

Lipids in aging and chronic illness: impact on survival

Csaba P. Kovesdy^{1,2}, Kamyar Kalantar-Zadeh^{3,4}

¹Division of Nephrology, Salem Veterans Affairs Medical Center, Salem, VA, USA

²Department of Medicine, University of Virginia, Charlottesville, VA, USA

³Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA

⁴David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Submitted: 28 November 2007

Accepted: 17 December 2007

Arch Med Sci 2007; 3, 4A: S74-S80
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Corresponding author:

Csaba P. Kovesdy, MD
Division of Nephrology, Salem
VAMC
1970 Roanoke Blvd., Salem,
VA 24153
Phone: 540 982 2463
Fax: 540 224 1963
E-mail: csaba.kovesdy@va.gov

Abstract

Hypercholesterolemia has been implicated as a risk factor for atherosclerosis by numerous observational studies in the general population. Observational studies in patients suffering from various chronic illnesses and in individuals with advanced age have indicated an inverse association between cholesterol level and mortality, suggesting that the classical Framingham paradigm may not apply to these groups. It is yet unclear what the reasons for these paradoxically inverse associations are. We present a summary of the descriptive studies that have examined the association between cholesterol levels and outcomes in a variety of patient groups. The various possible mechanisms behind the observed "lipid paradox" and the potential implications of reverse epidemiology of hypercholesterolemia in clinical medicine and public health are discussed.

Key words: lipids, mortality, chronic kidney disease.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in the general population [1]. Our current knowledge on the risk factors that are instrumental in the initiation and propagation of ASCVD was originally established by the Framingham study [2-6] and later corroborated by other observational studies. These studies have established a strong association between risk factors such as hypercholesterolemia, obesity, hypertension, and diabetes mellitus, and ASCVD-related outcomes. The early association studies were soon followed by randomized controlled trials aimed at correcting some of these risk factors, and which ultimately established a causal link between the risk factors and the subsequent outcomes [7-10]. These studies have had an immense impact on clinical practice, since they established therapeutic paradigms that promised to prolong the lives of large masses with interventions that were safe and easy to implement.

Hypercholesterolemia is one the best examples to indicate how knowledge gained from observational studies and subsequent interventional trials was successfully transplanted into mass-therapeutic interventions with a population-wide impact. The success of cholesterol lowering therapy for primary, secondary and tertiary prevention has

inevitably led to a desire to extend these beneficial treatments to as many patients as possible. This desire appeared especially warranted in the case of patients with a higher burden of ASCVD, where interventions based on the now widely accepted cholesterol-ASCVD paradigm should have reaped the most benefit.

It came, however, as a surprise that a number of observational studies in several distinct populations with a high ASCVD burden, such as individuals with chronic heart failure or end-stage kidney failure, failed to show the classical association between higher cholesterol and worse outcomes that we came to expect, and indicated that higher cholesterol was paradoxically associated with better outcomes [11-16]. Questions still abound about the meaning of these studies and their therapeutic relevance. We present an overview of the cholesterol-ASCVD relationship in various patient populations that display a reversal of the classical Framingham cholesterol paradigm, the so-called "lipid paradox", and discuss possible explanations for this phenomenon.

Populations with an inverse association between cholesterol level and mortality

Chronic kidney disease

Almost 20 million Americans suffer from chronic kidney disease (CKD), of whom 400,000 individuals have end-stage (stage 5) CKD and need maintenance dialysis [17]. Dialysis is a life-saving procedure, but the yearly mortality rate in patients undergoing maintenance dialysis is about 20%, which is worse than what is seen in many cancers, and is mainly a result of cardiovascular causes [18]. Whereas patients on dialysis are indeed suffering from a higher burden of the diseases linked to cardiovascular morbidity and mortality in the Framingham paradigm, observational studies that attempted to establish a link between classical risk factors such as obesity, hypertension and hypercholesterolemia, and cardiovascular outcomes have indicated a reversal of the expected relationship [16, 19-21]. These apparently counterintuitive associations or survival paradoxes have been referred to as "reverse epidemiology" [22, 23].

