I read with great interest the paper by Haberka et al¹ published in this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*). In their study, the authors found that epicardial adipose tissue (EAT) expresses glucagon-like 1 receptor (GLP-1R) and glucagon-like 2 receptor (GLP-2R) and both GLP-Rs correlate with the renin-angiotensin-aldosterone system (RAAS) in patients with coronary artery disease (CAD).

Epicardial adipose tissue is a novel cardiovascular risk factor, with peculiar anatomy, transcription, and proteasome.²,³ Its unobstructed contiguity with the adjacent myocardium and coronary arteries makes EAT unique and capable of bidirectional cross-talks with the heart. The fragile equilibrium between the cardioprotective thermogenic properties and the detrimental proinflammatory effects of EAT is often unbalanced.⁴,⁵ Hence, EAT easily turns into a pathogenic factor of cardiovascular diseases such as CAD, diabetes, and atrial fibrillation. However, there is a more recent feature that makes EAT an appealing therapeutic target and modifiable risk factor. Thanks to its responsiveness and measurability with either ultrasound or more accurate computed tomography, EAT can be a target of pharmaceutical agents modulating adipose tissue.

More specifically, and as confirmed by Haberka et al,¹ EAT expresses GLP-1R. Our group discovered for the first time that human EAT expresses GLP-1R.⁶ Immunofluorescence analysis showed the presence of GLP-1R protein within EAT whereas the signal was absent in the subcutaneous fat. Intriguingly, GLP-1R signal was detected in EAT of both diabetic and nondiabetic patients.⁶ GLP-1R mRNA was also found in the heart chambers,⁷ and given the functional proximity of EAT to the heart, this becomes even more exciting.

How can this finding open new avenues and strategies in the prevention and treatment of cardiovascular diseases? GLP-1 receptor agonists (GLP-1A) rapidly emerged as drugs with pleiotropic effects. GLP-1A provides weight loss and cardiovascular protective effects beyond the diabetes control, as several clinical trials have demonstrated.⁸,⁹ Subjects on either daily or weekly GLP-1A had better glycemic control, lost weight, and had lower rates of hospitalization or death due to cardiovascular causes.³,⁹

Can this be related to the presence of GLP-1R in EAT? It is plausible to run some hypotheses. GLP-1 can favor EAT preadipocyte differentiation into mature adipocytes.¹⁰ This effect can improve local insulin sensitivity and glucose homeostasis. GLP-1R activation can stimulate EAT thermogenesis and adipocyte browning.¹¹ Interestingly, EAT GLP-1R mRNA expression correlates with genes encoding for beta-oxidation and white-to-brown adipocyte differentiation.¹² This could contribute to the weight loss observed in patients taking GLP-1A. Our group showed that EAT thickness dramatically shrinks (between 20% and 30%) when liraglutide, daily GLP-1A or semaglutide or dulaglutide, weekly GLP-1As, are added on metformin.¹³,¹⁴ GLP-1 analogues may target EAT GLP-1R and therefore reduce local adipogenesis, improve fat utilization, induce brown fat differentiation and ultimately reduce EAT mass. The relation of EAT GLP-1R with the RAAS components, well reported by Haberka et al,¹ suggests an additional pathway. Particularly, the modulation of EAT angiotensin-converting enzyme (ACE) plays a role in the myocardial and perivascular inflammation, also in COVID-19 cardiac syndrome.¹⁵ Down-regulation of ACE2 increases EAT M1 macrophages whereas angiotensin (1-7) reduces EAT proinflammatory macrophages. GLP-1 agonistic effects may upregulate EAT ACE2 expression and then lower local inflammation, oxidative stress and endothelial damage. Findings of Haberka et al¹ certainly warrant future studies.
to evaluate whether and to what extent GLP-1As can modulate ACE-2 and overall the RAAS.

As previously observed by our group, Haberka et al1 found that GLP-2R is also expressed in EAT.1 The clinical significance of this finding is still unclear. However, GLP-2R analogues, te dulgu tidi and glepaglutide, have been recently associated with an improvement of obesity-related inflammation. The therapeutic potential of these novel GLP-2R analogues deserves future investigations.

In conclusion, it seems plausible that pharmacologically targeting EAT GLP-1R may induce previously unexpected beneficial cardio-metabolic effects. The potential of modulating EAT transcriptome and resume some of its physiological function (i.e., thermogenic) with targeted pharmacological agents (i.e., GLP-1As) can open new avenues in the pharmacotherapy of cardiometabolic diseases.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.


REFERENCES


