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Editorial

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MAFLD and Small Dense LDL Cholesterol: A Mechanistic Link

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Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) and Atherosclerotic Cardiovascular Disease (ASCVD)

MAFLD was proposed as a new taxonomy for non-alcoholic fatty liver disease (NAFLD), contemplating the metabolic overload independently of the presence or absence of other liver diseases especially for alcoholic liver disease[1]. The norms are based on evidence of hepatic steatosis, in addition to one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation[1]. Liver steatosis and ectopic fat accumulation in the skeletal muscle and cardiovascular system can be a major cause of insulin resistance and its consequences, such as T2DM[2], dyslipidemia, and ASCVD[3]. Strong evidence supports that NAFLD/MAFLD increases the risk of ASCVD morbidity and mortality[4-6].

MAFLD, Hypertriglyceridemia, and Small Dense Low-Density Lipoprotein (sdLDL) Particles

In NAFLD/MAFLD, an increased release of very-low-density lipoprotein (VLDL) from triglyceride-laden hepatocytes produces hypertriglyceridemia[6]. Particularly, atherogenicity of hypertriglyceridemia is primarily caused by increased triglyceride (TG)-rich lipoprotein (TRL) remnants, high prevalence of sdLDL particles, and low high-density lipoprotein (HDL)-cholesterol (HDL-C)[7]. Moreover, sdLDL particles are known to promote atherosclerosis more than the large buoyant LDL particles[8]. Although previous studies reported increased sdLDL subspecies in individuals with NAFLD[9], few studies measured sdLDL-C levels in MAFLD.

In the current issue, Hirano *et al.*[10] reported that sdLDL-C was associated with computer-tomography-determined fatty liver, independent of body mass index and visceral fat area (Fig. 1). Since sdLDLs are more closely related to fatty liver than hypertriycriceridemia, hepatic VLDL production may have a stronger effect on sdLDL-C levels than TG-induced remodeling of LDL particles[10]. Theoretically, TG-rich VLDL1 particles, namely liver-centered metabolic abnormalities, are primarily formed by insulin resistance, leading to the production of sdLDL particles, or by increased lipogenesis, a major cause of hepatic steatosis[6]. Apart from VLDL1 production, plasma TG levels also reflect concentrations of chylomicrons and VLDL2 and TG clearance with lipoprotein lipase (LPL) or hepatic TG lipase (HTGL)[6].

Future studies need to determine whether elevated sdLDL-C levels can predict CVD events in people with MAFLD or NAFLD more effectively than other lipid parameters. If so, the underlying mechanisms by which sdLDLs are produced and how these mechanisms cause CVD events in MAFLD or NAFLD should be elucidated.

Conflict of Interest

None.

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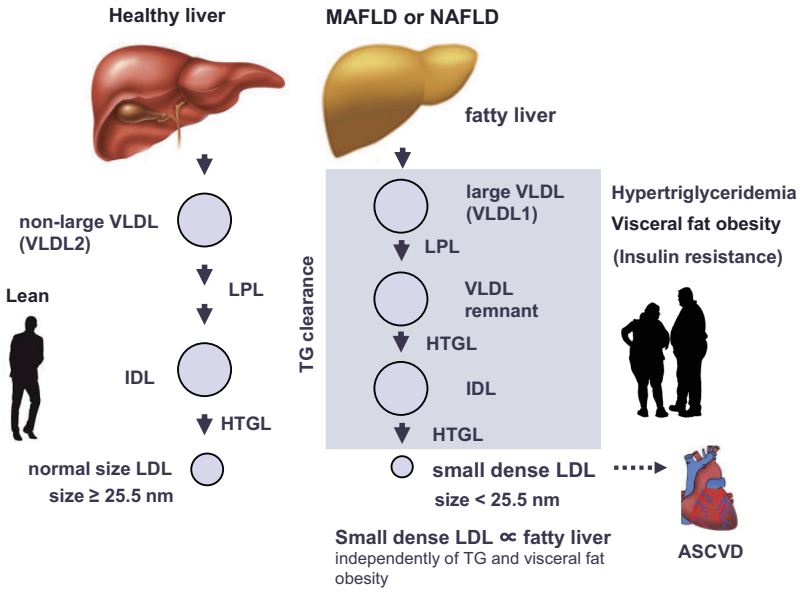

Fig. 1. Association between MAFLD/NAFLD, sdLDL-C, and ASCVD

Metabolic dysfunction-assosiated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease (NAFLD), is closely linked to elevated lelves of small dense low-density lipoprotein cholesterol (sdLDL-C), suggesting that sdLDL-C can predict ASCVD events effectively in people with MAFLD-NAFLD. ASCVD: atherosclerotic cardiovascular disease; See the text for details of the abbreviations.

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