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## POSTPRANDIAL CHOLESTEROL METABOLISM: A CLUE TO THE IMPACT OF TM6SF2 rs58542926 VARIANT ON LIVER AND CARDIOVASCULAR DISEASE IN NAFLD?

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### Abstract

**Background.** Nonalcoholic fatty liver disease (NAFLD) encompasses a histological spectrum, ranging from simple steatosis to steatosis plus necroinflammation (NASH), which can be differentiated only by liver biopsy. Genetic factors contribute to the pathogenesis of NAFLD. Genetic variation in the *transmembrane 6 superfamily member 2 protein* (TM6SF2) at rs58542926 was shown to confer susceptibility to NAFLD.

**Objective.** We examined the impact of this polymorphism on postprandial lipoprotein subfractions and on postprandial changes in cytokeratin-18 fragments in normolipidemic biopsy-proven NAFLD patients and matched healthy controls.

**Methods.** fifty-five nonobese, nondiabetic, normolipidemic biopsy-proven NASH patients and 55 age, sex, BMI-matched healthy controls underwent an oral fat load test, with measurement of plasma triglyceride-rich lipoprotein subfractions, total cholesterol, oxidized LDL, non-esterified fatty acids, E-selectin, ICAM, and cytokeratin-18 fragments.

**Results:** TM6SF2 T-allele carriers showed a lower postprandial triglyceridaemia and nefaemia, and a striking redistribution of cholesterol from smaller, more atherogenic VLDL2, LDL and oxLDL particles to larger VLDL1 subfractions than C-allele carriers. On multiple regression analysis, IAUC VLDL1-Cholesterol (VLDL1-Ch) during the oral fat load independently predicted NAFLD activity score ( $\beta=0.394$ ,  $p=0.022$ ), IAUC CK-18 ( $\beta=0.412$ ,  $p=0.018$ ) and fibrosis score ( $\beta=0.402$ ,  $p=0.019$ ), while IAUC oxLDL predicted circulating E-selectin ( $\beta=0.418$ ,  $p=0.011$ ) and ICAM-1 ( $\beta=0.451$ ,  $p=0.012$ ).

**Conclusions** These findings may partially explain the impact of TM6SF2 C>T variant on liver injury and CVD risk in NAFLD. TM6SF2 C>T variant modulates dietary cholesterol fluxes, with T-allele diverting toxic cholesterol away from the vessel walls into the liver, thereby promoting liver injury. Consistently, circulating VLDL-Cholesterol closely correlated with hepatic cholesterol content, inflammation, fibrosis, and cell injury in NASH. If confirmed by larger follow-up studies, these findings may provide the rationale for evaluating approaches using cholesterol-lowering medications to alleviate hepatic cholesterol overload and liver injury in TM6SF2 T-allele carriers, irrespective of fasting blood cholesterol levels.