Editorial

Interaction of genetic risk scores and adiposity: a significant influence on triglyceride levels

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Ahmad *et al.* (1) in their study aim to identify the interactions between adiposity and triglyceride associated genetic variants in the apparently healthy women from the Women's Genome Health Study (WGHS). The purpose of this study was to identify the link between lifestyle-related exposures and an inherent risk for higher triglyceride levels. Given the immense burden of cardiovascular disease (CVD) as the leading cause of mortality globally, it is important to understand and dissect contributing factors of CVD. Increased triglyceride levels that are generally found with obesity [body mass index (BMI) ≥25.0] have been correlated with higher risk for development of CVD (2). Two studies done in Denmark (3) and Sweden (4) as referenced by Ahmad *et al.* (1) attempt to explain this variability in that adiposity [BMI and waist circumference (WC)] in interaction with triglyceride associated single-nucleotide polymorphisms (SNPs) can accentuate the risk of developing higher triglyceride levels which in return leads to a higher risk of CVD. Ahmad *et al.* attempt to replicate these findings in the US population. The group analyzes blood samples of 23,294 American women in the WGHS database and calculates a triglyceride-weighted genetic risk score (TG-wGRS) based on the prevalence of 40 SNPs that have been associated with hypertriglyceridemia. They then do a meta-analysis combining results from WGHS with four Scandinavian Cohorts (INTER99, HEALTH2006, GlACIER, MDC) analyzing triglycerides levels based on the calculated TG-wGRS, BMI, and WC. The results of this study are remarkable in that they discover the following:

(I) Each unit increase in TG-wGRS was associated with a 1.011% increase in TG of normal BMI individuals *vs.* 1.013% in higher BMI individuals ($P_{interaction}$ =0.014);
(II) Each unit increase of TG-wGRS was associated with a 1.010 increase in TG of normal WC individuals *vs.* 1.012% in higher WC individuals. ($P_{interaction}$ =0.06);
(III) They found highly significant interaction of TG-wGRS and BMI with TG-rich lipoprotein (TRLP) $P_{interaction}$ <0.001).

These results demonstrate that the effects of genetic predisposition to a high TG level appear to be augmented by adiposity (BMI/WC). Epidemiologic and clinical data align with genetic data and support a causative role for TG and TRLPs in CVD (2). In the genome wide association studies, triglyceride effect size was significantly associated with CVD (r=0.46, P=0.02) (5). In a study using data from three Copenhagen population cohorts, three common APOA5 variants used to define 10 common genotype combinations were associated stepwise increase in triglyceride and cholesterol remnant. With each doubling of non-fasting triglyceride levels and calculated remnant (which is the cholesterol content of TRLPs) risk of myocardial infarction (MI) approximately doubled [odds ratios of 1.94 (95% CI: 1.40–1.85) and 2.23 (95% CI: 1.48–3.35), respectively] (6).

In conclusion, study by Ahmad *et al.* supports the previous data, that adiposity accentuates the effects of interaction between genetic factors and serum triglyceride

and TRLPs. Previously, in studies conducted by Pollin *et al.* (7) and Zubair *et al.* (8) found that intensive lifestyle modification and weight loss might partially alleviate interaction between genetic risk score and higher triglycerides. Thus, obese individuals with high triglycerides and TG-wGRS might benefit the most from intense lifestyle modifications and triglyceride lowering products such as omega 3 fatty acids. Further multiethnic population-based studies are needed to assess the effects of weight loss and triglyceride lowering medications across different genetic risk profiles.

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