

Paradoxical mortality differential of HDL cholesterol



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ABSTRACT

High-density lipoprotein (HDL) cholesterol has been known for ages to be cardio-protective due to its defensive action against genesis of atherosclerosis. Increasing the serum HDL cholesterol (HDL-C) as a prospective potential to prevent coronary heart disease could not prove beneficial in human trials that put forward a major concern about the role and functional contribution of HDL-C in human health. Many observational studies indicated that extreme high value of serum HDL-C is often associated with high cardiovascular mortality; therefore could be considered as detrimental for healthy survival. Furthermore, observational and genetic studies revealed a possible link between extreme low serum HDL-C and development of common noncardiovascular diseases such as infectious disease, autoimmune disorder, malignancy, type-2 diabetes, kidney, and pulmonary diseases. This review endeavors to update on the various reasons of mortality observed with extreme values of HDL-C reflected in the recent studies along with the probable role of HDL-C in the pathogenesis of these ailments.

Key words: High-density lipoprotein-cholesterol; Coronary heart disease; CHD-LDL, CHD, LDL

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INTRODUCTION

PARADOXICAL MORTALITY DIFFERENTIAL OF HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL

HDL cholesterol (HDL-C) has been considered as the good cholesterol for ages that prevents the atherosclerotic cardiovascular disease or coronary heart disease (CHD); has been supported by umpteen number of observational studies showing high risk of CHD among individuals having low serum concentration of HDL-C.¹ The higher the better concept percolated in late 90s to avert CHD and the reliance in HDL-elevating agents appeared so promising worldwide, that human trials with 4 major cholesteryl-ester-transfer-protein inhibitors (CETP-i) known to increase serum HDL-C were used in randomized trials to ascertain the beneficial effect of surged HDL on the prevention

of CHD.²⁻⁵ CETP-i agents effectively increase HDL-C, but trials in the long run revealed the deleterious effects of these drugs with higher risk of CHD even associated with higher incidence of all-cause mortality.² Enumerable no. of studies thereafter documented that very high levels of HDL never assure lower risk of CHD; and the same was found even equally applicable for certain genetic conditions having elevated HDL-C.⁶⁻⁸ It appears possible that clinicians may come across patients with very high and low values of HDL-C in their day-to-day practice needing set strategies for dealing with such conditions. Considering the findings of the earlier studies, it was decided to review the literature for deliberation on the bimodal mortality trend in relation to very high as well as low levels of serum HDL-C concentration and recommend suitable approach for the treating physician under actual clinical settings.

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THE OPTIMUM LEVEL OF HDL-C

Studies in the past revealed that higher value of HDL-C in serum is not inevitably the better and conducive for positive health and longevity.⁹ Extensive population-based data from the UK and US divulged the paradoxical correlation between blood HDL-C concentration and mortality due all-causes where the latter has been registered significantly high in very high and very low HDL-C level conceding an optimum level of HDL concentration of 1.5–1.99 mmol/L or 58–77 mg/dL favourable for healthy survival.¹⁰⁻¹² All-cause mortality was observed to be the least among the cohorts having HDL level in the optimum range 1.3–1.8 mmol/L or 50–70 mg/dL; however, the mortality was bi-modally higher among those who had HDL-C either above or below the optimum range.

Figure 1 shows the population distribution of HDL-C in general and bimodal high mortality with extreme values of HDL-C serum concentration. 73% men and 75% women showed serum HDL-C level in the range of 1–2 mmol/L or 39–77 mg/dL. The high mortality association due to all-causes is related to the extreme values of serum HDL-C giving U-curve depicted by blue dotted line. Subjects in the optimal range of HDL-C between 50 and 70 mg/dL had the lowest mortality.

