Lean Mass Hyper-Responder Phenotype

Society of Metabolic Health Practitioners

Lean mass hyper-responder (LMHR) phenotype

The LMHR phenotype has been recently identified in recognition of a small group of individuals who experience elevations in LDL after the adoption of therapeutic carbohydrate reduction (TCR). Typically, these individuals are lean and metabolically healthy with cholesterol readings defined as LDL cholesterol ≥200 mg/dL (5.2 mmol/L), HDL cholesterol ≥80 mg/dL (2.1 mmol/L), and TG ≤70 mg/dL (0.8 mmol/L). These values represent a metabolically healthy distribution due to the higher HDL and low triglyceride concentrations as defined by metabolic syndrome criteria. Generally, this population also demonstrates a pattern A LDL phenotype, not associated with CVD events.

It is still to be determined if elevated LDL in this context (good metabolic health and low inflammation) represents an increased risk for CVD, but early data are promising. The results of a recent study where 100 individuals with the LMHR phenotype were followed for one year showed there was no association between total exposure to, or changes in, LDL or ApoB, with changes in plaque. However, baseline plaque was associated with plaque progression.

LDL as an isolated metric of risk

LDL is **not** a good predictor of cardiovascular disease (CVD) risk when considered as an isolated metric, and this may be why it is not included in the standard criteria for assessing metabolic health. This may be especially relevant in the context of a low-carbohydrate or ketogenic diet, where **improvements** are observed in other metabolic health markers, particularly insulin resistance and dysglycaemia, which are key drivers of small dense LDL, the phenotype that primarily drives CVD risk. A recent paper states, 'LDL-c alone is not an efficient screening test because the distributions of blood LDL-c among patients with and without [carotid

artery disease] overlap, resulting in false positive and false negative detection rates'.

Atherogenic dyslipidemia

Atherogenic dyslipidemia is classically defined by the finding of high triglycerides, low HDL, and elevated small dense LDL. This profile is consistently improved with the application of a reduced carbohydrate or ketogenic diet, where reversal of the more atherogenic pattern B LDL subtype has been demonstrated.

Other risk factors

Risk factors that are consistently associated with cardiovascular disease (CVD) are diabetes, metabolic syndrome, hypertension, obesity, and hyperinsulinemia. Carbohydrate reduction has been shown to reliably reduce these risk factors.

Insulin resistance and hyperglycemia

Insulin resistance is an independent risk factor for CVD and is consistently reflected in studies as being a primary driver of CVD. This is supported by observations of the progression of CVD even in the presence of good glycemic control. Insulin resistance leads to the development of small dense LDL, the subtype of LDL that is implicated in CVD.
Hyperglycemia contributes to CVD via many mechanisms that include contributing to endothelial dysfunction and coagulation activation; both factors that accelerate atherosclerosis.

Remission of type 2 diabetes, metabolic syndrome, and insulin resistance are the primary factors that improve CVD risk

Therapeutic carbohydrate reduction has been shown to significantly improve (with reductions in medication) type 2 diabetes, metabolic

syndrome and insulin resistance, and may place these conditions into remission.

Stratifying risk

Risk stratification via the testing of cholesterol subtypes, considering family history, and imaging options may be used to help guide decisions on an individual basis. The American Heart Association has acknowledged the importance of a CAC score for determining patient risk and guiding treatment decisions. Blaha et al. 2016 states, 'Negative results of atherosclerosis-imaging tests, particularly coronary artery calcium score of 0, resulted in the greatest downward shift in estimated CVD risk'. Other imaging that may be considered is coronary computed tomography angiography (CCTA) or carotid intima-media thickness (CIMT).

Risk stratification should be considered in the context of patient preferences, metabolic health markers, which risk factors have improved while using TCR, and whether there are any competing conditions that are being managed using this approach. If patient preferences or clinical markers suggest changes are warranted, adding back a small amount of starchy vegetables (50 to 100 grams/day) has been found to reduce LDL concentration.

Conclusion

The majority of patients who initiate TCR for the treatment of type 2 diabetes, metabolic syndrome, obesity, and insulin resistance see significant improvements in their metabolic health with improvements or little change to their LDL or total cholesterol. In fact, the totality of evidence demonstrates TCR leads to improvements in conditions most highly associated with CVD and improved cholesterol profiles. Risk stratification using imaging and other factors can be used to guide decision-making in more complex cases.