

Pentraxin 3 in patients with type 2 diabetes and nonalcoholic fatty liver disease: a promising treatment target for glucagon-like peptide-1 receptor agonists

To the editor We have read with great interest the study by Trojak et al¹ concerning the association between serum pentraxin 3 (PTX3) levels and several established cardiovascular risk factors in patients with type 2 diabetes (T2D) with or without nonalcoholic fatty liver disease (NAFLD). Of note, in the whole cohort, the relative frequency of major comorbidities such as hypertension, dyslipidemia, and coronary artery disease was high, reaching up to 86.2%, 68.7%, and 36.2%, respectively, while patients' average glycemic control was rather insufficient.¹

Researchers have shown that in the NAFLD subgroup, serum PTX3 levels correlated positively and significantly with total and low-density lipoprotein cholesterol, triglycerides, apolipoprotein C3, and apolipoprotein B100.¹ The latter might provide novel pathophysiologic insights into the T2D/NAFLD concomitance and the related cardiovascular disease, leading to personalized treatment pathways.

Based on the aforementioned observations made by Trojak et al,¹ we question the potential impact of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on PTX3. These agents have now evolved as key players in the therapeutic management of T2D, especially in patients with established atherosclerotic cardiovascular disease, constituting the second-line treatment option, along with sodium-glucose cotransporter 2 inhibitors. In addition, they represent a promising treatment option in NAFLD/nonalcoholic steatohepatitis. In the hallmark LEAN (Liraglutide Efficacy and Action in Nonalcoholic Steatohepatitis) trial, liraglutide, one of the most widely used GLP-1RAs, led to a significant resolution of nonalcoholic steatohepatitis and delay in fibrosis progression, as compared with placebo; however, relevant evidence is still considered insufficient for treatment guidelines.²

Only 3 studies have assessed the direct impact of GLP-1RAs on PTX3. In their experimental study, Shiraki et al³ demonstrated that treatment with liraglutide led to a significant

downregulation of the expression of PTX3 in primary human umbilical vein endothelial cells incubated with tumor necrosis factor α , ($P < 0.05$), reinforcing the potential anti-inflammatory role of liraglutide. In a streptozotocin-induced diabetic rat model, Artunc-Ulkumen et al⁴ showed that treatment with exenatide resulted in a significant decrease in serum PTX3 levels, as compared with the nontreated group ($P < 0.05$), ameliorating the glucotoxicity-related inflammatory process. In the only human study available in the literature, Suzuki et al⁵ found that 6-month treatment with liraglutide in 46 patients with T2D led to an increase in serum PTX3 levels ($P < 0.0001$), which was interpreted on the basis of higher mRNA expression of PTX3 in adipocytes isolated from the visceral adipose tissue than in adipocytes isolated from the subcutaneous adipose tissue along with increase in the visceral to subcutaneous fat ratio.

Collectively, these data might suggest that PTX3 appears as a novel treatment target for GLP-1RAs, a drug class promising to bridge the gap between T2D and NAFLD and to prevent (on either primary or secondary basis) the related cardiovascular disease. Prospective human studies utilizing GLP-1RAs in patients with T2D and NAFLD, evaluating its effect on PTX3, are required in order to elucidate this reasonable and interesting hypothesis.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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HOW TO CITE Patoulias D, Kalogirou MS, Stavropoulos K, et al. Pentraxin 3 in patients with type 2 diabetes and nonalcoholic fatty liver disease: a promising treatment target for glucagon-like peptide-1 receptor agonists. *Pol Arch Intern Med.* 2019; 129: 648-649. doi:10.20452/pamw.14998

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Authors' reply We appreciate comments of Dr Patoulias et al¹ about the results of our study on pentraxin 3 (PTX3) in patients with type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD). The authors of the comment suggest that PTX3 could be a novel treatment target for glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with T2D and NAFLD. Nonalcoholic fatty liver disease is believed to independently increase risk of macro- as well as microvascular complications. NAFLD can progress to nonalcoholic steatohepatitis and other serious hepatic diseases; however, the majority of deaths among patients with NAFLD is attributable to cardiovascular diseases.² In our study, we demonstrated a strong correlation between PTX3 and lipids as well as apolipoprotein cardiovascular markers such as total and low-density lipoprotein cholesterol, triglycerides, apolipoprotein C3, and apolipoprotein B100. Pentraxin 3, an endothelial stress and inflammation marker, was earlier described as a predictor of cardiovascular events.

