18F-Fluorodeoxyglucose (FDG) in Atherosclerosis

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18F-Fluorodeoxyglucose (FDG) is a glucose analogue and the most-validated radiotracer for imaging high metabolically active inflammatory cells (e.g., macrophages) and tissues (e.g., atherosclerotic plaques) in animal models and humans [10]. The results have proven to be reproducible and modifiable via interventions that are anti-inflammatory [11]. FDG-PET imaging may mirror inflammatory activity in atherosclerosis due to the consumption of large amounts of glucose by inflammatory cells compared to other plaque cells.

Keywords: atherosclerosis ; 18F-Fluorodeoxyglucose

1. Lipid Accumulation & Inflammation in Plaque Development

Atherosclerosis is initiated by the deposition and accumulation of lipids and fibrous elements in the arterial wall [1]. Plaque development and progression is further initiated and largely driven by an innate immune response [2]. Low density lipoproteins (LDLs) are oxidised (oxLDL), promoting monocyte/macrophage recruitment and inducing an immune response [3]. Phagocytosis of oxLDL by innate immune cells, primarily macrophages, results in the formation foam cells and fatty streaks. The accumulation of lipids and leukocyte infiltration contributes to the formation of a necrotic core, tissue remodelling, and the development of a collagen-rich fibrous cap established by vascular smooth muscle cells [1][4].

2. ^{18}F-Fluorodeoxyglucose (FDG) -PET Detects Plaque Development and Inflammatory Cell Infiltrate

FDG is a glucose analogue and the most-validated radiotracer for imaging high metabolically active inflammatory cells (e.g., macrophages) and tissues (e.g., atherosclerotic plaques) in animal models and humans [5]. The results have proven to be reproducible and modifiable via interventions that are anti-inflammatory [6]. FDG-PET imaging may mirror inflammatory activity in atherosclerosis due to the consumption of large amounts of glucose by inflammatory cells compared to other plaque cells.

The interpretation of the uptake of glucose by inflammatory cells and non-specific uptake of cells in the arterial wall could prove challenging. The different subtypes of inflammatory macrophages have divergent roles in plaque development and progression. M1 macrophages are pro-inflammatory and more glycolytically active than M2 anti-inflammatory cells [7]. Another concerning factor that can also affect imaging results and outcome is the non-specific uptake by highly glycolytic cells in the arterial wall [8]. However, there are inconsistent reports in this area [9]. Tavakoli and colleagues hypothesized that differential regulation of macrophage metabolism by macrophage colony-stimulating factor (M-CSF; inflammatory resolving) and granulocyte-M-CSF (GM-CSF; proinflammatory) may contribute to the inconsistency of FDG vessel wall inflammation [9]. The metabolic profiles generated comparable levels of glucose uptake in cultured macrophages and murine atherosclerotic plaques. These findings suggest that although FDG uptake is an indicator of vascular macrophage burden and numbers, it may not necessarily differentiate morphologically unstable from stable plaque, or identify those at risk of rupture and symptomatic atherothrombosis [10]. Moreover, there is a wide range of vascular diseases in which macrophages and inflammation play an important role in the absence of atherosclerosis [10]. These include large artery inflammatory vascular diseases such as Takayasu arteritis, chemotherapy- or radiation-induced vascular inflammation, or foreign body reaction such as synthetic arterial graft. Due to the low sensitivity and non-specific nature of FDG uptake, caution is needed when interpreting vascular FDG uptake as a sole indicator of inflammatory atherosclerosis. What is critically needed for FDG-PET to become a major imaging modality for atherosclerosis is a prospective, event-driven investigation that links plaque FDG uptake to patient outcome [10].

Experimental studies of FDG-PET in atherosclerosis have shown that distribution of FDG within atherosclerotic plaques occurs predominantly in macrophages, and FDG uptake correlates with plaque inflammation in clinical imaging [11]. However, a consensus regarding the most appropriate FDG thresholds for defining plaque vulnerability is lacking, primarily because healthy patients, presumably without pathological arterial inflammation, have not, to our knowledge,

been systematically imaged [12]. Arterial FDG uptake was recently assessed in healthy control patients, those with risk factors, and patients with CVD to derive both uptake thresholds in each patient group and the reproducibility of the measures. Although the measured FDG metrics were reproducible and significantly different between patients who were healthy and who had disease, there was data overlap between patient categories, making FDG a non-specific signal for plaque inflammation and limiting its generalizability [12][13].

In addition, uptake of FDG in the heart, an organ of high metabolic activity, can present challenges in assessing inflammation [14][15]. This becomes of concern in the coronary arteries, where spillover from the physiologic activity of the heart obscures detection and accurate quantification of FDG uptake and plaque inflammation [14].

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