High circulating triglycerides are most commonly a marker of *ectopic* fat accumulation – connecting the clues to advance lifestyle interventions

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While the therapeutic importance of managing low-density lipoprotein-cholesterol (LDL-c) to reduce atherosclerotic cardiovascular disease (ASCVD) risk is well-established, the best course of action for modest or marked elevations of circulating triglycerides (TG) remains uncertain. LDL-c and TG concentrations are largely independently regulated – TG can be elevated with normal LDL-c and *vice versa* – and there is increasing evidence from genetic analyses and Mendelian randomization studies that elevated TG concentrations are causally related to ASCVD risk, independent of LDL-c. This supports the hypothesis that the much larger triglyceride-rich VLDL-c particles, which also carry apoB, contribute to ASCVD risk. However, pharmacologic interventions to lower TG have generally failed to affect ASCVD outcomes, most notably the fibric acid class of medications, niacin, and fish oil preparations, excepting benefits observed with some but not all eicosapentaenoic acid (EPA)-based formulations.

However, apart from uncommon genetic dyslipidemias (both mono- and polygenic), the focus on treating elevated TG concentrations *per se*, rather than treating the underlying cause, represents an opportunity frequently missed in cardiometabolic / cardiovascular preventative clinics. There are several secondary causes for elevated TG, such as nephrotic syndrome, liver disease, alcohol consumption, high carbohydrate/excessive calorie diets, obesity, and hypothyroidism to name a few. Furthermore, in patients with diabetes, especially those with severe insulin resistance, poor glycemic control causes elevated TG levels that improve with improved glucose control. Most importantly, however, modest or severe elevations in blood TG most often represent a circulating manifestation of ectopic fat in the context of obesity, with greater hepatic production of VLDL particles common when visceral and liver fat are elevated.[1] Indeed, in many people, excess blood TG levels derive

from continued excess caloric intake once the individual's capacity to store fat in metabolically healthy subcutaneous depots has been exceeded.[1]This leads to the energy surplus being converted into fat in visceral and ectopic tissues such as skeletal muscle, the liver, the pancreas, and the heart; but also, often concomitantly, in the form of *circulating* TG.

Several clues in the blood biochemistry and the patient's history and physical exam may help determine when higher circulating TG levels likely represent ectopic fat excess. Elevated circulating TG often co-exists with hepatic steatosis,[2] in the context of excess weight/adiposity, and can be detected by direct (ultrasound or MRI) or inferred by indirect intermediate measures (i.e., alanine aminotransferase [ALT] or gamma-glutamyl transferase [GGT]) of liver fat. These correlates of liver fat [2], as well high TGs, are particularly strongly linked to risk of incident diabetes, more so than risk of incident ASCVD.[3] Such adiposity-associated high TGs are often coincident with subtle or marked glucose elevations. The associated elevations in ALT levels often do not exceed the traditional upper limit of normal, as even circulating levels of 30-35U/L are independently associated with higher diabetes risk (as compared with levels <20U/L), and many individuals with high normal ALT levels may have excess liver fat.[4]

Thus, results of selected blood tests – TG, ALT, GGT, and HbA1c and/or fasting blood glucose – when examined together, can suggest the presence of ectopic fat in the liver and beyond. Given that type 2 diabetes in most individuals is a disease of excess ectopic fat, the patient's weight, together with knowledge of their family history of diabetes can also help in putting the biochemical results into better context (**Figure**).

Consider a typical case: a 45-year-old male individual without existing ASCVD referred for elevated TG despite being on a statin with LDL-c at target. His TG levels are 490 mg/dl, LDL-c 74 mg/dl and HDL-c 35mg/dl. He has a family history of type 2 diabetes and drinks minimal alcohol. He has a BMI of 29, waist circumference of 38 inches, being around 20 kg heavier than three years ago. Other blood tests show ALT 45 u/L, AST 32 U/L, GGT 32 u/L, HbA1c 46 mmol/mol (6.4%). Three years ago, TG was 196 mg/dl and ALT was 22 U/L. All these results strongly suggest this patient's current high TG levels are a manifestation of ectopic fat, with excess adiposity, evidence of pre-diabetes (on top of a family history) and, based on a high normal ALT, most likely elevated liver fat levels. His weight gain will have driven ectopic fat gain on the background of a type 2 diabetes susceptibility, and, notably, there are no clear signals linked to excess alcohol (as HDL-c and AST levels are not elevated, and GGT levels only modestly elevated, not uncommon with fatty liver disease). While some may argue other tests are needed to better understand the underlying cause, in this scenario, there is good evidence that lifestyle changes prioritizing diet-induced weight loss, together with increased physical activity, can reduce ectopic fat leading to parallel improvements in TG, ALT (and/or GGT) and HbA1c.[1] Indeed, observing such linked improvements provide indirect biological support for the efficacy of lifestyle-mediated lowering in ectopic fat; further, offering feedback of these biochemical changes can help motivate patients to try to sustain their weight loss and lifestyle change. Notably, intentional weight loss *per se* and reductions in associated TG levels will also reduce ASCVD risk, and lifestyle changes, unlike many drugs, also improve quality of life. It is also important to note that serial blood testing may help to reveal patterns of ectopic fat loss and gain in many patients, such that it is often possible to predict patients have put on or lost weight with blood results in hand even

before virtual or face to face appointments where actual attainment of body weight would take place.

