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Compared to LDL Cholesterol, Incident Cardiovascular Disease is More Frequently Linked to Residual Cholesterol

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Abstract

Hereditary, observational and clinical intercession studies demonstrate that coursing levels of Remainder Cholesterol (RC) are related with cardiovascular sicknesses. However, it is still unclear how well RC can predict cardiovascular mortality in the general population. The 19,650 adults in the United States who participated in our study were drawn from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2014. The Sampson formula was used to divide non-High-Density Lipoprotein Cholesterol (non-HDL-C) by Low-Density Lipoprotein Cholesterol (LDL-C) to arrive at RC. Subgroup analysis, restricted cubic spline analysis and multivariate Cox regression were used to investigate the connection between RC and cardiovascular mortality. Independent of conventional risk factors, elevated RC levels was linked to cardiovascular mortality.

Keywords: Cardiovascular disease • Non-HDL-cholesterol • Remnant cholesterol • Triglycerides

Introduction

A common lipid disorder linked to an increased risk of Cardiovascular Disease (CVD) is atherogenic dyslipidemia, which is characterized by elevated levels of circulating triglycerides and normal levels of Low-Density Lipoprotein Cholesterol (LDL-C) and low levels of High-Density Lipoprotein Cholesterol (HDL-C). Regardless of LDL-C concentration, it is thought to be one of the main contributors to lipid-dependent residual risk. A wide range of chronic cardio-metabolic disorders, including diabetes (pre-diabetes, type 2 diabetes and poorly controlled diabetes), overweight and obesity, metabolic syndrome and renal failure, all have atherogenic dyslipidemia. Atherogenic dyslipidemia is on the rise right now, mirroring the trend of these diseases coexisting and being influenced by an unhealthy lifestyle. Atherogenic dyslipidemia has a lipid profile that is characterized by: 1) a high level of serum triglycerides, which are found in very low-density lipoproteins, intermediate-density lipoproteins and their leftovers; every one of them are known as fatty substance Rich Lipoproteins (TRLs); 2) low groupings of HDL-C; and 3) a lot of small, dense LDLs in high numbers. Despite optimal LDL-C concentrations, all of these characteristics have been linked to an increased risk of cardiovascular disease [1].

The majority of cells are capable of quickly metabolizing triglycerides, but not cholesterol. Therefore, it has been hypothesized that the harmful component of TRLs is cholesterol, not triglycerides. TRLs and the leftover cholesterol (remnant-C) they carry have the ability to cross the arterial wall and are taken up by smooth muscle cells and macrophages. Similar to LDL-C, remnant-C accumulation in the arterial wall may play a causal role in the development of atherosclerosis because human cells typically cannot degrade cholesterol. Additionally, in atherogenic dyslipidemia, TRLs carry more cholesterol (absolute) than LDL and are larger and more prevalent. Therefore, it is not surprising that both observational and genetic studies have linked their remnant-C content to cardiovascular events and total mortality. However, studies on the relationship between triglycerides and remnant-C and Cardiovascular Disease (CVD) have primarily been conducted in north European and U.S. population samples, so there is a lack of information from populations in which TRLs and remnant-C are more prevalent (overweight, obesity and diabetes) as well as from Mediterranean cohorts [2].

Literature Review

In Spain, a randomized controlled trial known as PREDIMED (Prevencion con Dieta Mediterranea) examined the effects of the Mediterranean Diet (Med Diet) *vs.* a low-fat diet on the primary prevention of Cardiovascular Disease (CVD) in high-risk subjects. Diabetes, obesity and metabolic syndrome, conditions linked to insulin resistance, hypertriglyceridemia and atherogenic dyslipidemia, were prevalent among PREDIMED trial participants. Therefore, examining the relationship between triglycerides and TRLs and cardiovascular outcomes was a good fit for this group of high-risk individuals. Regardless of intervention group, other clinical phenotypes (obesity and diabetes), lifestyle confounders related to

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both lipid concentrations and cardiovascular risk, or lipid-lowering treatment, baseline triglycerides, estimated remnant-C and non-HDL-C, but not LDL-C or HDL-C, were associated with major CVD events in a primary prevention cohort of participants at high cardiovascular risk in the PREDIMED trial. The causal role of triglycerides in CVD was confirmed by our findings. In addition, observational studies, post hoc data from the Treating to New Targets trial, and Mendelian randomization studies added to our understanding of remnant-C's atherogenicity. Extremely low-thickness lipoproteins, renovated in the flow, go through hydrolysis by the lipoprotein lipase chemical, becoming moderate thickness lipoproteins and LDLs [3].

Remnant-C is the cholesterol content of the TRLs. In the fasting state, it is made up of very-low and intermediate density lipoproteins and in the no fasting state, it is made up of chylomicron remnants. Due to a delayed metabolism, these partially catabolized TRLs also accumulate cholesterol and are highly atherogenic (Central Illustration). Mechanisms related to atherosclerotic plaque formation and local inflammation may be responsible for the increased risk of MACEs associated with remnant-C. Because remnant-C is more easily captured and taken up by macrophages than LDL, remnant-C is more likely to penetrate the arterial wall, where it accelerates the formation of foam cells. The production of pro-atherogenic adhesion molecules, cytokines (tumor necrosis factor-), Interleukins (IL) (IL-1, IL-6 and IL-8) and cytokines (tumor necrosis factor) that trigger inflammation and the coagulation cascade through plasminogen activator inhibitor 1 may also be induced by residual-C from TRL hydrolysis. This large number of cycles might prompt plaque burst and, thus, MACEs [4].

