Letter

Diabetes Metab J 2019;43:727-728
https://doi.org/10.4093/dmj.2019.0172
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Increased Serum Angiopoietin-Like 6 Ahead of Metabolic Syndrome in a Prospective Cohort Study (*Diabetes Metab J* 2019;43:521-9)

Jin Hwa Kim

Department of Endocrinology and Metabolism, Chosun University Hospital, Chosun University College of Medicine, Gwangju, Korea

The liver plays a pivotal role in the development of metabolic disorders by the regulation of glucose and lipid metabolism and is now considered as an endocrine organ. Liver-derived proteins known as hepatokines have major functions in regulation of systemic metabolism and energy hemostasis [1]. Cumulative evidences suggest that hepatokines have been associated with metabolic dysfunction, including fetuin A, fibroblast growth factor-21 (FGF-21), retinol-binding protein 4 (RBP4), selenoprotein P, leukocyte derived chemotaxin 2 (LECT2), and angiopoietin-related growth factor (ANGPTL6, also known as angiopoietin-like 6) [2,3]. Hepatokines may be attractive as emerging therapeutic targets and provide crucial insights that could help us better understand the pathogenesis in metabolic syndromes.

ANGPTL6, which is a multimeric glycoprotein, is recognized as an angiogenic factor and has additional novel effects on energy expenditure and insulin sensitivity [4,5]. Increasing levels of ANGPTL6 was significantly associated with body weight loss and increasing insulin sensitivity in mice fed a high-fat diet. Conversely, ANGPTL6 deficiency was related to insulin resistance and hyperglycemia. It was suggested that ANGPTL6 antagonized obesity and insulin resistance [6]. However, human studies showed inverse results [7-9].

In this article entitled "Increased serum angiopoietin-like 6 ahead of metabolic syndrome in a prospective cohort study," Namkung et al. [10] prospectively evaluated the association between serum ANGPTL6 level and new-onset metabolic syndrome in a rural cohort in Korea. They showed that serum ANGPTL6 level was already significantly elevated before developing new-onset metabolic syndrome, which has an independent predictive value for metabolic syndrome. As the prevalence of metabolic syndrome increases, there is an increasing need to identify persons at risk in early so they may benefit from early precision interventions. Several biomarkers as a predictor of incident metabolic syndrome including albumin, uric acid, and serum calcium were suggested [11,12]. The authors suggested the concept that the upregulation of ANGPTL6 is a compensatory mechanism against metabolic stress and is a candidate biomarker of metabolic syndrome. They have clearly showed their results in this manuscript, and this approach is quite valuable and helpful to establish early identification and individual strategies for metabolic syndrome.

In my opinion, it would be interesting to evaluate the level of ANGPTL6 at diagnosis of metabolic syndrome in addition to basal ANGPTL6 levels. Whether there is a change in ANGPTL6 levels between basal and at development of metabolic syndrome will provide an additional information in these research fields. Hopefully a large prospective cohort study will be performed. I also expect to extend the study to discover whether there is an association between the level of ANGPTL6 and prognosis of cardiovascular diseases and mortality. Lastly, it would have more value if they can follow-up for longer, as the

Corresponding author: Jin Hwa Kim https://orcid.org/0000-0003-2703-7033
Department of Endocrinology and Metabolism, Chosun University Hospital, Chosun University College of Medicine, 365 Pilmun-daero, Dong-gu, Gwangju 61453, Korea
E-mail: endocrine@chosun.ac.kr

authors mentioned. Further studies revealing the underlined mechanism of these paradoxical increase in ANGPTL6 in metabolic syndrome in human will be interesting.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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