HIGH MORTALITY VERSUS HIGH SERUM HDL-C

High mortality with high serum HDL-C could be due to presence of unaccounted confounding factors that result in both high mortality and surge in HDL-C as revealed by Hamer et al.,⁹ and similar studies in the past; the same has been attributed to the effect of high TG (triglyceride)

and LDL-C (low-density lipoprotein) in serum along with disparity between functionality vis-a-vis biological composition of very high values of serum HDL-C.¹³

High mortality observed with extreme high values of HDL-C has been reported by many studies in different population settings, however, the reason for this association is not known. Several contributory possibilities have been documented in relation to this association.¹⁴ It has been documented in the polygenic determinants of extreme values of HDL-C study that 11% subjects had high HDL-C in contrast to 19% having low HDL-C as carriers of rare variants of gene¹⁵ and such conditions potentially manifested effect on human system with higher risk of disease and death reported in many studies especially related to CHD.¹⁶⁻¹⁸ Hypothetically it is possible that high concentration of serum HDL-C can alter the function and composition of HDL-C so that it causes entrapment and deposition of cholesterol in arterial intima like LDL compromising athero-protective effect of helping in reverse transport of cholesterol to liver.^{13,14,19} Alcohol consumption also interplay as a confounding factor by elevating HDL-C level¹⁰ and studies reported that high HDL among alcoholics having higher liver enzymes had higher all-cause mortality.²⁰

HIGH MORTALITY VERSUS LOW SERUM HDL-C

Infectious disease

Infectious diseases and associated septicemia with high risk of mortality were observed having link with low serum HDL-C concentration in Copenhagen City Heart Study.²¹ Similar associations have been confirmed by observational and genetic analytical study of UK Biobank data.²² HDL has

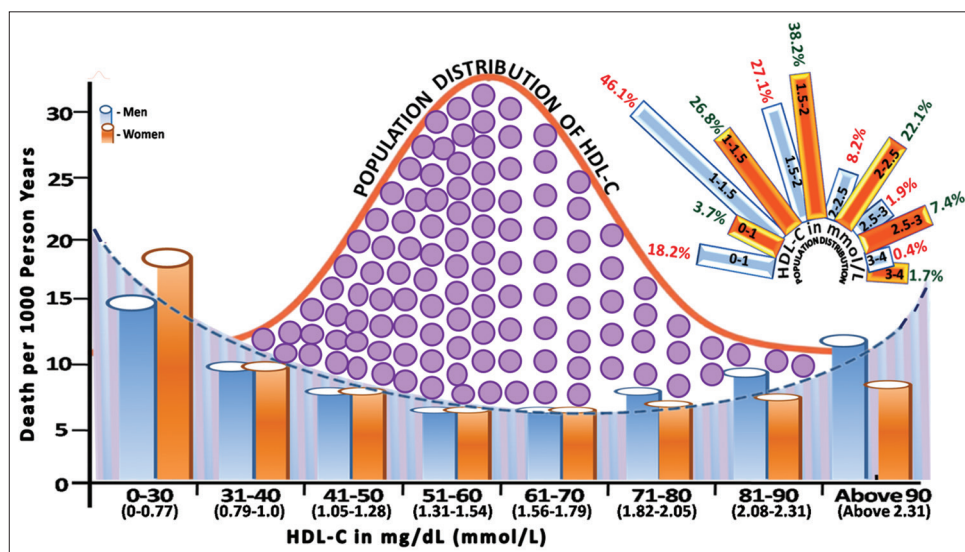


Figure 1: Bimodal high mortality with extreme values and population distribution of HDL-C. (Data taken from ref no. 10 and 12 for graphical representation)

probable role in clearance of pathogenic molecules from blood through macrophage action, thereby restricting the progress of inflammatory process.²³ CETP itself may have a significant role in inflammation control and clearance of bacterial load from the system through possible function of HDL in mitigating infections, thereby inflammation in the early stage.²⁴ Figure 2 depicts the distinctive mortality trend at the extreme values of serum HDL-C. While infectious disease, auto-immune disorder, cancer, type-2 diabetes, renal & pulmonary diseases cast the mortality shadow at the lower-most end of the spectra; fatality due to CHD, alcohol & dysfunctional HDL-C related disorders overcast the high-end values of serum HDL-C.

Autoimmune disease

Low to very low serum concentration of HDL-C with shrinking functional capacity was found associated with many common autoimmune disorders like rheumatoid arthritis, inflammatory bowel disease, psoriasis and SLE.^{25,26}

Similar findings have been documented in Copenhagen General Population Study and Copenhagen City Heart Study in prospective analyses.²⁷ Certain apolipoprotein M bound receptors in HDL-C are chosen as pharmacotherapeutic receptors for modulator drugs that help in treatment of autoimmune diseases such as multiple sclerosis and ulcerative colitis, giving an indirect evidence of connection of lipid mediators with autoimmune disorders.^{28,29} However, all such observational studies don't allow concrete assumption of causal effect due to the possibility of unknown confounders and causation.