Several studies indicate that low, rather than high, serum total cholesterol and LDL are associated with poor survival in dialysis patients [11-13, 15]. Recently Kilpatrick et al. [16] showed that the "cholesterol paradox" is universal across subgroups of dialysis patients except for African Americans, in whom higher LDL was associated with worse survival, a so-called "paradox within paradox". In an attempt to explain the inverse association between cholesterol level and mortality in patients on dialysis Liu et al. showed that higher total cholesterol was, in fact, associated with increased

mortality in a subset of patients without evidence of inflammation and malnutrition, while patients with such evidence retained the inverse association that was the characteristic of their overall patient cohort [14]. A similar interaction was described by Iseki et al. who showed higher mortality with higher total cholesterol only in dialysis patients with serum albumin levels higher than 4.5 g/dl [13]. These results implied that lower total cholesterol was in fact a surrogate marker of inflammation and/or malnutrition, hence therapy directed toward lowering cholesterol should not be withheld, especially given the additional, potentially beneficial non-lipid-related effects of statins, the most widely used cholesterol-lowering drugs [24, 25]. Based on this it came as a surprise that the only completed clinical trial aimed at improving outcomes through lipid lowering with a statin in diabetic patients on dialysis, Die Deutsche Diabetes Dialyse Studie (the 4D Study), [26] did not show a significant reduction in the composite outcome of death from cardiac causes, non-fatal myocardial infarction and stroke. The latter finding puzzled those who were contending that the reverse epidemiology of cholesterol would be an exclusively statistical phenomenon without any biological plausibility.

Until recently it was believed that the counterintuitive phenomenon of reverse epidemiology is restricted to dialysis patients and that the vast number of individuals with moderate degrees of CKD (stages 3 and 4) who are not on dialysis would follow the "Framingham paradigm". However, even CKD in its earlier stages is considered a strong and independent predictor of cardiovascular mortality, [21, 27-29] with death being far more common than progression towards end-stage in CKD [27]. Supporting the idea that the *cholesterol paradox* seen in ESRD can also be detected in patients with earlier stages of CKD, a cohort study in 986 men with CKD stages 1 to 5 not on dialysis showed an inverse association between lipids and survival [30]. Exploring the confounding effect of co-morbid conditions and the malnutrition-inflammation complex this study found the inverse association between cholesterol and mortality attenuated, but not reversed after multivariable adjustments [30].

Congestive heart failure

Individuals with congestive heart failure (CHF) currently number approximately 5 million in the USA and show striking similarities to CKD patients. Both patient populations have a high prevalence of comorbid conditions, a high hospitalization rate, a low self-reported quality of life, and an excessively high mortality risk, mostly due to cardiovascular causes [18, 31]. CHF patients with hypercholesterolemia have also displayed lower mortality

[32-35] and lower serum cholesterol is associated with higher death risk in these patients [32].

Geriatric populations

There are currently over 10 million octogenarians and nonagenarians in the USA, and their proportion is growing [36]. The incidence of cardiovascular disease in the elderly is high [37]. A reversal of the traditional relationship between cardiovascular risk factors and survival outcomes has also been observed in these populations. Although not regarded as a universal finding, but several studies have indicated that low, rather than high total and LDL cholesterol levels have been associated with increased mortality in the elderly [37-41].

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) affects approximately 16 million Americans and is the fourth leading cause of death worldwide [42]. Cardiovascular mortality accounts for roughly 50% of deaths in COPD patients, [42] but the relationship between cholesterol and mortality is reversed in these patients too. While studies examining cholesterol and outcomes in COPD are sparse, one large study found a trend towards lower risks of hospitalizations and death in men with COPD who had higher cholesterol levels [43].

Acquired immune deficiency syndrome (AIDS)

HIV infection and AIDS has been associated with accelerated rates of atherosclerosis and cardiovascular disease [44]. The association between classical risk factors of CVD and outcomes

in HIV and AIDS is complex, since highly active antiretroviral therapy can be associated with changes in body composition including lipodystrophy, and may induce an atherogenic lipid profile [44, 45]. Nevertheless, low BMI, weight loss, and low total cholesterol have all been associated with poor prognosis in AIDS populations [46, 47].

Cancer survivors

Observational studies have shown that among the 13 million American survivors of cancer higher blood lipid levels are associated with better survival [48].

Pathophysiology of lipid paradox

Several hypotheses have been advanced to explain the lipid paradox in such chronic disease states as CHF and CKD that are associated with wasting (Figure 1).

