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LETTER TO THE EDITOR

Circulating follistatin as a novel biomarker of type 2 diabetes mellitus risk

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Dear Editor,

The prevalence of type 2 diabetes mellitus (T2DM) has risen dramatically. Thus, precise and timely identification of the risk for development of T2DM still needs to be improved by novel biomarkers.

Follistatin is a protein, first described as a component of the follicular fluid, which is expressed in many tissues [1]. It is mainly secreted by the liver, glucagon/insulin ratio being a key determinant of its circulating level in humans [1]. It promotes insulin resistance in white adipose tissue, while its inactivation reduces hyperglycemia in mice [2]. In humans, circulating follistatin levels are increased in T2DM and positively associated with glycated hemoglobin and fasting glycemia [3].

The recently published study by Wu et al. [4] examining the relationship between plasma follistatin and incident T2DM has provided an insight into the potential utility of this biomarker in predicting future T2DM risk. The association between baseline plasma follistatin and incident T2DM was examined in 2 cohorts: the Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC) and the Innovative Medicines Initiative-Diabetes Research on Patient Stratification-Metabolic Syndrome in Men (IMI-DIRECT-METSIM) [4]. In the former, 577 of 4195 participants who developed T2DM during a mean follow-up of 19.07 ± 5.09 years had higher baseline plasma follistatin comparing with those who did not progress to T2DM after adjustment for multiple risk factors [4]. Additionally, its levels correlated with indicators of glucose tolerance, insulin secretion, and insulin sensitivity after adjustment for multiple risk factors [4]. However, addition of follistatin to the model adjusted for multiple risk factors did not improve prediction, indicating that follistatin on its own may not be efficient [4]. In the latter, 53 of 1079 subjects developing T2DM over 4 years also had higher baseline plasma follistatin levels, after adjustment for multiple risk factors [4].

Moreover, the authors analyzed the Tübingen Diabetes Family Study cohort (210 subjects without diabetes), in which plasma follistatin was positively correlated with free fatty acids and visceral fat mass, and negatively with adipose tissue insulin sensitivity and leg fat mass [4]. There was also an association between follistatin and liver fat content, although it disappeared after adjustments for visceral and leg fat mass, and for insulin sensitivity in the adipose tissue [4].

These results are in conflict with experimental evidence pointing to a potential beneficial role of follistatin. In a mouse model of T2DM, intravenous follistatin gene delivery improved glycemic control [5]. Moreover, in muscles of lean and diet-induced obese mice, follistatin increased both basal and insulin-stimulated protein synthesis [6].

Hence, elevated plasma follistatin level is associated with an increased risk of incident T2DM independently of established risk markers. However, there is also experimental evidence pointing to a potential beneficial role of follistatin. Accordingly, more experience is needed to delineate the role of follistatin as a potentially attractive therapeutic target for T2DM prevention.

This article is based on previously conducted studies and does not contain any novel data from studies with human participants or animals performed by any of the authors.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval This article is based on previously conducted studies and does not contain any novel data from studies with human participants or animals performed by any of the authors.

Conflict of interest This manuscript was written independently, and the authors did not receive financial or professional help for its preparation. Stella Papachristou declares no potential conflicts of interest. Djordje S. Popovic declares associations with Abbott, Alkaloid, AstraZeneca, Boehringer-Ingelheim, Berlin-Chemie, Eli Lilly, Galenika, Krka, Merck, Novo Nordisk, PharmaSwiss, Sanofi-Aventis, Servier, and Worwag Pharma. Nikolaos Papanas has been an advisory board member of TrigoCare International, Abbott, AstraZeneca, Elpen, MSD, Novartis, Novo Nordisk, Sanofi-Aventis, and Takeda; has participated in sponsored studies by Eli Lilly, MSD, Novo Nordisk, Novartis, and Sanofi-Aventis; received honoraria as a speaker for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Elpen, Galenica, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Takeda, and Vianex; and attended conferences sponsored by TrigoCare International, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Pfizer, and Sanofi-Aventis. None of the above-mentioned companies had any role in this article, which has been written independently, without any financial or professional help, and reflects only the opinion of the authors, without any role of the industry.

References

1. Hansen JS, Rutti S, Arous C, et al. Circulating follistatin is liver-derived and regulated by the glucagon-to-insulin ratio. J Clin Endocrinol Metab. 2016;101:550–60.
2. Tao R, Wang C, Stöhr O, et al. Inactivating hepatic follistatin alleviates hyperglycemia. Nat Med. 2018;24:1058–69.
3. Hansen J, Rinnov A, Krogh-Madsen R, et al. Plasma follistatin is elevated in patients with type 2 diabetes: relationship to hyperglycemia, hyperinsulinemia, and systemic low-grade inflammation. Diabetes Metab Res Rev. 2013;29:463–72.
4. Wu C, Borné Y, Gao R, et al. Elevated circulating follistatin associates with an increased risk of type 2 diabetes. Nat Commun. 2021;12:6486.
5. Davey JR, Estevez E, Thomson RE, et al. Intravascular follistatin gene delivery improves glycemic control in a mouse model of type 2 diabetes. FASEB J. 2020;34:5697–714.
6. Han X, Møller LLV, De Groote E, et al. Mechanisms involved in follistatin-induced hypertrophy and increased insulin action in skeletal muscle. J Cachexia Sarcopenia Muscle. 2019;10:1241–57.