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Commentary

Have a heart: failure to increase GLP-1 caused by heart failure increases the risk of diabetes

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Incretins represent a group of gut-derived peptide hormones that, at physiological concentrations, potentiate the release of insulin. Work leading to the discovery of incretins began as early as the late 1800s where scientists, including Claude Bernard who is widely considered the father of modern physiology (Rehfeld, J.F. The Origin and Understanding of the Incretin Concept. *Front. Endocrinol. (Lausanne)* (2018) **9**, 387; Robin, E.D. Claude Bernard. Pioneer of regulatory biology. *JAMA* (1979) **242**, 1283–1284), attempted to understand the pancreas as an important organ in the development of diabetes mellitus and blood glucose control. After the seminal work of Paulescu and Banting and Best in the early 1920s that led to the discovery of insulin (Murray I. Paulesco and the isolation of insulin. *J. Hist. Med. Allied Sci*. (1971) **26**, 150–157; Raju T.N. The Nobel Chronicles. 1923: Frederick G. Banting (1891–1941), John J.R. Macleod (1876–1935). *Lancet* (1998) **352**, 1482), attention was turned toward understanding gastrointestinal factors that might regulate insulin secretion. A series of experiments by Jean La Barre showed that a specific fraction of intestinal extract caused a reduction in blood glucose. La Barre posited that the fraction's glucose lowering actions occurred by increasing insulin release, after which he coined the term 'incretin'. In the 1970s, the first incretin was purified, glucose insulinotropic polypeptide (GIP) (Gupta K. and Raja A. Physiology, Gastric Inhibitory Peptide *StatPearls* Treasure Island (FL); 2020), followed by the discovery of a second incretin in the 1980s, glucagon-like peptide-1 (GLP-1). Interest and understanding of the incretins, has grown since that time.

Glucagon-like peptide-1 (GLP-1) is a 36 amino acid peptide hormone secreted by L-cells in the proximal intestine. In response to the ingestion of a meal, plasma levels of GLP-1 rapidly increase to potentiate insulin secretion by activating pancreatic β-cell GLP-1 receptors (GLP-1Rs). GLP-1R activation leads to increased cAMP and enhances the intracellular calcium increase caused by glucose [1]. In addition to the insulin potentiating actions of GLP-1, this incretin hormone is widely recognized for its potential pleiotropic actions. For example, the role of GLP-1 is actively being tested for its potential role to regulate normal physiological functions including satiety [2], taste [3], and thermogenesis [4]. Moreover, GLP-1 is being widely studied for its potential role in pathological conditions including weight loss and diabetes [5], cognitive and neurodegenerative diseases [6], non-alcoholic fatty liver disease [7], preeclampsia [8], and renal disease [9].

Clinical data also suggest that there is a link between heart failure severity, impaired plasma glucose regulation, and GLP-1. The proposed link between heart failure and GLP-1 is based on the clinical observation that glucose homeostasis is impaired in patients with heart failure. For example, Tenenbaum et al. showed that with increasing heart failure severity, the risk of developing diabetes was increased, and that the rate of developing diabetes was increased 1.7-fold in patients with severe heart failure (NYHA class III) [10]. Similarly, Zareini et al. reported that the incidence of developing new-onset diabetes was increased in patients who had been hospitalized for heart failure, and that the development of new-onset diabetes in this population increased the risk of death [11]. Despite the known relationship between heart failure

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and the subsequent development of impaired glucose homeostasis, little is understood about the potential underlying mechanisms that may cause these changes.