Malignancies

Many observational studies in the recent past documented a significant association of low serum HDL-C with higher risk of cancer.³⁰ Women's Health Study revealed that the cancer risk was lower in subjects with high HDL-C level (hazard ratio: 0.85 [95% CI, 0.75–0.97]) against those having the low.³¹

Copenhagen General Population including Copenhagen Heart Study documented that low levels of HDL-C and apolipoprotein A1 were associated with increased risk of several cancers most preponderantly hematologic and neural malignancies and to a minor extent involving breast and respiratory tissues.³² Some cancers manifest in high levels of LDL receptor to gain lipids from LDL and others express in SCARB1 receptor (Scavenger receptor) to derive lipids from HDL.³³ Thus, HDL perhaps add to the progress and development of certain types of cancer but not all making its actual role and function in cancer aetiology unclear.

Type-2 diabetes mellitus (T2DM)

T2DM patients often manifest with dyslipidemia having high triglycerides with low serum HDL-C.³⁴ No. of observational works in the past consistently showed association of low serum HDL-C with risk of developing T2DM.^{35,36} Genetic studies have been generally inconclusive in the context of association between the genetically determined low serum HDL-C and higher incidence of T2DM.³⁷⁻³⁹ Indirectly, CETP inhibition was found associated with better glycemic control and lesser incidence

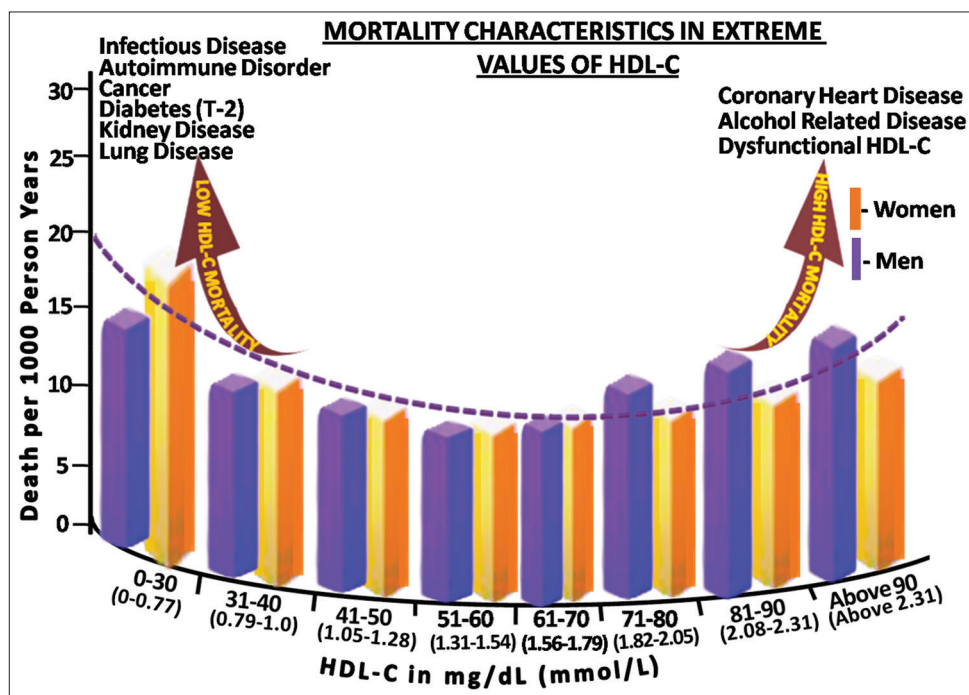


Figure 2: Bimodal high mortality with extreme values of serum HDL-C and the characteristics of disease association at both ends

of diabetes.

Torcetrapib (CFTP-i) and other similar pharmacological agents showed comparable results among pre-diabetics.^{40,41} However, these findings of better glycemic control and lesser risk of diabetes with CETP inhibitors are clouded with so many confounders that causal conclusion remained undecided.

