

Editorial for “Quantitative magnetic resonance imaging assessment of the relationships between fat fraction and R2* inside carotid plaques, and circulating lipoproteins”

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Chronic inflammatory disease atherosclerosis is a leading cause of death worldwide and is considered responsible for more than one-third of all deaths in the United States. American Heart Association (AHA) Consensus Group proposed a histological classification of human atherosclerotic disease with six different categories which indicate the usual sequence of plaque progression (1). According to the influential PARISK study, coagulation, inflammation, lipid

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metabolism, intimal injury, and smooth muscle cell proliferation are the sequential histopathological processes involved in atherosclerotic disease. The study associates lipid-rich necrotic core (LRNC) and intraplaque hemorrhage (IPH) within the atheromatous plaque with increased incidence of plaque rupture that can cause acute cardiovascular disease and stroke (2).

Statin treatment is known to decrease the low-density lipoprotein (LDL) levels and LRNC, further reducing cardiovascular events. However, previous studies trying to correlate LDL with the size of atheromatous plaques, including those with LRNC, have yielded conflicting conclusions, suggesting both the presence and absence of positive correlations. Those research publications relied on operator-dependent post-processing and image assessment of signal alterations in T1, T2*, and proton density (PD) weighted images, but did not yield purely quantitative results of plaque composition. The utilized sequences were also not specific for fat and blood, limiting the accuracy of measurements of LRNC and IPH. The current literature also lacks dedicated research publications investigating the relationship of LDL levels with IPH.

The current prospective study by Good (3) tries to address these issues. The authors have utilized a quantitative MRI (qMRI) technique to directly measure the physical properties of fat (in LRNC) and iron (in IPH) within the atheromatous plaque and the vessel wall of the patients identified with $\geq 50\%$ carotid stenosis on duplex ultrasound doppler and excluded those considered for surgical intervention. High-resolution maps were obtained for the fat fraction (FF) and R2* relaxation rates, the biomarkers for LRNC and IPH respectively, using the four-point gradient-echo Dixon sequence (4). They were generated at baseline and 1-year following intensified lipid-lowering therapy, including intake of statins and ezetimibe. Fasting lipoprotein panel was collected at both times, and the strength of association between the lipoproteins, FF and R2* were assessed by statistical analysis. The changes between the baseline data and follow-up were also analyzed.

The authors found a significant reduction in total cholesterol and LDL levels due to statin therapy and ezetimibe after one year. There was a significant decrease in vessel wall volume at a group level, though not the plaque volume. No substantial reduction in FF or R2* was seen either. No significant correlation could be established between changes in plaque burden and changes in FF and R2* over the year. No significant correlation was seen between changes in FF and changes in R2* at a group level, even though a decrease or increase in plaque parameters was seen at an individual level. The FF values remained comparable between the vessel wall and the plaque. However, R2* was lower in the vessel wall than the plaque, both at baseline and follow-up study.

A study that had analyzed biopsied carotid endarterectomy tissue had showed reduced lipid content in high-grade plaques after three months of statin treatment compared to a group that did not receive statin treatment (5). It is well-established that small lipoproteins and LDL promote plaque progression, and statin intake resulting in decreased LDL reduces cardiovascular events (6). However, just like multiple previous publications, this study also could not establish any linear relationship between the circulating LDL levels and plaque burden and composition of the atheromatous plaque, including its overall size, LRNC, and extent of IPH. The plaque progression and composition are likely influenced not only by the circulating LDL but a wide

variety of factors that can have negative and positive implications on plaque behavior. Multitude other factors like systemic inflammation, diabetes, hypertension, smoking, lifestyle, and genetic factors also influence the plaque formation and progression (7), which were not investigated in this study.

However, compared with previous studies, the study did indicate a slowing of atheromatous plaque progression in response to statin treatment. This may be due to stabilizing changes within the plaque, rendered by statin, regardless of levels of circulating LDL (8). It is now firmly established that the atheromatous disease is not limited to the protruding atheromatous plaque only but is also distributed along the length of the entire vessel wall (9). FF and R2* distribution showed a different pattern between the vessel wall and the plaque, as was quantified for the first time in this study. FF was high in both the vessel wall and the atheromatous plaque; however, R2* levels were lower in the vessel wall than the plaque.

The lack of a control group that did not receive any statin treatment can be considered a scientific limitation of this study. However, in the current state of knowledge that has established the benefit of statin treatment, withholding it would be unethical. The inter-observer analysis was not performed due to the lack of additional team members with a skill set to segment and analyze vessel walls and plaque. This can be addressed in future studies. Radiological structural imaging improvement sometimes lags the functional benefit for the patient but catches up later. The follow-up in this study was limited to only one year. Investigating beyond the timeline of one year might yield a reduction in FF and R2* at a group level, as was seen in a few other studies investigating lipid-lowering therapies (8). Future studies with longer timelines are needed to investigate and confirm this. More aggressive statin therapy with a more ambitious target of cholesterol reduction than < 1.4 mmol/L employed in this study may also yield positive plaque reduction results. With exclusion criteria of patients considered for surgical intervention, generally those with $> 70\%$ stenosis and inclusion criteria of documented $> 50\%$ stenosis, the authors have evaluated only a specific segment of atheromatous disease. Expanding the scope of a study to include a wider swath of atheromatous disease and including subjects with less severe stenosis and more severe stenosis may also yield different results.

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