Interpreting New Thoughts on HDL Through the Lens of Chesapeake Bay’s Tangier Disease

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**Recommended Citation**
Tabacco, John (2023) "Interpreting New Thoughts on HDL Through the Lens of Chesapeake Bay’s Tangier Disease," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 13: Iss. 5, Article 6.
DOI: 10.55729/2000-9666.1243
Available at: https://scholarlycommons.gbmc.org/jchimp/vol13/iss5/6

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Interpreting New Thoughts on HDL Through the Lens of Chesapeake Bay's Tangier Disease

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In March of 2023 an underwater earthquake was felt on the shores of a small and relatively unknown island 15 miles out into the Chesapeake bay. An island with its own English dialect, a vestige of past settlers, Tangier island is literally shrinking due to rising waters lines as well as a population that is seeing its main commerce independent fishing as an increasingly difficult way of life. In 1959 a 5 year old boy on Tangier was discovered by a Navy medical doctor to have enlarged yellow tonsils and hepatosplenomegaly as well as signs of neuropathy. On further investigation at the NIH under Donald Frederickson, MD and Louis Alvioli, MD these were discovered to be the result of a gene deletion in the ABCA1 gene which encodes the ATP binding Cassette, a known system with many functions, one of which is the packaging and exporting of High Density Lipoprotein (HDL) “good” cholesterol from inside the cell's reticulo endothelial system to the general circulation where it can do its work. This mutation essentially leads to drastically reduced HDL cholesterol and reduced apo A-1 lipoprotein causing tissues of the lymphatic system, nervous system, and vasculature to become engorged with accumulation of cholesterol esters entrapped in foamy macrophages. These cells then congest the tissues ability to function properly. Furthermore an increase in atherosclerotic events occur in patients suffering from Tangier’s Disease due to absence of the protective HDL.

Equally important to the discovery of this Genetic disease was the ripple effect that it would have for the next 50 years in medicine both positive and as we would soon find out potentially problematic. This seminal paper by Frederickson Et. Al in 1961 has been referenced by over 250 papers. Spurring on our thoughts as one of the seminal papers that helped our understanding of both HDL cholesterol and its unique role in reduction of harmful LDL cholesterol. Much of this thought has changed however in the last 6 months, as HDL continues to prove enigmatic.

A similar earthquake occurred off of Tangier island, occurred in the lipometabolism world jarring our notion of HDL benefits. In November of 2022 an article was published by the Journal of American College of Cardiology which challenged both traditional notions of how we interpret High density Lipoprotein (HDL) colloquially known as “good cholesterol.” The article concluded that we as medical practioners have perhaps been overstating the benefits of HDL and that perhaps they did not have the protective effect once believed. On a deeper level however what was shown was large differences in how HDL protected white American versus black americans underscoring the need for multiple populations to be included in future studies.

Zakai et al. at Oregon Health & Science University reviewed a population of nearly 23,901 American adults that were prior enrolled in the REGARDS trial revealing that low HDL cholesterol was associated with an increased risk of heart disease in white adults, but not in black adults. Additionally, higher HDL cholesterol levels were not associated with reduced cardiovascular disease risk for either group. The population of patients were enrolled initially to identify racial and geographical differences in America’s stroke belt this registry was given the acronym REGARDS. Study participants were enrolled in the REGARDS study between 2003 and 2007 and followed for 10–11 years.

Elevated HDL cholesterol has been commonly held as a predictor of good cardiovascular health and a protector from poor outcomes such as Coronary artery disease. More concerning of course is that it has often been used in a physicians care of a patient as evidence as to treat or not to treat a
patient with borderline or elevated LDL cholesterol with a statin. Recent evidence from the REGARD study shows it is no longer prudent to possibly avoid the statin you may have been putting off due to elevated high density lipoprotein. Moreso this can further inform that our risk ratio system of evaluating patient health may need increased scrutiny.

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Equally problematic is that Similar to our mostly white Tangier Disease population, many studies completed in the late 20th century were conducted on a white population. The REGARDS study illuminates the importance of not overestimating the protective power of elevated HDL while also underlining the need for more diverse study groups in randomized control trials. Similar to our Tangier disease group who are mostly white, this study shows that low HDL is still a marker of poor health outcomes for white Americans. More studies are necessary to determine what pharmacodynamics are at play in populations that do not benefit from HDL as shown in the REGARDS study.

Conflict of interest

The author declares no conflict of interest.

References