Association between Inflammation and Malnutrition as Risk Factors of Cardiovascular Disease

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Key Words

High-density lipoprotein · Vascular endothelium · Sarcopenia

Abstract

Cardiovascular disease is the leading cause of death among dialysis patients. The relative risk of mortality increases as serum albumin concentration and body mass index decline. While these are generally associated with nutritional status, inflammation causes sarcopenia and decreased albumin concentration by reducing synthesis of proteins and increasing their catabolic rate. While inflammation can arise from atherosclerotic blood vessels, systemic inflammation from any source can alter the vascular endothelium and plasma protein composition in ways that promotes vascular injury. High-density lipoprotein synthesis is decreased and the high-density lipoprotein present is less capable of reducing inflammation. Activation of neutrophils favors lipoprotein oxidation. Surprisingly, while obesity is associated with cytokine production in patients without renal failure, as well as among dialysis patients, increased body mass index, whether reflecting muscle mass or adipose tissue, is associated with a decline in mortality rates.

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The incidence of cardiovascular events and death from cardiovascular disease is massively increased in dialysis patients [1]. Hypoalbuminemia, thought to be primarily an indicator of malnutrition, was recognized as having a strong association with mortality in these patients [2]. Subsequently, it became recognized that serum albumin concentration was controlled at least in part by inflammation by its association with C-reactive protein (CRP) [3] and proinflammatory cytokines [4]. Isolated protein calorie malnutrition does not lead to hypoalbuminemia except at preterminal levels of starvation [5].

Body composition is affected by both nutrition and inflammation [6]. While inadequate nutritional intake can result in a decrease in serum albumin [7] and muscle protein wasting [7, 8], inflammation can also affect these nutritional measures [9, 10]. Indeed, malnutrition alone, except preterminally [5], has very little effect on plasma protein composition. It is the combination of both malnutrition and inflammation that effects the greatest change [11]. Inflammation, acting through nuclear factor- κ B stimulates ubiquitin-mediated proteolysis of muscle leading to muscle protein catabolism [12] and impairs repair mechanisms [13] leading to loss of muscle mass [14]. Thus, inflammation plays an important role in mediating loss of muscle mass [12, 15]. This in turn leads to reduction in creatinine generation [16]. The decline in serum creatinine, reflecting a decline in creatinine generation, is associated with both nutritional factors and inflammation [6].

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Inflammation causes a decline in serum albumin concentration by a combination of mechanisms. Albumin synthesis is decreased [17]. One of the adaptive responses that defends albumin mass when protein is restricted is that of a reduction in the fractional catabolic rate of albumin. Plasma protein composition including serum albumin levels, and to a lesser extent muscle mass, is maintained at nearly normal levels in subjects with anorexia nervosa, in part by a reduction in resting energy expenditure, total net protein catabolism and also a decrease in the fractional catabolic rate [18]. In contrast, patients with wasting and infection as a consequence of the human immunodeficiency virus have an increased resting energy expenditure that is even more marked in the presence of diagnosed infection [19] as well as hypoalbuminemia. Alterations in the albumin fractional catabolic rate play an important role in sustaining albumin concentration during protein restriction [20, 21]. Inflammation removes this adaptive mechanism for responding to periods of decreased nutritional intake [10]. The level of inflammation that results in changes in nutritional markers, muscle wasting and hypoalbuminemia is great.

The potential sources of cytokines are several. Atherosclerosis is an inflammatory process [22]. Atherosclerosis nutritionally induced in a porcine model can be demonstrated to recruit CRP to the site of atherosclerosis [23]. CRP itself may play a role in promoting or propagating vascular injury through complement recruitment [24]. At the same time, pyrogenic infections are associated with a subsequent increase in cardiovascular events [25]. Inflammatory processes themselves are risk factors for cardiovascular disease in a variety of populations including those with rheumatoid arthritis [26] and those with bacterial infections [27]. Thus, inflammation can report and play a role in classically initiated vascular injury, while at the same time, inflammation may independently initiate or propagate vascular injury by mechanisms detailed below.

The third potential source of cytokines and the inflammatory response is that associated with release of cytokines by adipocytes [28]. Truncal obesity is associated with increased levels of tumor necrosis factor- α and other downstream cytokines [29], yet obesity is associated with increased survival among dialysis patients [30]. This presents an apparent paradox in linking cytokine activity to cardiovascular risk in this population known as 'reverse epidemiology' [31]. Visceral fat is associated with the metabolic syndrome and alterations in lipoprotein composition that would be expected to result in increased vascular disease. This same association is true in dialysis patients

having increased visceral fat [32], and indeed, increased visceral fat mass was associated with increased carotid intimal media thickening, plaque score and stiffness. Others have shown a relationship between carotid atherosclerosis and inflammation, specifically CRP levels and levels of soluble intracellular adhesion molecule and vascular cell adhesion molecule [33]. It is unknown why increased body mass index in the dialysis patient population is not then associated with increased cardiovascular events.

Mechanisms Linking Inflammation Causally to Vascular Injury

There are multiple mechanisms whereby the inflammatory response can alter blood lipids [34, 35], the vascular endothelium [36], and plasma protein composition in such a way as to favor and promote vascular injury. Additionally, alterations in lipoprotein composition associated with renal failure reduce defense mechanisms that would otherwise mitigate the effects of inflammation on vascular structure (fig. 1).