Reduced renal functions

Many cohort studies documented a connection between low HDL-C to enhanced risk of nephropathy and reduced renal function.⁴²⁻⁴⁴ Mendelian randomization studies using genetic variants of HDL-C reported a supporting causal association between higher HDL-C and heightened kidney function.^{45,46} A meta-analysis of patients with chronic kidney disease on treatment with fibrates registered a significant reduction in albuminuria, along with an undesirable reduction in estimated glomerular filtration rate (e-GFR) without much effect on the outcome of end-stage renal disease (ESRD).⁴⁷ Therefore, it remained inconclusive to determine the possible role of fibrate induced high HDL-C on renal function not only due to conflicting nature of the final outcome but also due to the restricted ability of fibrates to augment serum HDL-C as compared to their concurrent effects on the triglycerides and LDL-C. Notwithstanding the effect of fibrates on e-GFR and ESRD, many observational and genetic data support that low serum HDL-C is convincingly associated with decreased kidney function resulting in the possibilities of fatally incriminating kidney disorders.

Pulmonary disorders

HDL with apolipoprotein A1 were proposed as one of the most probable leads for the interception and treatment of various pulmonary disorders including no. of common lung diseases.⁴⁸ Interestingly, significant and convincing clues were detected linking HDL to the physiology of pulmonary function; and many observational studies also documented an important association between low HDL-C and risk of the lung disease including shrinking pulmonary function.⁴⁹

On the other hand, many studies reported that the association between low serum HDL-C and risk of bronchial asthma among children is mostly inconsistent and inconclusive.⁵⁰⁻⁵⁴ Although some of the works put forward an association between low HDL-C and asthma among children, while others not.⁵⁰

However, high HDL-C has been reported with better pulmonary function, reduced broncho-mucosal sensitivity and attenuation of aerosolized allergen sensitization; and interestingly in asthmatic patients, higher serum HDL-C, and apolipoprotein A1 were seen manifested with less

airflow difficulty and lower counts of eosinophil in the blood.^{55,56} May be, it is apparently indicating the possibility of HDL and apolipoprotein A1 actionable as therapeutic medium in asthmatic conditions,⁴⁸ but findings of such observational studies need credible confirmation of causal relation through suitable studies to resolve unknown confounders and inconsistent observations.

CONCLUSION

HDL-C level in blood has a significant contribution in formulation of strategies for calculation of cardiovascular risk and starting of lipid-lowering drugs.^{57,58}

In 2019, European Society of Cardiology and European Atherosclerosis Society in the clinical advisory for comprehensive control of dyslipidemia acknowledged lipid modification to decrease cardiovascular risk; actually subdued certain facts about HDL-C.⁵⁹ On the basis of observations from the Copenhagen General Population Study and the Copenhagen City Heart Study, it was advocated that extreme high values of HDL-C >2.3 mmol/L or 90 mg/dL should not be considered a good prognostic index and such subjects need to be instituted with lipid lowering agents.⁵⁹

Observational studies reflected that treating physicians should not merely infer that high HDL-C is always connected with a good prognosis and better health prospect. Actually, it appeared convincing to imply cautious clinical assessment and continuum-care of subjects with very high HDL-C to ascertain possible ways of negating the effect of other allied risks that may compound high HDL-C risk more. In this accord, the cutoff levels of HDL-C for drawing clinician's attention should be 2.0 mmol or 77 mg/dL and 2.5 mmol or 97 mg/dL for men and women, respectively. In such condition with very high HDL-C, the predictor value of ratios of total cholesterol and LDL-C to HDL-C may not always hold true.

Effect of HDL-C on immunity has been emphasized by numerous studies having implications on several major and minor non-cardiovascular diseases.⁶⁰ In these diseases, the deranged immune system has been linked with HDL-C level in the subjects. However, such findings are mostly drawn from the observational studies, therefore, convincingly do not assert any conclusive causal association and need careful interpretation on clinical application.

Animal experimental and human genetic studies are needed to ascertain a cause and effect relationship of HDL-C in the pathogenesis of common non-cardiovascular diseases. While HDL-C raising - a probable therapeutic

mode for the prevention of CHD proved scientifically counterproductive, yet the role of very low HDL-C in the genesis of many non-cardiovascular diseases merits attention for future research for widening the existing knowledge on the extra-cardiac role of HDL-C.

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JM- Principal Investigator, Concept and design of the study, prepared the first draft of manuscript; **DM**- Statistical analysis and interpretation, manuscript preparation, literature review and revision; **SG**- Collection and compilation of data, coordination.

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