Our study group consisted of consecutive patients with T2D who were referred to the Department of Metabolic Disease, University Hospital, Kraków, Poland due to poor glycemic control. This group was characterized by high prevalence of not only central obesity, arterial hypertension, and dyslipidemia but also hepatic steatosis. In general, they represented typical patients with T2D in real clinical practice.

In recent years, several cardiovascular outcome trials (CVOTs) in patients with T2D that examined novel hypoglycemic therapies produced positive results. The use of these new drugs, as compared with standard diabetes care aiming at similar glycemic control, resulted in a decrease of cardiovascular risk, including a reduction of 3-point major adverse cardiovascular events and

cardiovascular deaths.³ This was rather unexpected to the majority of diabetes experts as a generation of CVOTs in patients with T2D performed in the previous decade, such as ADVANCE (Action in Diabetes and Vascular Disease), VA-HIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial), and ACCORD (Action to Control Cardiovascular Risk in Diabetes), failed to prove possible cardiovascular benefits for intensive hypoglycemic therapy in those patients. Two types of hypoglycemic drugs contributed to the recent landmark findings, namely, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and GLP-1RAs. The publication of the positive results of CVOTs³ involving medications from both groups sparked a discussion on possible mechanisms other than just hypoglycemic action of the described beneficial cardiovascular effects. Evidence points to improvement in classical cardiovascular risk factors, such as obesity, dyslipidemia, or arterial hypertension. However, there is also confidence that they do not fully explain the advantageous action of either SGLT-2 inhibitors or GLP-1RAs. Therefore, there is a belief that some other, nonclassical cardiovascular risk factors could have been involved.³

As correctly pointed out by Dr Patoulias et al,¹ an effect of GLP-1RAs on PTX3 was observed in humans and in vitro studies. Thus, PTX3 and related metabolic pathways could be perceived as candidates for such nontraditional, rarely considered action of injectable incretins. Moreover, PTX3, an inflammation marker correlating with the decrease of cardiovascular risk factors in patients with NAFLD and T2D, may constitute an interesting treatment target. Interestingly, in the LEAN (Liraglutide Efficacy and Action in Nonalcoholic Steatohepatitis) study⁴ the GLP-1RA treatment also demonstrated a positive effect on NAFLD, which was documented by liver biopsy. The Lira-NAFLD (Effect of Liraglutide Therapy on Liver Fat Content in Patients With Inadequately Controlled Type 2 Diabetes) study⁵ confirmed the efficacy of liraglutide in reducing liver fat content also in patients with NAFLD and T2D. In this study, 6 months of treatment with liraglutide at a dose of 1.2 mg/d significantly reduced liver fat content in patients with inadequately controlled T2D, which was accompanied by body weight reduction.

Of note, SGLT-2 inhibitors also seem to possess some immunomodulatory and antioxidant properties. However, their effect on PTX3 has never been examined, while data on NAFLD in humans are limited. In the EFFECT-II study,⁶ the authors compared the effect of monotherapy with dapagliflozin, omega-3 carboxylic acids, combined treatment, or placebo, on liver fat content assessed with magnetic resonance imaging in patients with T2D and NAFLD. The results indicated that only combined treatment with an SGLT-2 inhibitor, dapagliflozin, and omega-3 carboxylic acids significantly reduced liver fat content in comparison with placebo. Monotherapy with

dapagliflozin in these patients reduced all measured biomarkers of hepatocyte injury and fibroblast growth factor 2, suggesting a disease-modifying effect in NAFLD.⁶

Summarizing, we fully support the hypothesis presented by Dr Patoulis et al¹ that GLP-1RAs are a class of drugs that not only prevent cardiovascular events in patients with T2D but also promise to act on other related comorbidities, such as NAFLD, that are common in those patients. This could constitute an important element of individualized therapy in patients with T2D, NAFLD, or cardiovascular disease with the aim to improve their prognosis. In this context, PTX3 could be a valuable biomarker and possible treatment target for GLP-1RAs.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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HOW TO CITE Waluś-Miarka M, Kapusta M, Miarka P, et al. Pentraxin 3 in patients with type 2 diabetes and nonalcoholic fatty liver disease: a promising treatment target for glucagon-like peptide-1 receptor agonists. Authors' reply. *Pol Arch Intern Med.* 2019; 129: 649-650. doi:10.20452/pamw.14999

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