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EDITORIAL

Cholesterol revisited

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ABSTRACT

Medical literature of the last century has been besieged with articles denouncing cholesterol as the main culprit for cardiac disease along with other medical conditions. It is only recently that critical reviews of the literature have more clearly defined the role of cholesterol in both physiological and pathological processes in the body, and it is now being viewed as more of a secondary molecule of concern.

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INTRODUCTION

The famous Framingham Heart Study,[1] starting around 1948, and perhaps the longest ever longitudinal follow up of patients with cardiac diseases incriminated cholesterol[2,3] and hypertension as the main culprits for causing heart disease, a view that is still maintained by the public, as well as several schools of thought in the medical and scientific communities. The evidence for this conviction was initially derived mostly from observational studies of retrospective hospital and community health records; later, it was supplemented and reinforced by finding cholesterol and its esters in the atheromatous plaques of arteries, where it caused tissue damage as well as maintained ongoing inflammation that ultimately resulted in a coronary event in relation to vessel blockage or rupture of the atheroma.[3] This was labelled as the 'smoking gun' and the case for cholesterol as a cause of coronary artery disease appeared to be firmly supported by scientific evidence.

Since then, scientists and medical professionals have embarked on a strenuous campaign to prevent coronary artery disease, and atherosclerosis in general, by food and lifestyle modifications, later augmented by the pharmaceutical industry which brought out a series of cholesterol lowering medications, each successive variety claiming better and better clinical effects.[2,3] Moreover, many randomized clinical trials also supported the role of cholesterol lowering as an effective strategy against coronary artery disease.

Molecular biologists were spurred to look deeper into cholesterol metabolism and how it contributed to endothelial injury and development of an atheroma. In the process, various subunits of total cholesterol were discovered and labelled as 'good' or 'bad' cholesterol based on the concept of their contribution to or prevention of atherosclerosis.[2,3] Additionally, nomograms were established, albeit in multiple versions, for 'normal' blood cholesterol levels to be desirable for healthy arteries that would be clinically relevant to prevent atherosclerosis.[2] These data were vigorously supported by medical organizations globally and continue to be endorsed by organizations such as the American College of Cardiology and the American Heart Association in their guidelines for cardiac health.[4]

However, as for almost everything else, there developed two sides to the coin. Physiologists and biochemists underlined the essential role of cholesterol in the body, particularly its essential role in every cell membrane, as well as being a backbone of hormonal chemistry. As such, the debate ensued about whether cholesterol was as bad as outlined by previous research.[5] Moreover, stringent measures to decrease blood cholesterol to desirable levels did not prevent the development of coronary artery disease or atherosclerosis in general, and some cholesterol lowering medications caused serious side effects as well.[2-5]

The view that emerged from this debate led to a great deal of exoneration of cholesterol as the main risk factor for atherosclerosis and cardiac disease.[6] Cholesterol came to be viewed as an 'innocent bystander' whose presence in atheromatous plaques was due to a 'leaky' or injured endothelium that allowed many blood chemicals to pass through the endothelial barrier into the vascular subendothelium.[7,8] The main insult of endothelial injury caused by factors such as hypertension, smoking, stress, diabetes, and others, subsequently led to the cascade of events that resulted in a plaque, which if not resolved or reversed, progressed to vascular blockage or rupture into the vessel lumen.[2,3] Such a view fit neatly into the observation that lowering blood cholesterol to 'normal values' did not have the desired effect on abolition of the atheromatous process.

There is no doubt that cholesterol can be implicated in the ongoing subendothelial tissue injury and ongoing inflammation that is the hallmark of an established atheroma. If cholesterol did not enter through the leaky endothelium, perhaps there would be limited pathology in the subendothelium which could be resolved by the repair processes of the vascular wall. Therefore, the role of cholesterol should be reviewed as a main factor in maintaining and propagating the atheromatous process, rather than as an initiator of it.

Given such a view, the suggested and recommended guidelines also fall into place, because lowering blood cholesterol would also decrease the entry of more cholesterol molecules into the subendothelium and lessen the ongoing inflammation there. Since cholesterol is actively needed by all cells of the body, certain blood levels would make it difficult for 'extra' unutilized cholesterol in the blood to be passed on into the subendothelium. It also makes sense to keep such optimal levels of blood cholesterol because endothelial injuries are an ongoing event, and if the repair processes are given sufficient time and cholesterol levels are kept low, the chances of the injuries becoming atheromatous would be significantly lessened.

Based on these observations, current and future research should focus on methods to enable extraction of cholesterol from subendothelial sites, or to nullify the cholesterol-induced inflammation through selective chemical mediators and drugs. Such efforts can be aided by nanotechnology that allows guided nanorobots to deliver such helpful molecules to the subendothelium. Nanorobots also offer the promise of acting as molecular surgeons to chip away at bulging atheromatous plaques and allow normal blood flow through the vascular lumen.

A promising avenue for future research includes genetic modifications to reduce the effects of genes that raise cholesterol levels and to strengthen the genetic pathways that maintain healthy cholesterol levels.[3]

A further matter of concern is how to ensure compliance with the suggested guidelines, given that human habits are notoriously difficult to modify. Despite decades of endeavours to have the public comply with smoking cessation policies, prevalence of smoking is still high even among the educated population, including the medical community. Indeed, newer forms of smoking materials have emerged in recent decades.

Similarly, the consumption of foods rich in fats has not declined, rather we see a recent increase in such habits after most saturated fats were delisted as molecules of concern by various authorities. It appears that long range sustained efforts will have to be undertaken, including the non-availability of foods seen as unhealthy from the marketplace, and mandatory annual medical checkups to detect early signs of any disease process, before we are able to label human health as free from the risks of major health issues, including cardiac disease.

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