Time-discrepancy of competing risks

Survival advantages that exist in hypercholesterolemic individuals with chronic disease states may, in the *short-term*, outweigh the harmful *long-term* effects of these risk factors in causing cardiovascular disease and death [22]. Dialysis patients may not live long enough to die of the adverse effects of high cholesterol, because they are more likely to die from consequences of undernutrition [20]. The time discrepancy or differential between these two sets of competing risk factors can explain why the treatment of hypercholesterolemia may be practically irrelevant in individuals with chronic disease states and high rate of short-term death, in whom long-term

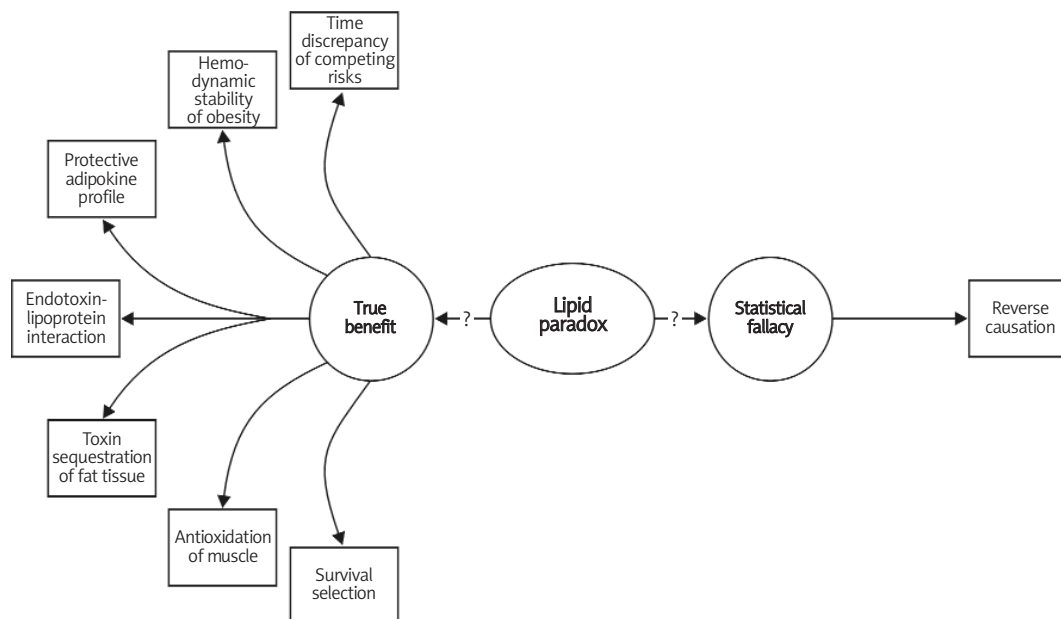


Figure 1. Putative mechanisms of action responsible for the “lipid paradox”

survival is quite low. Currently 2/3 of all dialysis patients in the USA die within 5 years after starting dialysis, which is worse than the mortality of many cancer patients [20]. Similar to dialysis patients, the short-term mortality in most populations with chronic disease states is excessively high as a result of their protein-energy wasting conditions. Such individuals will not live long enough to die of consequences of hyperlipidemia, which need years to decades to exert their deleterious impact on survival.

Altered lipoprotein metabolism

Under uremic circumstances the metabolism of atherogenic lipoproteins such as LDL, IDL and HDL is altered, and is characterized by lowered catabolic rates along with decreased production rates [49-52]. This results in an overall longer half life in spite of net "normal" plasma concentrations. The modification of these lipoproteins by inflammation, oxidation, carbamylation and glycation is more pronounced (due in part to the longer residence time and to the effect of the uremic milieu), which can then lead to an enhanced atherogenic potential [53]. The plasma level of these lipids may not be a good measure of their atherogenic potential; hence the term *dyslipidemia* (rather than *hyperlipidemia*) may be a more appropriate term to use in patients with CKD. Illustrating this concept, a recent study showed that a higher pro-inflammatory to anti-inflammatory HDL ratio was associated with increased death risk in dialysis patients [54]. While the altered lipoprotein metabolism clearly adds an additional layer of complexity to this issue, it does not explain the linear inverse association between the traditional lipid levels and mortality in patients with CKD, and it also does not explain the same association in patient groups with other chronic diseases who have normal kidney function.

Mechanisms related to obesity

With cholesterol level being a surrogate marker of nutritional status, physiologic mechanisms linked to the individual's nutritional status could provide additional explanations for the better survival seen with higher cholesterol levels. Several hypotheses exist about how obesity might be beneficial in the short term. Obesity may be associated with a more stable hemodynamic status, and it may mitigate stress responses and heightened sympathetic and renin-angiotensin activity [55]. The altered cytokine and neuroendocrine profiles of obesity could also confer a relative survival advantage: increased production of adiponectines [56] and soluble tumor necrosis factor alpha receptors [57] by adipose tissue may neutralize the adverse effects of tumor necrosis factor alpha. Higher catabolic rate in cachexia may lead to generation of excessive amounts of

