Glucagonlike Peptide-1 Receptor Imaging in Individuals with Type 2 Diabetes

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Radiolabeled exendin 4, the glucagonlike peptide-1 (GLP-1) receptor agonist, has great prospects for imaging and perhaps quantification of pancreatic β-cells. The GLP-1 receptor is found in high density in the pancreas and liver and plays a key role in postprandial blood glucose homeostasis, including stimulation of insulin synthesis and promotion of β-cell proliferation. β-cells constitute only a small volume of the pancreatic mass, comprising up to 2% of the pancreatic mass and 65%–80% of endocrine cells in the islets of Langerhans. A synthetic peptide agonist of the GLP-1 receptor, exendin-4, also known as exenatide, is used for the treatment of diabetes mellitus, making it an ideal peptide for radiotracer development (*1,2*). The desire to quantify β-cell mass has been a focus of radiotracer research since the initial first-in-humans studies by Boss et al., which have led to a variety of SPECT and PET radiotracers focused on different targets of glucose metabolism. Initially, Boss described a high-specificity and nanomolar-affinity radioiodinated tracer for the GLP-1 receptor (*3*). It is assumed from studies by Eng et al. that the GLP-1 receptor density reflects β-cell mass (*4*). Improvements in the spatial resolution and sensitivity of PET scanners have fueled the recent focus on PET radiotracers for this application.

In this issue of *The Journal of Nuclear Medicine,* the article by Eriksson et al. (*5*) demonstrates a stepwise approach necessary for GLP-1-receptor–targeting radiotracer development from the lab to the clinic. The authors investigated the utility of ^{68}Ga-labeled 1,4,7-tris(carboxymethylaza)cyclododecane-10-azaacetyl (DO3A)-exendin-4 (^{68}Ga-exendin4) in adults with type 2 diabetes (T2D) and its association with β-cell mass in overweight-to-obese T2D individuals, building on prior studies (*6,7*). Furthermore, the authors provided a simplified imaging protocol, a step toward higher throughput needed for large clinical trials.

The strengths of this article include the description of preclinical data collected in vitro and in vivo using nonhuman primates. The in vitro studies define binding specificity and internalization characteristics and were followed by nonhuman primate studies evaluating dose escalation and self-blocking effect. The evaluation of biodistribution and physiology in nonhuman primates provided safety information and guidance for the application in human adults.

In addition to the preclinical data, the authors also provided the initial evaluation in overweight-to-obese individuals. This study of 13 human subjects, 12 men and 1 woman, gives information on biodistribution and kinetics in the mostly male subjects. The results of this study show high pancreatic uptake compared with background activity. An unsuspected finding was variability in pancreatic radiotracer uptake across patients. This prompted further investigation, which revealed no association of uptake with pancreatic volume or patient age, as β-cell mass is thought to be uniformly distributed and to decrease with age.

The self-blocking evaluation described in this paper is an important analysis used in the evaluation of a novel radiotracer to show strong binding in the presence of cold peptide, representing endogenous proteins or administered medication. This competitive binding is of great importance because the treatment dose of exenatide is in the microgram range. The authors studied the effect of higher mass by coinjecting the study participants with up to 0.2 μg/kg. The study team did not observe a difference in the volume of distribution at the lower dose; however, a decrease in binding was seen at 0.45 μg/kg. We found this information encouraging for the development of an ^{18}F-labeled exendin-4 analog, which suffered the drawback of requiring a higher amount of labeling precursor and difficulties of purification. Compared with ^{68}Ga, ^{18}F-labeled tracers offer several distinct advantages, including longer half-life (118 vs. 60 min), higher amount of starting activity (cyclotron bombardment vs. limit on the ^{68}Ge generator synthesis), and ideal imaging qualities. All warrant the need to develop an ^{18}F-labeled exendin-4 analog. A successful ^{18}F-labeled exendin-4 analog can also enable the distribution of large-scale, multicenter trials needed for tackling the complex question of β-cell mass quantification and monitoring and provides less focus on sophisticated equipment and expertise (cyclotron and radiochemist) while still allowing joint efforts in research.

The proposed goal of this study was achieved by providing a recommendation for a protocol to be used in human subjects for subsequent phase II and III trials in adults. This phase I study also evaluated the safety and utility of a safe dose range, resulting in a proposed dose. Technical efficacy was achieved by providing image generation and procedural feasibility, which is addressed in the discussion. A limitation of this study is related to sample size. Although a phase I study does not require a control population or randomization, a larger cohort pool enables the establishment of a better baseline. The small sample size makes it impractical to consider a variety of subject characteristics. Further investigations should evaluate female subjects and subjects of racial backgrounds known to have a high incidence of diabetes.

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As stated in the abstract, the overall goal of this project is to enable longitudinal studies of the GLP-1 receptor in the human pancreas. The next step in this research would be a test–retest study to evaluate the within-subject variability of tracer uptake. The changes caused by the pathologic progression of T2D or type 1 diabetes (T1D) are likely to be small and will have to be followed over time to assess disease stability or progression. A tracer with small test–retest variability would be crucial to detect the difference throughout the course of disease. This would allow for monitoring changes in density, occupancy, or functionality (*8*). The intrasubject variability is an important step needed to assess feasibility for repeat studies to evaluate the efficacy of medications. One of the questions to be answered is the reason for subject variability in tracer uptake. Is this caused by the status of the GLP-1 receptor, the volume of the pancreas, or other reasons? Additional studies to elucidate the relationship will provide additional insight to show clinical utility in the monitoring of treatment. A radiotracer to evaluate the density of the β-cell mass would have a great impact on the management of disease, on understanding of the pathologic processes, and on evaluation of the ability of medical treatment to stabilize or potentially reverse disease.

The overall impact of this work extends beyond this subgroup of T2D. Diabetes is not only an adult disease. T1D is a pediatric disease with onset typically in the second decade of life and is characterized by a progressive destruction of up to 70% of β-cell mass. T1D is increasing in prevalence and accounts for up to 10% of cases of diabetes worldwide (*9*). Diabetes progression is evaluated clinically on the basis of insulin needs; however, insulin needs do not necessarily predict β-cell mass, as there is a significant loss of β-cell mass before detection. This promising PET radiotracer can potentially have a pivotal role in the assessment of the stage of disease and response to therapy for both T1D and T2D. If successful, the translation to pediatric care will have the potential to alter the progression of disease in adolescents and young adults, thus improving the quality of life for children and adults with diabetes. This article is an important contribution to the literature and successfully shows technical efficacy, reproducible image generation of the pancreas, and procedural feasibility with a proposed protocol.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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