Hypertension Research (2024) 47:1227–1228
https://doi.org/10.1038/s41440-024-01609-7

COMMENT

Is remnant cholesterol a new therapeutic target for preventing hypertension?

Ayako Kunimura[1,2] · Katsuyuki Miura[2,3]

Keywords Remnant cholesterol · Hypertension · Dyslipidemia · Risk factors

Received: 8 January 2024 / Accepted: 20 January 2024 / Published online: 5 March 2024

Remnant cholesterol (RC), the triglyceride-rich precursors to low-density lipoprotein cholesterol (LDL-C), has been regarded as highly atherogenic [1]. Fasting RC primarily comprises very-low-density lipoproteins and intermediate-density lipoproteins, as well as non-fasting RC comprises a confluence of these lipoproteins with chylomicron remnants [1, 2]. RC has been demonstrated various proatherogenic effects, such as local or systemic inflammation, thrombus formation, and endothelial dysfunction [3–5]. Elevated RC levels were reported to be related to hyperinsulinemia [6], and to exhibit a robust and causal association with a development of atherosclerotic cardiovascular disease, cardiovascular death, and all-cause mortality irrespective of optimal treatment for LDL-C levels [7].

The coexistence of dyslipidemia and hypertension has been observed in previous studies [8, 9]. Previous cross-sectional studies have also demonstrated that elevated RC levels were associated with the prevalence of hypertension independently from other traditional risk factors in general population [10]. Although the comorbidity of dyslipidemia or RC and hypertension may, in part, be attributed to shared risk factors induced by an unhealthy lifestyle in most cases: obesity or overweight, physical inactivity, and hyperinsulinemia, there is a possibility that high RC levels could be an independent predictor of hypertension development [8, 11]. Furthermore, the previous longitudinal study from a Japanese Cohort of the Seven Countries Study has revealed that high RC levels were associated with the development of hypertension after 10 years in community-dwelling normotensive subjects [11]. In this study, a total of 681 participants aged >40 years with no history of hypertension at baseline who received health examinations were evaluated. Then, they demonstrated that a baseline RC level was significant factor for incident hypertension even after adjustment for other hypertension-related factors. However, as no other longitudinal studies which assessed the relationship between RC levels and development of hypertension were found afterward, it has been unresolved issues whether RC is an independent risk factor of incident hypertension, or is a mere comorbidity of hypertension.

In this issue of *Hypertension Research*, Guo et al. provide important evidence regarding the prospective association between RC levels and incident hypertension by utilizing the data from the UK Biobank, encompassing 295,062 participants without history of hypertension at baseline (mean age 55.1 years, 40.6% men, mean body mass index 26.6 kg/m^2, and 94.7% White) [12]. Over the 12 years of follow-up, 39,038 participants developed hypertension. As a result, the authors demonstrated that each 1 mmol/L increase in RC levels was associated with a 27% higher risk of incident hypertension (hazard ratio: 1.27; 95% confidence interval: 1.23–1.31) after adjustment for traditional risk factors, and this association was more distinct in younger participants (age <60 years), those without diabetes, and those with a BMI < 30 kg/m^2. Restricted cubic spline curves further elucidated a positive association between RC and incident hypertension. Then, the authors concluded that elevated RC levels were associated with an increased risk of hypertension development independently from traditional cardiovascular risk factors. Additionally, they suggest that monitoring RC levels is possibly useful to identify individuals at higher risk of hypertension development.