Atherosclerosis is associated with increased expression of adhesion molecules, such as soluble intracellular adhesion molecule and vascular endothelial growth factor. Vascular endothelial growth factor is released following activation of neutrophils following bacterial infection [37], plays an important role in the maintenance of endothelial integrity [38], but also increases vascular permeability to serum proteins [39]. The biological roles of these proteins provide potential mechanisms whereby inflammation may cause vascular injury by altering the binding of macrophages and other leukocytes to the vascular endothelium. Induction of adhesion molecules facilitates the transmigration by leukocytes [40] and increases mononuclear cell adhesion [41].

Inflammation is associated with cardiovascular disease and stroke in otherwise healthy subjects [42]. While the levels of acute phase proteins remain stable in non-dialysis populations [43], inflammation episodically occurs in hemodialysis patients [44].

Inflammation may also downregulate the ATP-binding cassette transporter A1 receptor [45] necessary for the transfer of cholesterol to nascent high-density lipoprotein (HDL) in the initiation of reverse cholesterol transport.

Fibrinogen is a positive acute phase protein which correlates with CRP and is also an independent cardiovascular risk factor [46]. Fibrinogen levels are increased in dialysis patients and correlate with other markers of inflammation [47].

Fig. 1. Inflammation initiates increased synthesis of positive acute phase proteins, including CRP, fibrinogen and SAA. Apo AI, the principal protein necessary for HDL synthesis, is decreased resulting in reduced HDL levels. SAA also displaces Apo AI from HDL decreasing its capacity as a reducing agent. Neutrophil activation releases myeloperoxidase which in turn oxidizes LDL. Lecithin cholesterol ester transferase, an enzyme activated by Apo AI that esterifies free cholesterol and is necessary for maturation of HDL, is reduced. Levels of paraoxonase and aryl hydrocarbon hydrolase, enzymes utilized by HDL in reducing oxidative injury, are also reduced; thus, HDL fails to block cytokine-mediated expression of the endothelial-derived adhesion molecules soluble intracellular adhesion molecule and E-selectin. Neutrophils are activated releasing myeloperoxidase-oxidizing LDL allowing it to be taken up more easily on the endothelium. LRP = Lipoprotein receptor-related protein; IL-6 = interleukin-6; TNF- α = tumor necrosis factor- α ; Lp(a) = lipoprotein (a).

Changes in Lipoprotein Concentration and Composition

HDL is an important defense mechanism against atherosclerosis, serving both as an anti-oxidant, reducing oxidized low-density lipoprotein (LDL) [48], and decreasing the expression of adhesion molecules induced by cytokines on vascular endothelial cells [49]. HDL levels decrease progressively as renal function fails [50], in part due to a decreased synthesis [51] resulting from down-regulation of apolipoprotein (Apo) AI gene expression by the liver [52]. HDL structure is also deranged [53]. In inflamed individuals without renal failure, HDL levels also decrease [34] and the Apo AI that normally composes about half of the proteins in HDL is replaced by serum amyloid A (SAA) [54, 55]. This form of HDL is chemoattractive to macrophages as well as the vascular endothelium and has reduced the capacity to minimize oxidized LDL [54, 55]. Inflammation alters HDL structure and function removing anti-inflammatory properties by reducing the levels of aryl hydrocarbon hydrolase and paraoxonase-1 [55]. Inflammation and the changes in HDL metabolism that occur in renal failure, independently of inflammation, are synergistic in reducing this important defense mechanism against the effects of fur-

ther inflammation and produce a positive feedback loop.

Therefore, LDL is more likely to be oxidized during an inflammatory event because of a decreased ability of HDL to protect it and, as a consequence, of increased action of myeloperoxidase, a product of activated neutrophils that chlorinates a tyrosine residue on Apo B100 [34]. Normally, HDL also suppresses the effects of cytokines on their induction of adhesion molecules by endothelial cells [49]. Inflammation alters HDL structure and function to decrease these anti-inflammatory properties. Inflammation would be anticipated to cause a decrease in HDL as well as an increase in triglyceride levels. These same characteristics predict cardiovascular disease in women [56] and are closely associated with markers of inflammation, including SSA levels. This specific acute phase protein directly affects HDL levels [35] and function as well as triglyceride content, suggesting that inflammation may not only play a role in vascular disease, but may also provide a link between progression of renal disease and the lipoprotein abnormalities associated with progression.

Thus, inflammation alters vascular structure and function in ways that allow cholesterol accumulation, decreases the capacity of the endothelium to unload lipids to

HDL, alters HDL both quantitatively and qualitatively so that it is less able to participate in reverse cholesterol transport and serves as an antioxidant. At the same time, oxidation is increased.

Changes in body composition, decreased muscle mass and decreased levels of albumin and prealbumin normally associated with malnutrition also result from a change

in the composition of proteins synthesized by the liver. While the amino acids diverted from muscle and negative acute phase proteins for either energy generation or synthesis of proteins necessary for host defense may serve a protective role under significant inflammatory stress, cachexia has frequently been attributed to malnutrition alone.

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