Editorial

Diabetes Metab J 2022;46:257-259
https://doi.org/10.4093/dmj.2022.0060
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Variability of Metabolic Risk Factors: Causative Factor or Epiphenomenon?

Hye Jin Yoo

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

Recently, a close relationship has been shown in numerous epidemiological studies between variabilities of various metabolic risk factors and a wide range of diseases including new onset diabetes mellitus, chronic kidney disease, cardiovascular diseases (CVDs), and all-cause mortality [1]. In terms of pathology, fluctuation of blood pressure (BP) and blood glucose (BG) levels cause detrimental cardiometabolic events. Wide BP variability, which is mainly caused by increased arterial stiffness, baroreflex dysfunction, and prolonged sympathetic activation, induces shear stress on the vessel wall and consequently exacerbates atherosclerosis progression [2,3]. High glucose fluctuation provokes the activation of oxidative stress and production of inflammatory cytokines, inducing endothelial dysfunction [4,5]. In numerous studies, swings in BG as well as sustained hyperglycemia were consistently shown to increase the risk of microvascular and macrovascular complications [6]. Therefore, lowering BG fluctuation has been another important treatment target using a continuous glucose monitoring system in routine clinical practice. In addition to BP and BG variability, recent growing evidence supports that variability of other metabolic risk factors, such as lipids, body weight, and gamma-glutamyl transferase, can increase the risk of various diseases [7-9].

Although the Framingham study and *post hoc* analysis of the Treating New Target (TNT) study revealed that low-density lipoprotein (LDL) variability increased the risk of CVD in subjects with or without CVD [10,11], somewhat conflicting results were found in Korean nationwide population-based cohort studies. Kim et al. [12] showed that total cholesterol variability increased the risk of myocardial infarction (MI), stroke, and all-cause mortality, and Park et al. [13] demonstrated that in statin-naïve healthy young people, the associations between lipid variability and risk of MI and stroke varied depending on the measure of lipid variability used. These controversial results might be caused by different study populations, lack of standardized variability indices, and diverse interval and number of blood lipid measurements. To date, in most studies regarding the relationship between lipid variability and CVD, the main emphasis has been on ischemic vascular insults. However, current studies focusing on other CVDs such as heart failure (HF) and atrial fibrillation (AF) have been published. In those studies, for the highest quartile in total cholesterol variability compared with the lowest quartile, the risk of HF and AF increased by 17% and 8%, respectively [14,15]. In a recent study published in *Diabetes and Metabolism Journal*, Park et al. [16] showed that, over the median follow-up of 3.7 years, coefficient of variation (CV) and variation independent of the mean of LDL-cholesterol and all the variability parameters of apolipoprotein B (apoB) were significantly associated with development of subclinical left ventricular diastolic dysfunction (LVDD). However, the mean of any lipid variability measurement was not associated with risk of LVDD. Furthermore, this association between CV in LDL and risk of LVDD did not significantly correlate with sex, increasing/decreasing trend from baseline, or use of stain and/or other lipid-modifying agents. Subclinical LVDD is an important structural risk factor for HF with preserved ejection fraction (HFpEF), mainly derived from insulin resistance [17]. HF, which is the most common

Corresponding author: Hye Jin Yoo https://orcid.org/0000-0003-0600-0266
Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea
E-mail: deisy21@naver.com

cause of hospital admission in patients ≥65 years of age, has become a critical public health concern [18]. Due to the limitation in methods to reverse and cure HF, determining the risk factors for HF and applying a preventive strategy to high-risk subjects are important. Based on the present study, maintenance of stable LDL-cholesterol level might be helpful for preventing HF, and monitoring of LDL-cholesterol variability provided additional information regarding the risk of HF. Notably, LDL-cholesterol and apoB variability were closely associated with very early structural and functional changes in the heart, preceding clinical manifestation. As the authors mentioned, due to the relative short-term follow-up period for the apparently healthy population, mean LDL-cholesterol and apoB level were not associated with LVDD. This results also indicates that LDL-cholesterol variability was a very sensitive marker for LVDD. A commonly cited mechanism to explain the association between high variability in biological parameters and poor clinical outcome is that variability might reflect general frailty and only an epiphenomenon underlying an unhealthy systemic condition. However, the present study results showed an association of lipid variability with the very early phase of diastolic dysfunction, the subclinical outcome, within 3.7 years. Furthermore, this positive relationship was observed in the statin non-user subgroup during the period of variability check-up, which excludes the possibility that non-adherence to statin was the underlying mechanism between LDL-C variability and subclinical LVDD. High cholesterol variability induces fluctuation of plaque composite, making subjects more vulnerable to rupture [19], which is a main underlying mechanism explaining the relationship of cholesterol variability with ischemic CVD. However, in the present study, only three subjects developed regional wall motion abnormality consistent with ischemic heart disease, indicating that the influence of cholesterol variability on unstable plaque formation could not be the cause. The most reliable theory to explain the study results is that higher LDL-cholesterol or apoB variability is associated with endothelial dysfunction, oxidative stress, and inflammatory processes, which are considered to play a crucial role in the pathogenesis of LVDD and HFpEF. Therefore, to confirm the present study results, further research to clarify the underlying molecular mechanism and well-designed randomized controlled clinical trial with the intervention to stabilize LDL-cholesterol near the lower level should be performed. The results showing significant association with very early structural and functional changes in the heart prior to clinical manifestation indicate that lipid variability directly affects the pathogenesis of HF.