toxic metabolites; these can be more effectively sequestered when abundant adipose tissue is present [58]. Indeed weight loss and reduction in adipose tissue reserve is associated with the imminent release of, and significant increase in circulating lipophilic hexachlorobenzene and other chlorinated hydrocarbons [59]. A recent study in dialysis patients showed that obese patients had a relatively smaller proportion of the so-called "high metabolic rate compartment" and viscera, [60] whereas patients with a lower body mass or BMI had a higher proportion of these urea generating compartments relative to their body size. These findings may provide an explanation as to why loss of body fat has recently been found to be associated with increased death risk in dialysis patients [61]. Weight loss may also be associated with reduced skeletal muscle oxidative metabolism, leading to a weakened anti-oxidant defense [62].

Endotoxin-lipoprotein hypothesis

Higher concentrations of lipoproteins may confer a survival advantage in chronic disease states, since lipoproteins (including circulating cholesterol molecules) can actively bind and neutralize circulating endotoxins, hence attenuating the propensity of the endotoxins to cause inflammation, accelerated atherosclerosis and poor outcomes [63]. This so-called "endotoxin-lipoprotein" hypothesis was originally introduced to explain the seemingly protective role of hypercholesterolemia in cardiac cachexia of CHF patients [64]. Hence, it is possible that higher circulating cholesterol levels play a protective role against the deleterious effect of endotoxins that may be more frequently absorbed from leaky guts in the setting of edematous states such as in dialysis or heart failure patients [62, 63].

Reverse causation

It is possible that lower cholesterol is not the cause but merely a consequence of conditions that lead to poor outcomes in patients with chronic disease states who exhibit a paradoxical risk factor profile. Reverse causation is a known possible source of bias in epidemiologic studies that examine associations without a clear distinction for the direction of the causal pathway [65]. While it is plausible to attribute the association between low cholesterol and higher mortality to reverse causation, this fails to explain why high cholesterol is associated with better outcomes in the populations discussed above.

Survival selection

Out of approximately 300 million Americans only 10 to 11 million (5 percent) are older than 80 years. Reaching such an advanced age could be viewed

as a "survival selection", and there is a possibility that affected individuals are genetically protected against the ravages of cardiovascular disease and other fatal conditions. A similar explanation can be used for dialysis patients who represent the 5% survivors of the entire spectrum of CKD, as are CHF patients who are the survivors of a large population with cardiovascular disease [20, 66]. Hence, geriatric populations or dialysis or CHF patients could be genetically and/or phenotypically dissimilar to their peers who did not survive. The "survival selection" hypothesis, however, cannot explain the survival paradoxes observed in other chronic disease states such as rheumatoid arthritis or in patients with earlier stages of CKD, nor can it explain why the described paradoxical associations reverse and become yet again "conventional" in dialysis or CHF patients after successful kidney or heart transplantation [18, 67].

Clinical and public health implications of "Reverse Epidemiology" for lipid management

In today's environment of ever growing patient numbers, shorter doctor visit times, institutional and regulatory pressures to implement population-wide "standardized" interventions, and aggressive pharmaceutical marketing campaigns, it is not surprising that a one size fits all type of approach to cholesterol management appears very enticing. It is still unclear how this approach will be affected by the evidence amassed in the above cited observational studies. The field of reverse epidemiology is still in its infancy, and up to this point it has generated more questions than answers. The biologic plausibility of the inverse associations between cholesterol level and mortality still needs to be elucidated. Therapeutic targets need to be clarified by designing randomized controlled trials specifically targeting the affected patient populations. We caution against dismissing all the observational data purely because they contradict established paradigms.

To date there are tens of millions of patients who display high morbidity and mortality from chronic disease states, and whose disease courses and outcomes appear to be different than that of the population of Framingham, MA more than 40 years ago. While there are no clear answers yet to guide therapy in these patients, the realization of what we don't know is a very important step in scientific discovery. Today the field of reverse epidemiology is where conventional epidemiology was 40 years ago. Time will tell how it will evolve; at least the questions surrounding the role of cholesterol may soon have a more definitive answer, once the results of ongoing randomized controlled trials in affected patient populations will become available [68, 69]. For the time being we cannot advocate a change in current

clinical practices, given the lack of prospective studies testing the role of cholesterol in patients with chronic illnesses. Changing our current practice pattern could take 40 or more years, but we may one day prescribe cholesterol-raising medications to certain patients. After all, paradigm shifts can lead to scientific revolutions [70].

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