In summary, while excellent tools to target ASCVD risk factors exist, and new ones may come on board, it is timely to discuss ectopic fat in cardiology[5], as excess weight and linked ectopic fat (fatty liver, high blood TG levels) and type 2 diabetes are increasingly common. Therefore, when confronted with a patient with elevated TG, we suggest clinicians first check whether this abnormality could represent ectopic fat by undertaking measurement of its common co-travellers of a liver fat intermediate (ALT ± GGT), dysglycemia (HbA1c), and in some cases, liver ultrasound or MRI in some centers, before and after weight change. By doing so, lifestyle changes become incentivised and prioritized, leading to multiple "upstream" health benefits beyond lowering "downstream" cardiovascular risks.

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References

1. Taylor R, Al-Mrabeh A, Sattar N. Understanding the mechanisms of reversal of type 2 diabetes [Internet]. Lancet Diabetes Endocrinol. 2019 [cited 2021 Jan 8];7:726–736. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213858719300762
2. Kotronen A, Yki-Järvinen H, Sevastianova K, Bergholm R, Hakkarainen A, Pietiläinen KH, Juurinen L, Lundbom N, Sørensen TIA. Comparison of the relative contributions of intra-abdominal and liver fat to components of the metabolic syndrome. *Obesity (Silver Spring)* [Internet]. 2011 [cited 2022 Apr 7];19:23–28. Available from: https://pubmed.ncbi.nlm.nih.gov/20539297/
3. Sattar N, McConnachie A, Ford I, Gaw A, Cleland SJ, Forouhi NG, McFarlane P, Shepherd J, Cobbe S, Packard C. Serial metabolic measurements and conversion to type 2 diabetes in the West of Scotland Coronary Prevention Study: Specific elevations in alanine aminotransferase and triglycerides suggest hepatic fat accumulation as a potential contributing factor. *Diabetes* [Internet]. 2007 [cited 2022 Mar 17];56:984–991. Available from: https://pubmed.ncbi.nlm.nih.gov/17395744/
4. Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, Avillach P, Egger P, Dhalwani NN, Kendrick S, Celis-Morales C, Waterworth DM, Alazawi W, Sattar N. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. *BMJ* [Internet]. 2019 [cited 2021 Jan 18];367:l5367. Available from: https://pubmed.ncbi.nlm.nih.gov/31594780/

5. Després JP, Carpentier AC, Tchernof A, Neeland IJ, Poirier P. Management of Obesity in Cardiovascular Practice: JACC Focus Seminar. J Am Coll Cardiol. 2021 Aug 3;78(5):513-531. doi: 10.1016/j.jacc.2021.05.035. PMID: 34325840; PMCID: PMC8609918.

Figure Legend

This figure depicts the pieces of evidence that should be assessed to establish whether elevated plasma triglyceride levels fit with a pattern consistent with ectopic fat, noting that not everyone with ectopic fat will have all features. It is not uncommon to see patients with ectopic fat who have slightly elevated ALT levels (often at the high end of the normal range ± elevated GGT). In some cases, ALT levels will be above the upper limit of normal, that is supportive of non-alcoholic fatty liver disease, especially when alcohol intake is low. In many people with ectopic fat, GGT levels can also be modestly raised. Evidence of dysglycemia is also common in those with ectopic fat (e.g., elevated HbA1c, in the pre-diabetes range or worse) and/or a family history of type 2 diabetes, in conjunction with excess weight. Being aware of this common pattern should help providers explain to their patients why their trilgyceride levels are elevated (i.e., excess weight leading to adverse storage of fat), and such an explanation could help motivate lifestyle changes and weight loss. Should patients lose weight, relevant blood tests will often improve in parallel thereby providing biological feedback of health gains. These points are important as intentional weight loss reduces diabetes and cardiovascular risks and can help patients avoid starting more medications. Recognizing such patterns is increasingly important as more patients than ever before are living with excess adiposity and related metabolic disorders. Of course, it is always important to exclude secondary causes of raised triglycerides first.

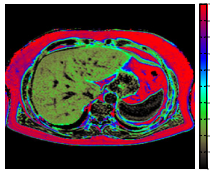
↑ blood triglyceride

(LDL-c **not** necessarily high and could be at target)

1. Exclude secondary causes e.g. excess alcohol, nephrotic syndrome, hypothyroidism

2. Check for signs of excess adiposity? (overweight or obese)

3. Check for excess liver fat intermediates e.g. *high-normal* ALT (±GGT) levels OR liver ultrasound /MRI



4. Check for dysglycemia? ↑HbA1c or fasting glucose? Ask about family history of type 2 diabetes

If Yes, consider high triglyceride to be **ectopic fat**

Suggest weight loss ± ↑activity

If diagnosis correct, triglyceride, ALT, GGT, HbA1c levels will often improve in parallel with weight loss providing motivation to sustain weight improvements and lower CV and diabetes risks