CONFLICTS OF INTEREST

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

REFERENCES

1. Lee SH, Kim MK, Rhee EJ. Effects of cardiovascular risk factor variability on health outcomes. Endocrinol Metab (Seoul) 2020;35:217-26.
2. Bae EH, Lim SY, Han KD, Oh TR, Choi HS, Kim CS, et al. Association between systolic and diastolic blood pressure variability and the risk of end-stage renal disease. Hypertension 2019;74:880-7.
3. Kishi T. Baroreflex failure and beat-to-beat blood pressure variation. Hypertens Res 2018;41:547-52.
4. Costantino S, Paneni F, Battista R, Castello L, Capretti G, Chiandotto S, et al. Impact of glycemic variability on chromatin remodeling, oxidative stress, and endothelial dysfunction in patients with type 2 diabetes and with target HbA1c levels. Diabetes 2017;66:2472-82.
5. Liu TS, Pei YH, Peng YP, Chen J, Jiang SS, Gong JB. Oscillating high glucose enhances oxidative stress and apoptosis in human coronary artery endothelial cells. J Endocrinol Invest 2014;37:645-51.
6. Park MJ, Choi KM. Association between variability of metabolic risk factors and cardiometabolic outcomes. Diabetes Metab J 2022;46:49-62.
7. Hong SH, Han K, Park S, Kim SM, Kim NH, Choi KM, et al. Gamma-glutamyl transferase variability and risk of dementia in diabetes mellitus: a nationwide population-based study. J Clin Endocrinol Metab 2020;105:dgaa019.
8. Hong SH, Lee JS, Kim JA, Lee YB, Roh E, Yu JH, et al. Gamma-glutamyl transferase variability and the risk of hospitalisation for heart failure. Heart 2020;106:1080-6.
9. Roh E, Hwang SY, Kim JA, Lee YB, Hong SH, Kim NH, et al. Body weight variability increases dementia risk among older adults: a nationwide population-based cohort study. Front Endocrinol (Lausanne) 2020;11:291.
10. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH; TNT Steering Committee and Investigators. Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovas-

cular outcomes: insights from the TNT trial. J Am Coll Cardiol 2015;65:1539-48.
11. Kreger BE, Odell PM, D'Agostino RB, Wilson PF. Long-term intraindividual cholesterol variability: natural course and adverse impact on morbidity and mortality: the Framingham Study. Am Heart J 1994;127:1607-14.
12. Kim MK, Han K, Kim HS, Park YM, Kwon HS, Yoon KH, et al. Cholesterol variability and the risk of mortality, myocardial infarction, and stroke: a nationwide population-based study. Eur Heart J 2017;38:3560-6.
13. Park JB, Kim DH, Lee H, Hwang IC, Yoon YE, Park HE, et al. Mildly abnormal lipid levels, but not high lipid variability, are associated with increased risk of myocardial infarction and stroke in "statin-naive" young population: a nationwide cohort study. Circ Res 2020;126:824-35.
14. Kwon S, Lee SR, Choi EK, Lee SH, Han KD, Lee SY, et al. Visit-to-visit variability of metabolic parameters and risk of heart failure: a nationwide population-based study. Int J Cardiol 2019;293:153-8.
15. Lee SR, Choi EK, Han KD, Lee SH, Oh S. Effect of the variability of blood pressure, glucose level, total cholesterol level, and body mass index on the risk of atrial fibrillation in a healthy population. Heart Rhythm 2020;17:12-9.
16. Park J, Kang M, Ahn J, Kim MY, Choi MS, Lee YB, et al. Mean and variability of lipid measurements and risk for development of subclinical left ventricular diastolic dysfunction. Diabetes Metab J 2022;46:286-96.
17. Plitt GD, Spring JT, Moulton MJ, Agrawal DK. Mechanisms, diagnosis, and treatment of heart failure with preserved ejection fraction and diastolic dysfunction. Expert Rev Cardiovasc Ther 2018;16:579-89.
18. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56-528.
19. Waters DD, Bangalore S, Fayyad R, DeMicco DA, Laskey R, Melamed S, et al. Visit-to-visit variability of lipid measurements as predictors of cardiovascular events. J Clin Lipidol 2018;12:356-66.