Diabetic Complications Consortium

Application Title: Dynamic Positron Emission Tomography Imaging with ^{11}C-ER176 to Delineate Macrophage Activation in Diabetic Gastroparesis

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1. Project Accomplishments:

Diabetic gastroparesis (DG) is a well-established complication of diabetes mellitus and results in nausea, vomiting, early satiety, and abdominal pain. These symptoms can cause significant morbidity as well as increase mortality. Diabetic animal models of delayed gastric emptying as well as molecular studies on human full-thickness gastric biopsies have shown that macrophage-driven injury to the interstitial cells of Cajal (ICC) and other components of the enteric nervous system is central to the pathophysiology of DG. There are currently no noninvasive ways to determine macrophage-based inflammation in the muscularis propria of the gastrointestinal tract. Activated state of macrophages can be reflected by upregulation of the 18-kDa translocator protein (TSPO). The overall goal of this project is to demonstrate feasibility of dynamic ^{11}C-ER176 PET imaging to identify macrophage-driven immune dysregulation in gastric muscle of patients with DG. Non-invasive quantitative assessment with PET can significantly add to our diagnostic armamentarium for patients with diabetic gastroenteropathy. If a clear immune dysregulation is identified in a subset of patients, it can be targeted using immunosuppressive or immunomodulatory therapies. Furthermore, if validated, this imaging technique can facilitate clinical trials aimed at targeting immune dysregulation in DG, thus offering new therapies in a disorder with significant unmet need.

We have completed recruitment of the proposed 4 patients with DG and 4 age and sex-matched healthy volunteers. In addition, we recruited 4 age and sex-matched patients with diabetes but without gastroparesis. To reach n=12 recruitment, 14 subjects were screened of which 2 screen failed. One patient with DG and two with diabetes without gastroparesis had Type 1 diabetes. All 12 participants underwent ^{11}C-ER176 PET/CT after written informed consent. Diagnostic image quality was rated on a 5-point Likert scale (ratings≥3 considered diagnostically acceptable). Gastric ^{11}C-ER176 uptake was qualitatively compared between the three groups. The maximum standardized uptake (SUV_{max}) in the gastric fundus, body, pylorus and second portion of the duodenum were compared using Kruskal-Wallis test. Additionally, EUS guided gastric muscle biopsies from the 4 DG patients were obtained as proposed.

2. Specific Aims:

To determine feasibility of dynamic ^{11}C-ER176 PET to identify macrophage-activation in diabetic gastroparesis

Hypothesis 1: Patients with diabetic gastroparesis demonstrate increased uptake for ^{11}C-ER176 in gastric body and antrum compared to matched controls

Results: Age (mean ± standard deviation) of three groups was comparable (DG: 50±7 years, Diabetic without gastroparesis: 48 ± 13, Healthy: 47 ± 11). 11/12 participants were Caucasians. BMI of the participants in the 3 groups was also similar. No patient had any adverse effects attributable to ^{11}C-ER176 injection. Image quality of all PET scans was diagnostically acceptable. Qualitatively, there was no difference in the intensity or pattern of gastric ^{11}C-ER176 uptake between the three groups. Quantitatively, the uptake was higher in pylorus in diabetics compared to healthy volunteers (SUV_{max} healthy 4.6±0.2, diabetics 8.4±4.1, DG 5.5±1.0, p=0.04) but there was no statistically significant difference in the uptake in gastric fundus (9.0±1.6, 13.1±8.3, 7.8±1.9 respectively, p=0.3), body (7.7±1.9, 13±9.2, 7.8±1.9, respectively, p=0.8), and duodenum (6.2±2.1, 9.5±6.8, 7.0±1.8, respectively, p=0.6). There were no correlations between SUVmax and HbA1c or fasting blood glucose.

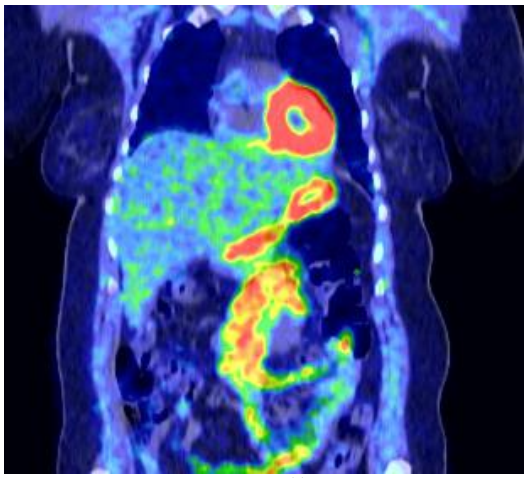

Figure: Representative ^{11}C-ER176 PET/CT scanning image from a study subject demonstrating tracer uptake in the stomach and small bowel. Also seen is patchy physiological uptake in the liver.

Hypothesis 2: Increased uptake of ^{11}C-ER176 associates with a shift towards pro-inflammatory macrophage milieu on tissue assessment made by targeted biopsies of gastric muscle

Results: Immune cell staining using CD45 immunoreactivity in gastric body did not show any qualitative differences between the DG patients and controls. However, considering core biopsy, the tissue yield was limited which precluded more detailed assessment of pro-inflammatory markers. Two patients had adverse effects: one related to endoscopy (sore throat, uvular abrasion) and another unrelated to study procedures (urinary tract infection). There were reported to the IRB as well as study monitoring team as per protocol.

Overall conclusion: PET imaging with next-generation TSPO-specific radiotracers is feasible in DG. However, in our study, the pattern or intensity of ^{11}C-ER176 uptake could not differentiate between patients with or without DG. Possible reasons include lack of sufficient sensitivity to detect signal from activated macrophages on the background of physiologic gastric uptake, lack of ligand specificity for specific macrophage phenotypes in DG, gender effect, or small sample size. Investigation of other non-invasive tools are warranted for evaluation of immune dysregulation in neurogastrointestinal disorders.

3. Publications:

None.

Results will be presented at the upcoming American Neurogastroenterology & Motility Society (ANMS) 2023 meeting in Austin, TX by post-doctoral fellow Dr. Elisia Maalouf. Subsequently, a brief report manuscript will be submitted to the Neurogastroenterology & Motility (NGM) journal. The results have been uploaded on Clinical trials.gov (NCT04762719). The presentations, publication and submission to clinicaltrials.gov will ensure that data is disseminated widely as per NIH data sharing policy.