Discussion

Illustration at the center The PREDIMED cohort found that Very Low-Density Lipoproteins (VLDLs) are remodeled in the circulation by Lipoprotein Lipase (LPL), with ensuing reduction in size, becoming Intermediate-Density Lipoproteins (IDLs) and Low-Density Lipoproteins (LDLs), which are taken up by the liver. Remnant cholesterol metabolism and cardiovascular risk derived from low and high Remn Leftover cholesterol is the cholesterol contained in fatty oil rich lipoproteins, comprised of VLDL and IDL in the fasting state, in addition to chylomicron remainders subsequent to taking care of. Even if LDL-C levels are controlled, the circulating remnant cholesterol concentration, which is highly correlated with triglycerides, contributes to residual cardiovascular risk over time. Due to delayed metabolism, these partially catabolized triglyceride rich lipoproteins become highly atherogenic and enrich in cholesterol in the bloodstream [5].

Triglyceride rich lipoproteins are also more common and larger in atherogenic dyslipidemia and they can carry more cholesterol than LDL. Since most cells can corrupt fatty substances, and none can debase cholesterol, the cholesterol leftovers can be saved in the blood vessel intima to a comparative degree, much more straightforward, than cholesterol from LDL. In the primary prevention cohort of the PREDIMED trial, which consisted of participants with overweight/obesity and diabetes who were prone to delayed triglyceride catabolism, baseline remnant cholesterol was associated with an increased risk of major cardiovascular events, regardless of high or low LDL-C levels. There were at least two ways in which the current population sample differed from those in previous studies that linked triglycerides, TRLs or remnant-C to CVD risk. In the first place, the PREDIMED companion included subjects at high cardiovascular gamble with stoutness (47%) and diabetes (49%) [6].

Subsequently, a significant commitment of leftover C to remaining gamble could be anticipated in these members. Second, the majority of previous studies that demonstrated a causal link between remnant-C and Cardiovascular Disease (CVD) were carried out on population samples from north European and American populations. In Mediterranean regions, where a culturally driven dietary pattern was thought to explain part of the lower incidence of cardiovascular events compared to northern Europe or the United States, there was little evidence for the role of remnant-C in CVD risk. Additionally, this study's analytical models addressed potential confounding factors in the relationship between remnant-C and CVD risk. Information was adapted to potential modulators of TRL science, like weight, diabetes, sex and way of life factors. Furthermore, the findings were unaffected by any ongoing lipid-lowering treatment. A portion of the participants' residual CVD risk was also explained by elevated remnant-C, according to studies of statin-treated cohorts. Patients with high remnant-C levels were more likely to develop coronary artery disease, even when treated with statins [7].

In our cohort of participants with no previous cardiovascular disease but high cardiovascular risk, Remn-C was the primary cholesterol fraction contributor to MACEs; these individuals took statins frequently and had triglyceride levels that were moderately elevated. It was to be expected that MACEs were also independently associated with total triglycerides, which were highly correlated with remnant-C and non-HDL-C, a measure that includes all atherogenic lipoproteins and frequently has a higher predictive value of atherosclerotic CVD than LDL-C when triglycerides are elevated. Members with leftover C levels ≥ 30 mg/dl (75th percentile of the partner) had a higher gamble of MACEs, whether or not LDL-C was at ideal levels (≤ 100 mg/dl; 2.59 mmol/l). Agreeing with the notable expanded cardiovascular gamble of supposed atherogenic dyslipidemia (raised fatty oils and low HDL-C), this blend of lipid modifications, present in 14% of the accomplice, was unequivocally connected with the gamble of MACEs [8].

In high-risk primary prevention subjects not eligible for statin treatment or already treated with moderate or high-dose statins, it could be inferred from the present data that treatment of residual risk, measured as triglycerides or remnant-C, was probably more beneficial than further reducing LDL-C. A few helpful methodologies are accessible to bring down fatty substances and remainder C levels. In subjects with atherogenic dyslipidemia, fibrates have a more profound triglyceride-lowering effect and effectively reduce CVD risk, whereas high-intensity statin treatment only modestly lowers triglycerides. When statin and/or ezetimibe doses have been optimized or there is intolerance to statins, PCSK9 inhibitors can be used, but these medications also have a modest effect on triglyceride levels. Interestingly, high-portion n-3 unsaturated fats, especially icosapent ethyl (ethyl eicosapentaenoic corrosive) and more up to date specialists, such RNA-based antisense-oligonucleotide inhibitors of apolipoprotein C-III and angiopoietin-like 3 qualities, uniquely decrease TRLs. However, even if risk-specific LDL-C targets have been met, randomized clinical trials are needed to determine whether this strategy is superior to a more intensive LDL-C lowering strategy for the prevention of Cardiovascular Disease (CVD), particularly in

subjects who are at high CVD risk and have elevated triglycerides [9,10].

Conclusion

In a group of Mediterranean subjects at high risk with a high prevalence of diabetes and obesity, our findings demonstrated that level of triglycerides and estimated remnant-C, but not LDL-C or HDL-C, were associated with CVD outcomes independently of lifestyle characteristics and other cardiovascular risk factors. Leftover C ought to be viewed as a particular treatment focus in this populace. When LDL-C target levels have been reached, randomized controlled trials with hard CVD outcomes are needed to compare the benefits of interventions aimed at lowering remnant-C to standard cholesterol-lowering therapy.

Acknowledgement

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Conflicts of Interest

None.

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