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TG and HDL: the entangled pair

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Two recent publications from the New England Journal of Medicine (NEJM) [1;2] echoed in international and national news agencies (Agence France Presse [AFP]; Dallas news). The AFP journalist highlighted the importance of high triglycerides (TGs), but not low levels of high-density lipoprotein (HDL) cholesterol, as a risk factor for cardiovascular diseases (CVDs). Are HDL levels actually not relevant for CVDs in contrast to what the current guidelines are advocating [3]? Let us take a look at the data provided by the NEJM studies. In the first study [1], members of the Triglycerides and High-Density Lipoprotein (TG and HDL) Working Group sequenced the exome of 3734 persons and then tested the association of plasma TG with rare sequence variants. The gene most strongly associated with plasma TG encoded apolipoprotein C3 (ApoC3). Carriers of *ApoC3* variants with lower TG levels displayed lower ApoC3 plasma levels and reduced risk of CVDs. Functionally, it makes sense that low ApoC3 levels favor increased TG levels because ApoC3 is an inhibitor of the lipoprotein lipase that participates in the catabolism of TGs [4]. As transfer of TG to HDLs accelerates their turn-over [4] reduced TG levels are also expected to positively affect HDL levels. Additionally, hydrolysis of TG-rich lipoproteins provides material for HDL synthesis. Via this effect, lower ApoC3 can also contribute to elevation in HDL levels [4]. It came therefore as no surprise that the NEJM study reported increased HDL levels in loss-of-function ApoC3 carriers. Such an association between loss-of-function of ApoC3 with reduced TG levels and increased HDL levels had in fact been described earlier in the Amish population [5] but the global impact of this mutation on CVD was not determined.

The second NEJM study [2] applied a reverse approach. The authors initially demonstrated an association of TG levels and CVD risk and then determined that loss-of-function mutations in *ApoC3*, which they found associated with low TG levels, were also predictive for lower risks of CVD. In this case again, an inverse relationship was observed between TG and HDL levels.

In conclusion, the two NEJM studies nicely demonstrated the impact of a TG-modulating protein (ApoC3) on CVD risks but, as in most observational studies, cannot isolate the individual contributions of entangled biological parameters, such as TGs and HDLs, in the development of CVDs. In particular, the data reported in these studies cannot be used as evidence that TG levels causally determine CVD risks, as the authors in fact carefully pointed out (but not the journalist).

Finally, in the context of HDLs and diabetes, recently reviewed in depth [3;4], a new observational study reports that low HDL levels predict earlier and greater intensity treatment with oral hypoglycemic agents and insulin in type 2 diabetic individuals [6]. This work is in line with a large number of studies reporting that HDL levels predict incidence of type 2 diabetes development. Its novelty stems from the finding that in individuals with established diabetes, low HDL levels predict hastened deterioration of glucose control. Here again, causality cannot be inferred. As HDL and TG levels are so closely entangled, TGs may as well contribute to beta cell dysfunction in diabetic patients as reported in a recent retrospective study [7].

Reference List

• 1. **Loss-of-function mutations in APOC3, triglycerides, and coronary disease**. *N.Engl.J.Med.* 2014, **in press**.

This study reports the association of mutations in the APOC3 gene that are associated with decreased TG levels and reduced risk of coronary heart disease. This paper show the power of exon sequencing in identifying rare variants/mutations that has the potential to be causal for the phenotypic traits of a disease. Compared to genome wide association studies, such approach, by identifying mutations in candidate proteins, provide researchers molecular and structural information to generate hypothesis-driven functional experiments to investigate the causal mechanisms of the studied disease.

• 2. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A: **Loss-of-function mutations in APOC3 and risk of ischemic vascular disease**. *N.Engl.J.Med.* 2014, **in press**.

In contrast to the previous study, this work did not start with exon sequencing of a cohort of patients, but rather with the establishement of a link between high TG levels and CVD risks. Then a candidate gene approach was undertaken that showed that mutations in the *ApoC3* gene, associated with reduced TG levels, were also associated with reduced ischemic vascular disease risks. This and the previous study are fine examples of genetic studies that can pinpoint the importance of genes in the aetiology of a diseas.

3. Vollenweider P, von Eckardstein A, Widmann C: **HDLs, diabetes, and metabolic syndrome**. *Handb.Exp.Pharmacol.* 2014, **In press**.

4. von Eckardstein A, Widmann C: **HDL, beta cells and diabetes**. *Cardiovasc.Res.* 2014, **In press**.

5. Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, Post W, McLenithan JC, Bielak LF, Peyser PA, Mitchell BD, Miller M, O'Connell JR, Shuldiner AR: **A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection**. *Science.* 2008, **322:**1702-1705.

6. Waldman B, Jenkins AJ, Davis TM, Taskinen MR, Scott R, O'Connell RL, Gebski VJ, Ng MK, Keech AC: **HDL-C and HDL-C/ApoA-I predict long-term progression of glycemia in established type 2 diabetes**. *Diabetes Care* 2014.

7. Shimodaira M, Niwa T, Nakajima K, Kobayashi M, Hanyu N, Nakayama T: **Serum triglyceride levels correlated with the rate of change in insulin**

secretion over two years in prediabetic subjects. *Ann.Nutr.Metab.* 2014, **64:**38-43.

Further recommended reading

Churilla JR, Johnson TM, Curls R, Richardson MR, Boyer WR, Devore SR, Alnojeidi AH: **Association between alcohol consumption patterns and metabolic syndrome**. *Diabetes Metab.Syndr.* 2014, **8:**119-123.

Raising HDL levels is proposed to be a therapeutical approach in the context of CVDs and diabetes. This notion is based on the inverse relationship observed between HDL levels and risks of developing such diseases. The present study confirms the association between alcohol consumption and HDL levels. It also indicates that individual consuming alcohols are less likely to develop a metabolic syndrome. Considering alcohol, when moderately consumed, as therapeutic beneficial raises ethical and medical issues however. Nevertheless, it is certainly worthwhile to experimentally assess, at the molecular level, how alcohol exerts its beneficial effect as this may lead to the identification of molecules that could be targeted for the development of anti-atherogenic and anti-diabetogenic drugs.

Kurano M, Hara M, Tsuneyama K, Sakoda H, Shimizu T, Tsukamoto K, Ikeda H, Yatomi Y: **Induction of insulin secretion by apolipoprotein M, a carrier for sphingosine 1-phosphate**. *Biochim.Biophys.Acta* 2014.

The HDL components mediating their beneficial effects in pancreatic beta cells are not definitely characterized yet. ApoM, an apolipoprotein found in about 10% of HDLs, has the capacity to bind sphingosine-1-phosphate (S1P). This latter molecule is able to activate various signals in cells, including anti-apoptotic pathways. The present study indicates that ApoM favors insulin secretion in a S1P receptor-dependent manner. It will be interesting in future

studies to determine if ApoM-containing HDL particles are the only HDL particles that mediate beneficial effects in beta cells.