interventions aiming at reducing vascular inflammation may help to identify novel therapies and risk stratification methods. Clinically available radiotracers are of interest in characterizing atherosclerosis and vascular plaque inflammation: for example, ^{11}C-PK11195 shows activated macrophages in plaque inflammation (19), ^{18}F-fluorocholine shows choline transport (20), and ^{11}C-acetate measures fatty acid synthesis in the atheroma's lipid core (21). Molecular imaging also probes mechanisms such as angiogenesis or apoptosis and offering novel opportunities to characterize atherosclerosis.

Given that annually 15 million people worldwide have a stroke, a better understanding of atherosclerosis progression toward unstable plaque would be welcomed. The study by Bucerius et al. (13) represents an important step in understanding ^{18}F-FDG-PET uptake in relation to diabetes, and it is timely questioning how to take into account elevated blood glucose, thus outlining a need for further careful investigations to understand the fluctuations of ^{18}F-FDG-PET uptake in inflammation in relation to glucose homeostasis. Forthcoming prospective studies on the ability to predict plaque rupture and clinical events will help define the potential clinical utility of vascular ^{18}F-FDG-PET imaging, but the question of how to correct ^{18}F-FDG-PET uptake in relation to fasting blood glucose will arise again.

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