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LETTER TO THE EDITOR

Comment on Aksoy et al.: FDG and FDG-labelled leucocyte PET/CT in the imaging of prosthetic joint infection

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Dear Sir,

We read with interest the article by Aksoy et al. entitled "FDG and FDG-labelled leucocyte PET/CT in the imaging of prosthetic joint infection" recently published in the *European Journal of Nuclear Medicine and Molecular Imaging* [1], with the aim of increasing the sensitivity and specificity of nuclear medicine imaging techniques for diagnosing prosthetic joint infections (PJI).

The diagnosis of infectious diseases cannot disregard a careful understanding of the pathophysiology that underlies the infectious process: after the initial attachment of bacteria, biofilm is formed at the prosthesis-bone interface and from this moment granulocytes, IgM and cytokines (i.e. interleukin-8) are progressively recruited to the site of infection. Mature granulocytes, continuously produced by bone marrow, accumulate by active migration into infected tissue, mainly due to chemotactic attraction [2]. This process of peripheral blood granulocyte migration and recruitment into infected sites may take several hours (4–24 h). This is the basis for the use of sequential images with radiolabelled white blood cell (WBC) scintigraphy (after 1, 3–4 and 20–24 h) for imaging infections. This WBC scan has been validated in many infections and it is considered the gold standard technique for imaging PJI [3–6]. van der Bruggen et al. showed that the diagnostic accuracy of combined ^{111}In-labelled WBC imaging with single photon emission computed tomography (SPECT) and ^{99m}Tc-sulphur colloid was 95 % for diagnosing bone and joint infections, reaching hereby a level of evidence of 2–3b according to the Oxford criteria. High diagnostic accuracy was also obtained with ^{99m}Tc-WBC or ^{111}In-WBC combined with ^{99m}Tc-methylene diphosphonate (MDP) [4]. Similarly, Gemmel et al. concluded that combined in vitro labelled WBC/bone marrow scintigraphy represented the current imaging modality of choice for diagnosing PJI, and a more accurate assessment of joint replacement complications was reached by adding SPECT, with an overall accuracy of about 90 %.

Similar accuracy can be obtained by the use of specific image interpretation criteria that compare the accumulation of

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radiolabelled WBCs over time at delayed (after 3–4 h) and late images (after 20–24 h) [7, 8]. Accordingly, images are visually classified as: (a) negative if no uptake or a significant decrease in uptake from delayed to late images is present, (b) positive when uptake is seen in both delayed and late images with increase in activity or extent in time and (c) equivocal when uptake in delayed and late images is the same or slightly decreasing [6].

Such criteria allow differentiation between infection-related accumulation of leucocytes and their physiological uptake by active marrow and in sterile inflammation [9–11]. When SPECT/CT is performed, the diagnostic accuracy is increased by a more detailed localization of labelled WBC accumulation, particularly for differentiating soft tissue from bone uptake [6].

When using [^{18}F]fluorodeoxyglucose (FDG) for diagnosis of infection, the target of the radiopharmaceutical is not limited to activated granulocytes, as it also includes other cells involved in inflammation (i.e. macrophages, lymphocytes). Therefore, [^{18}F]FDG specificity in acute infection and for the differentiation between inflammation and infection is limited, regardless of any interpretation criteria proposed (any periprosthetic activity, regardless of location or intensity; periprosthetic activity, without corresponding activity on the marrow image; only bone-prosthesis interface activity, regardless of intensity; semi-quantitative analysis; lesion to background ratios). Based on these considerations, it is in our opinion unclear why the authors used a non-specific tracer for acute infection such as [^{18}F]FDG to compare to the relatively new technique of [^{18}F]FDG-labelled leucocytes, the main focus of this manuscript. In addition, despite [^{18}F]FDG-labelled WBCs having a clear advantage in terms of spatial resolution due to the better intrinsic characteristics of the PET/CT camera, several limitations were found for this procedure: (a) the labelling efficiency of [^{18}F]FDG leucocytes is significantly less than that for ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) or ^{111}In-oxine, (b) as a consequence of this low labelling efficiency and of the short half-life of ^{18}F (110 min), higher doses of radioactivity are necessary to allow observation of the pathologic accumulation of the cells in the infection site (this should be at least three times the amount of radioactivity that will eventually be injected into the patients) [9–11] and (c) it is not feasible to perform imaging any later than 4–6 h after injection (in fact, in this article images were acquired 3 h post-injection), thereby preventing the evaluation of the late phase of leucocyte recruitment (20–24 h post-injection) that is especially important in chronic infection where the accumulation of leucocytes is much less than in acute infection. In addition, the message of the authors in the conclusions is not supported by evidence-based data. Indeed, it is not adequate given available literature as well as the results presented in the article to propose PET/CT with [^{18}F]FDG-labelled WBCs as an alternative to WBC SPECT/CT for the diagnosis of PJI. Moreover, it fails to provide a real picture of the world since SPECT/CT is currently widely, routinely and effectively performed [2–8, 10–14].

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