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LETTER TO THE EDITOR

Is the effect of hyperglycemia on liver ^{18}F-FDG standardized uptake value really clinically significant?

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Dear Sir,

We have read with interest the recent work by Eskian et al. entitled "Effect of blood glucose level on SUV in ^{18}F-FDG PET-scan: a systematic review and meta-analysis of 20,807 individual standardized uptake value (SUV) measurements" [1]. Our group was surprised by the authors' recommendations to keep patients euglycemic (< 110 mg/dl) when assessment of the liver is intended (especially for tumor-to-background ratio), which invariably would require pre-scanning insulin administration for hyperglycemic patients. The authors combined individual data of 11 different centers, and found that patients with blood glucose > 125 mg/dl have an absolute liver SUV_{max} and SUV_{mean} approximately 0.5 (~20% increase) and 0.2 (~10% increase) higher than euglycemic patients, respectively. We give merit to the authors for the attempt to reach a consensus regarding the effect of glycemia on ^{18}F-FDG PET-scan, but there are two concerns that limit the recommendations of the present study.

First, the authors did not provide a more thorough analysis of the heterogeneity among the studies, which could have impacted on the actual difference seen in the glycemic ranges. Reasons for heterogeneity are many in this study. A SUV variability of 10–25% can be expected solely due to differences in scanner and protocol among the 11 different sites [2], not to mention differences in FDG dosing among centers that were also correlated with SUV_{max} in the multivariate analysis. Our group recently published a review and the largest single-center study with more than 5000 subjects to investigate the impact of hyperglycemia on liver SUV_{max} [3, 4], in which we were able to control for the same scanner, imaging protocol, and reader to decrease those confounding factors. We found that patients with hyperglycemia have a statistically significant higher SUV_{max}, but the effect is too small (~5% higher) to be of potential clinical relevance or prompt the administration of pre-scanning insulin for glucose correction (Supplementary File 1). The effect of heterogeneity is particularly important in the work of Eskian et al., because the proportion of patients of each individual research group was not constant among the different glycemic ranges. Whereas the data from our center related to more than 90% of the subjects ($n = 4653$) in the euglycemic group, our dataset comprised only 27% ($n = 14$) in the > 200 mg/dl range — thus, the difference herein seen in SUVmax could just be due to a multicenter variability. Thus, it would be interesting if the authors could provide a heterogeneity analysis for each glycemic range comparing differences in SUV among centers.

Second, the effects on SUV measurement from insulin used to correct pre-scanning hyperglycemia are conflicting. Insulin could possibly reduce the accuracy of SUV measurement by modifying the biodistribution of ^{18}F-FDG. Most studies have reported no differences in the FDG uptake with the use of insulin to correct hyperglycemia [5–7]. One author reported differences in muscle and brain uptake when exogenous insulin was given prior to PET/CT to correct hyperglycemia [7]. Given the inconsistency in the literature, there is no consensus among international guidelines about the use of pre-scanning insulin. According to the guidelines provided by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine, reduction of blood glucose level by administration of insulin can be

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considered in some cases (especially if glycemia > 200 mg/dl), respecting a minimum 4-h interval between insulin and FDG administration and choosing rapid-acting insulin over other types [8, 9]. The guidelines of the National Cancer Institute, the American College of Radiology, and the Netherlands Society of Nuclear Medicine discourage the correction of hyperglycemia with insulin, and recommend rescheduling the PET/CT scan when blood glucose levels are > 200 mg/dl [10]. In addition, correction of pre-scanning hyperglycemia requires training of staff on administration of insulin (especially when intravenous) and identification and correction of potential adverse effects, mainly hypoglycemia.

In summary, it is very likely that the difference in SUV uptake reported by Eskian et al. in this multi-center study is a result of the heterogeneity of instruments and protocols used in the different centers. The large amount of data from our center provides evidence that the difference in SUV uptake according to glycemic ranges in the liver is negligible. Also, the true impact of pre-scanning insulin on FDG-uptake is still not well enough understood to support using it to keep all patients within the euglycemic range (< 110 mg/dl), as suggested by the authors.

Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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