The precise elucidation of the prospective association between RC and the risk of hypertension development remains unknown (Fig. 1). There still be a possibility that shared risk

✉ Ayako Kunimura
kunimura.ayako.525@mail.aichi-med-u.ac.jp

[1] Department of Cardiology, Aichi Medical University, Aichi, Japan

[2] Department of Public Health, Shiga University of Medical Science, Shiga, Japan

[3] NCD Epidemiology Research Center, Shiga University of Medical Science, Shiga, Japan

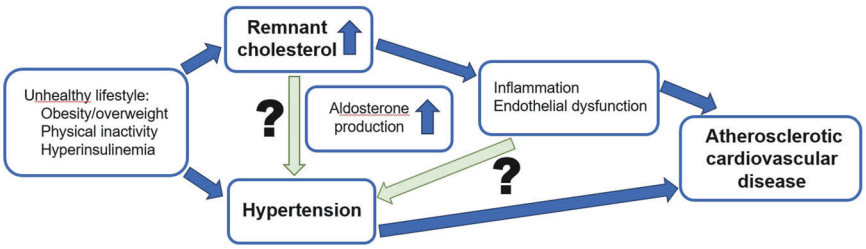

Fig. 1 The possible relationship between remnant cholesterol and development of hypertension

factors for both RC and hypertension exert an influence on this association [8, 11]. It is also possible that the previously documented effects of RC, such as instigating local and systemic inflammation, endothelial dysfunction, and increased aldosterone production, may contribute to the relationship by inducing sodium retention, peripheral vascular resistance, and vasoconstriction, ultimately leading to elevated blood pressure [4, 5, 7, 13]. Further experimental research is warranted to show a direct causative role of RC in the development of hypertension. Moreover, additional randomised clinical trials are warranted to demonstrate the beneficial effect of a RC-lowing treatment strategy in preventing a development of hypertension. By obtaining such research findings in the future, we could establish a novel preventative approach for hypertension development. In any case, we should keep paying attention to RC, and it is crucial for establishing a new preventative strategy, not only for atherosclerotic disease but also for hypertension.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. Endocr Rev. 2019;40:537–57.
2. Raja V, Aguiar C, Alsayed N, Chibber YS, ElBadawi H, Ezhov M, et al. Non-HDL-cholesterol in dyslipidemia: review of the state-of-the-art literature and outlook. Atherosclerosis. 2023;383:117312.
3. Joshi PH, Khokhar AA, Massaro JM, Lirette ST, Griswold ME, Martin SS, et al. Remnant lipoprotein cholesterol and incident coronary heart disease: The Jackson Heart and Framingham offspring cohort studies. J Am Heart Assoc. 2016;5:e002765.
4. Fujioka Y, Ishikawa Y. Remnant lipoproteins as strong key particles to atherogenesis. J Atheroscler Thromb. 2009;16:145–54.
5. Varbo A, Benn M, Tybjærg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Circulation. 2013;128:1298–309.
6. Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, et al. Relationship between insulin-resistance and remnant-like particle cholesterol. Atherosclerosis. 2002;164:167–70.
7. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013;61:427–36.
8. Park C, Fang J, Hawkins NA, Wang G. Comorbidity status and annual total medical expenditures in U.S. hypertensive adults. Am J Prev Med. 2017;53:S172–s81.
9. Matsubara K, Yamamoto Y, Sonoyama K, Igawa G, Furuse M, Yatsuhashi T, et al. Current status of lipid management of hypertensive patients. Hypertens Res. 2003;26:699–704.
10. Satoh A, Adachi H, Tsuruta M, Hirai Y, Hiratsuka A, Enomoto M, et al. High plasma level of remnant-like particle cholesterol in the metabolic syndrome. Diabetes care. 2005;28:2514–8.
11. Kasahara A, Adachi H, Hirai Y, Enomoto M, Fukami A, Yoshikawa K, et al. High level of plasma remnant-like particle cholesterol may predispose to development of hypertension in normotensive subjects. Am J Hypertens. 2013;26:793–8.
12. Guo D-C, Gao JW, Wang X, Chen Z-T, Gao Q-Y, Chen Y-X, et al. Remnant cholesterol and risk of incident hypertension: a population-based prospective cohort study. Hypertens Res. 2024 https://doi.org/10.1038/s41440-023-01558-7.
13. Saha S, Bornstein SR, Graessler J, Kopprasch S. Very-low-density lipoprotein mediates transcriptional regulation of aldosterone synthase in human adrenocortical cells through multiple signaling pathways. Cell Tissue Res. 2012;348:71–80.