Cholesterol: a Century of Research and Debate

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To The Editor: The excellent article by Dr Elmehdawi RR entitled "Hypolipidemia: A word of caution" has once again shown the multifaceted properties of cholesterol which is the most highly decorated molecule in biology [1]. Thirteen nobel prizes have been awarded to scientists who devoted major parts of their careers to cholesterol [2].

The word cholesterol is derived from the Greek words, chole= bile; steros= solid; ol= alcohol. Ever since it was first isolated from gallstones in 1784, cholesterol has exerted a hypnotic fascination for scientists from most diverse domains of science and medicine. Organic chemists have been fascinated with cholesterol because of its complex four ring structure with its steroid nucleus. Biochemists have also been interested because cholesterol is synthesized from a simple two-carbon substrate, acetate, through the action of at least 30 enzymes. Besides, cholesterol drew the attention of physiologists and cell biologists because of its essential function in animal cell membranes, where it modulates fluidity and maintains a barrier between cell and environment and being the raw material for the manufacture of steroid hormones and bile acids. Physicians started studying cholesterol after it has become evident that elevated levels of blood cholesterol accelerate the formation of atherosclerotic plaques leading to heart attack and stroke. Over the course of nearly a century of investigation, researchers have developed four lines of evidence: experimental, genetic, epidemiologic, and therapeutic - that irrefutably established the causal connection between cholesterol carrying low density lipoprotein (LDL) and atherosclerosis [3]. Few other major diseases have been subject to such intensive and ultimately fruitful research. Building on that knowledge scientists have been successful in developing an effective course of therapy – the statin drugs which are inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG CoA reductase), the rate limiting enzyme in cholesterol biosynthesis.

High –density lipoprotein (HDL) cholesterol represent a strong inverse predicator of cardiovascular events. Recent studies have illustrated the clinical significance of high-density lipoprotein cholesterol in patients with low levels of low-density lipoprotein cholesterol [4, 5]. HDL cholesterol levels were predictive of major cardiovascular events in patients treated with statins. This relationship was also observed among patients with LDL cholesterol below 70 mg per deciliter.

As suggested by Dr Elmehdawi, caution needs to be asserted as we focus on aggressive management of hyperlipidemia due to the possible complications of drug induced hypolipidemia including intracerebral hemorrhage and sepsis [1]. There has been controversy in the literature concerning the contribution of hypercholesterolemia to subsequent development of dementia [6]. Longitudinal studies have established that midlife elevated serum cholesterol level is associated with an increased risk of subsequent Alzheimer's disease [7].

However, two large randomized controlled trials failed to show that statins (pravastatin and simvastatin) reduced dementia [8, 9]. Hypocholesterolemia is also a predisposing factor for infection in certain conditions as well as a prognostic indicator during sepsis [1]. But a recent systematic review, which analyzed studies of the literature comparing the outcome between statin and non- statin users among patients suffering from sepsis or other infections, reported a major consensus that statins may have a positive role in treatment of patients with sepsis and infection [10]. Heart failure (HF) is a common and a serious condition that is usually due to coronary artery disease (CAD). Hypercholesterolemia is a major risk factor for CAD but, paradoxically, patients with advanced HF often have low cholesterol, which is associated with poor prognosis [11]. Hence, even after 200 years of first being isolated, and nearly 100 years of fruitful research, this Janusfaced molecule continues to evoke controversy, and the debate on the role of cholesterol in biomedicine and the future direction of cholesterol-lowering therapy continues.

References

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