The current study by Arruda et al. [17] in this volume of *Clinical Science* picks up on this clinical observation and sets out to advance the understanding of the link between heart failure, glucose homeostasis, and GLP-1. The central hypothesis of the work is that the bioavailability of GLP-1 is attenuated after heart failure. In order to test this hypothesis, the authors designed experiments in non-diabetic humans with severe heart failure. This study examined blood GLP-1 levels after an 8-h fast, and again 15 min after a meal in 49 heart failure patients and 40 healthy controls. The blood samples were used to assess levels of glucose, insulin, dipeptidyl peptidase-4 (DPP-4, an enzyme that metabolizes GLP-1), and GLP-1. Perhaps the most important finding of the clinical study is that the expected postprandial increase in GLP-1 is significantly blunted in the non-diabetic heart failure patients relative to the response in healthy controls. Consistent with the blunted GLP-1 response, the heart failure patients had increased postprandial plasma glucose, and the inclusion of serum DPP-4 activity provides additional mechanistic insight given that higher DPP-4 activity is associated with the blunted postprandial GLP-1 response in the heart failure patients. Taken together, this study points to a direct effect of heart failure on the GLP-1 response that likely results from changes in DPP-4 which may provide an explanation for the increased future risk of developing diabetes in heart failure patients.

In order to delve further into this proposed mechanism, the authors designed an experiment using a rat model of heart failure caused by radiofrequency ablation of the left ventricle. The rat study used this experimentally induced heart failure to assess the impact vildagliptin, an inhibitor of DPP-4 to prevent the metabolism of GLP-1, treatment on cardiac function and metabolic endpoints. Importantly, the GLP-1 response to an oral glucose test was blunted in the non-diabetic rats with heart failure, thus mimicking the observation from the clinical study. Moreover, when the rats with heart failure were treated for 4 weeks with the DPP-4 inhibitor, the GLP-1 response to an oral glucose load was enhanced and metrics of left ventricular function, as assessed by echocardiography, were improved. Consistent with these findings, the authors measured urinary cAMP, a downstream signaling pathway activated by GLP-1, and showed that urinary cAMP was lower in the rats with heart failure, but was restored in the heart failure rats treated with a DPP-4 inhibitor. Thus, the authors appear to have added an important piece to the mechanistic puzzle for understanding the risk of developing diabetes after heart failure using both clinical observations and pre-clinical experiments.

A strength of this study is the powerful approach to take a clinical observation and more directly test the potential mechanism behind that observation using an experimental model that closely mimics the human response. One of the interesting findings of the rat study was the observation that plasma insulin was increased in response to heart failure just as was plasma glucose. Upon an initial reading, this could be interpreted as contrary to the concept that the GLP-1 response, one that is supposed to potentiate insulin release, is attenuated. However, the authors offer as an explanation that the rats have already begun to develop signs of metabolic derangements, including insulin resistance, during the short 6-week period following the radiofrequency ablation.

Another important consideration raised by this study is the potential role of DPP-4. Although DPP-4 inhibitors are known to prevent the metabolism of GLP-1, there is a growing body of literature showing that, much like GLP-1, there are potential pleiotropic effects of DPP-4. For example, recent evidence suggests that DPP-4 inhibition may protect against glomerular podocyte injury [12], attenuate peripheral neuropathy [13], slow the development of vascular stenosis [14], and even attenuate complement activation though the lectin pathway for reasons that remain incompletely understood [15]. Given the complex hemodynamic, neural, endocrine, and immunological changes that occur as a result of heart failure, it will be important in future studies to better understand how these integrated physiological systems are changing in response to DPP-4 inhibition, and how these changes might afford greater metabolic and cardiovascular protection. Finally, the authors allude to the marked sex difference whereby diabetic women are at significantly greater risk for developing heart failure than diabetic men (although diabetic men have greater risk than non-diabetic men [16]. Understanding the factors that are permissive for this sex difference will ultimately be critical to discern treatment strategies targeted specifically for men and for women.

Quality scientific studies are often straightforward in their experimental design and yield clear results with justified, reasoned conclusions. Importantly, these types of studies contain elements that may not be fully explained, or drive the field toward new questions that remain to be answered. Through their straightforward design, clear results, and remaining questions (i.e. increased insulin, pleiotropic actions of DPP-4 inhibition, sex differences), Arruda et al. offer such a quality study that has made an important advance to the field [17].

Competing Interests

The author declares that there are no competing interests associated with the manuscript.

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Abbreviations

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor.

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