



# A fascinating association between HDL as a multi-potent particle and hypertension

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## HDL, as a multi-potent particle

HDL is an interesting lipoprotein that is typically considered as good particle for atherosclerotic cardiovascular diseases (ASCVD). In fact, HDL cholesterol has been shown to be inversely associated with ASCVD in a number of observational studies [1]. As such, many researchers have tried to demonstrate that raising HDL cholesterol level by variety of ways could reduce the ASCVD events, but these trials have failed to achieve their goals so far [2]. On the other hand, recent studies have clarified that the function of HDL, rather than the quantity of HDL is important. In fact, cholesterol efflux capacity of HDL particle has been shown as a much better biomarker for ASCVD risk assessments [3]. In line with these findings, it has been shown that extremely high HDL cholesterol level has been shown to be worse clinical outcomes, probably because of abundance of dysfunctional HDL particles in such a situation [4]. So, HDL function has attracted a lot of attention as a potential biomarker to reduce so-called “residual risk” under LDL cholesterol lowering therapies [5]. However, we need to be careful when we talk about the function of HDL, because HDL particle has many biological properties, including anti-inflammatory, anti-oxidative, regulation of glucose homeostasis, endothelial repair, and vasodilatation other than cholesterol efflux (Fig. 1) [6–9]. There are many clinical situations, such as inflammatory diseases, diabetes, and renal dysfunction where HDL cholesterol level is significantly decreased, while there are other situations such as use of steroid and exercise where HDL cholesterol is

significantly increased. So, targeting any functions of HDL can be quite attractive pathways for various diseases. For example, anti-inflammatory properties of HDL may be an important treatment target for sepsis [10]. In this article Ding, et al. performed a Mendelian randomization study to identify biomarkers potentially causally associated with pre-eclampsia [11]. They found inverse association between large sized HDL cholesterol and pre-eclampsia. In addition, they checked potential side effects via phenome-wide association study. Most of the readers, including myself should be very surprised to see this mysterious association at first; however, considering the fact that HDL particle has a variety of functions, including endothelial repair and vasodilatation, it is quite understandable that HDL particle is associated with pre-eclampsia. The authors discussed the potential beneficial mechanisms of HDL particle, especially large-size HDL particle might be their reverse cholesterol transport. However, it has been shown that large-sized HDL particle has less impact on reverse cholesterol transport, compared with small-sized HDL particle [12]. So, endothelial repair and vasodilatation may be the major causes for this beneficial phenomenon. In order to clarify their findings, we suggest 2 ways. The first approach can be investigations on “human knockout”. This is quite a useful way to see the causal association between a biomarker and outcomes. In this case, I would suggest to see if individuals with cholesterylester transfer protein (CETP) deficiency who exhibit increased level of larger sized HDL have protective properties for pre-eclampsia and/or hypertension [13]. In addition, detailed analyses on individuals with HDL deficiencies, such as Tangier disease, apolipoprotein A-1 deficiency, and LCAT deficiency would also be informative [14]. The second approach can be investigations using HDL-raising medical therapies. There can be several approaches for this purpose. For example, CETP inhibitors should be one of the best candidates because it can

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Graphical Opinion

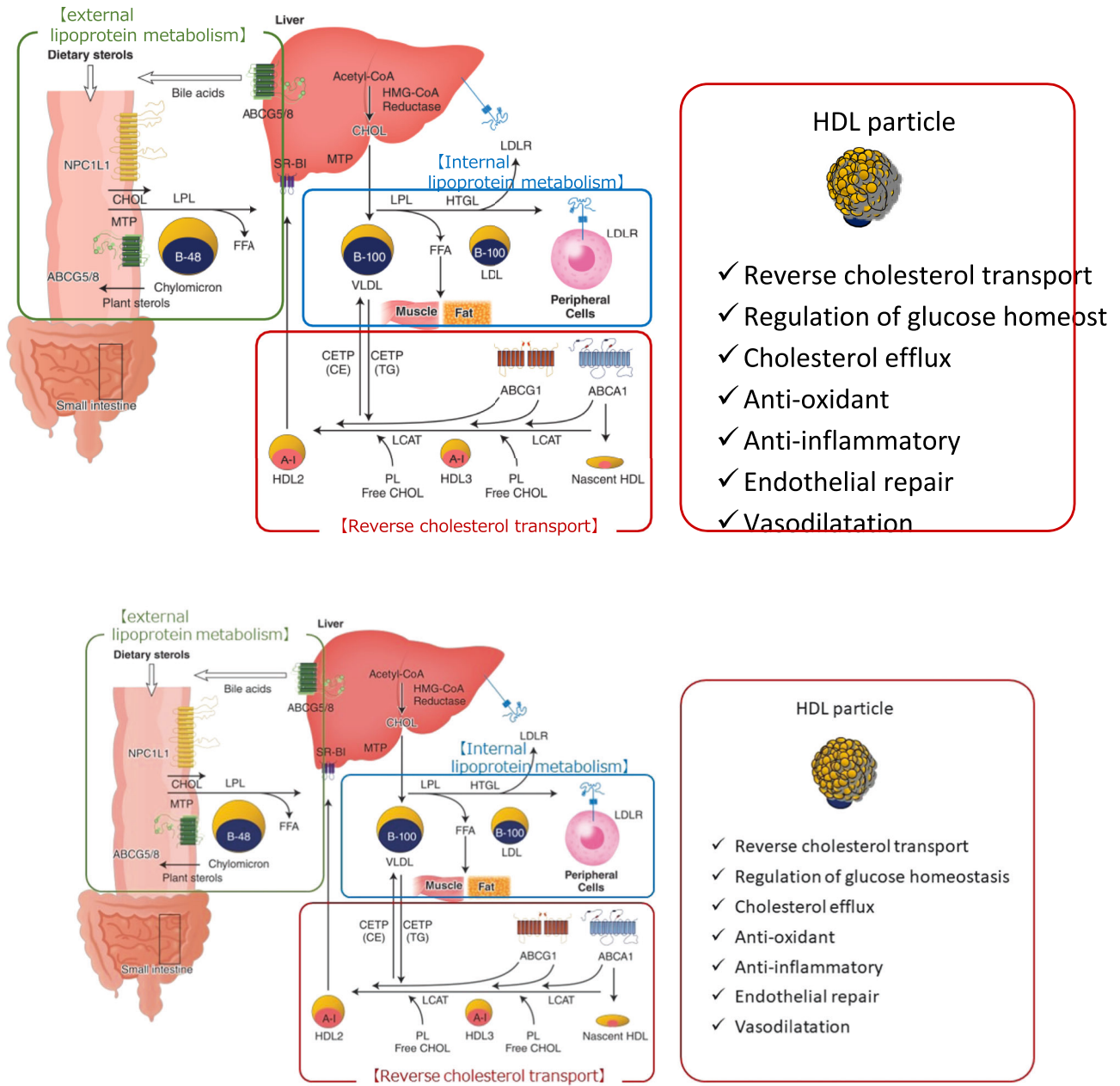


Fig. 1 Lipoprotein metabolism and functions of HDL

significantly increase HDL level, especially large-sized HDL particles [15].

Conclusion

HDL targeted therapies, especially those considering their functions in detail should be reconsidered as potential magic

bullet for variety of situations, including pre-eclampsia and/or hypertension.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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