Cholesterol, HDL and Lymphatic Clearance of the Arterial Wall

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Abstract
Reverse cholesterol transport in the arterial wall was first postulated in 1981. In the last 36 years, great strides have been made in identifying the factors which cause impedance and diminished access of cholesterol laden high density lipoprotein (HDL) and foam cells to the lymphatic circulation. Initiating factors are endothelial dysfunction, oxidation of cholesterol, inflammation, monocyte migration and expression of cytokines and chemokines that inhibit cholesterol transfer and lymphatic access. Lymphatic vessels are intimately involved in this inflammatory process and the lymphatic flow is dependent on constriction, spasm, sclerosis, fluidity and external physical compression. Lifestyle changes in stress reaction, exercise and diet can profoundly influence this process.

Opinion
The lymphatic circulation as the pathway for reverse cholesterol transport (RCT) in the arterial wall was first described in 1981 [1]. In that article this route was clearly described “since HDL can transport cholesterol from tissue back to liver by way of the lymphatic’s for excretion this enhanced lymphatic clearance may be the explanation for its beneficial effects”, it was also postulated that slowing of lymphatic clearance increased tissue accumulation of foam cells. At that time, the role of inflammation, cytokines, cell adhesion molecules and neuropeptides had not been delineated in this disease but was prefigured in the statement, “local changes of type, amount, or physical properties of the mucopolysaccharides may represent the initial lesion (viz. atherosclerosis) and observation paralleling the connective tissue proliferation and increase cellularity seen in lymphstasis”[1].

Since that time, 35 years ago, great advances have been made in the identification of proteins, peptides, lipids and carbohydrates that are involved in not only the inflammatory process but in basic metabolism. In the recent decade, increasing numbers of papers have supported the role of lymphatics in reverse cholesterol transport [2-8]. These papers suggest that delay of clearance of oxidized cholesterol from the arterial wall increases inflammation, which consequentially further retards cholesterol egress [6-8]. Several reports identify an immune involvement in the arteriosclerotic process [9-12]. Cholesterol, an essential molecule to sustain life, is transported through the capillaries to the tissue where it is utilized to create hormones, bile salts, cell membranes, pro-vitamins and other necessary metabolites [13]. However, some of it passes through dysfunctional arterial endothelium to settle in the intima [14]. There are multiple reasons for loss of integrity and endothelial penetration. Aging [15] turbulence, shear stress, hypertensive denudation, inflammation and other metabolic disorders permit the rapidly oxidized LDL [14,16-18] to enter the intima initiating the endothelial inflammatory process involving vascular cellular adhesion molecules, and other pro-inflammatory proteins [19]. Monocytes enter the intima becoming macrophages and further the inflammatory process secreting other cytokines and chemokines [19]. The macrophages become cholesterol laden foam cells that create further inflammation unless the cholesterol can be transferred to HDL or the foam cells can migrate through the arterial wall to the lymphatic’s [19].

As postulated in 1981, the development of arteriosclerosis depends on how efficiently the cholesterol can be cleared from the sub intimal space [20]. In the small arteries this does not appear as a problem however in the large and midsized arteries the lymphatics occur in the outer half of the media and in the adventitia [2]. Furthermore, the continuity of internal elastic membrane was considered an obstacle for HDL access to lymphatic circulation. As inflammation progresses, the hypertrophied...
inflamed arterial wall and foam cells create further oxidative stress producing cytokines and chemokines immobilizing the macrophages, increasing fibroblasts and collagen matrix, making access to the lymphatic system more difficult [21]. Expressed myeloperoxidase alters the discoid HDL rendering it incapable of accepting cholesterol from the foam cells [22]. Expression of neuro-polyptides increases the inflammation, delaying reverse cholesterol transport [23-25]. Thus the foam cells play a critical but reversible role in atherogenesis and remove significant amounts of cholesterol when unimpeded [26]. Foam cells migration can be inhibited by reactive oxygen species created by NADPH oxidase in the presence of oxidized LDL [19]. However, antioxidants like resveratrol and N-acetylcysteine can restore normal plasticity [19]. Furthermore cholesterol clearance is also accomplished by transfer of the cholesterol from the foam cells to the nascent HDL through the adenosine triphosphate by the cassette ABC A1 transport mechanism.

The longer the arterial wall is exposed to this inflammatory process, the greater the progression of atherosclerosis with [27] tissue destruction. However we know that if we increase the lymphatic flow we can improve cholesterol egress, thus decreasing arterial wall inflammation. Decreasing inflammation further improves lymphatic flow which further clears the tissue toxins and extravascular cytokines, messaging the neuro-endoctrine immune system to express reparative cytokines and macrophages.

So it would seem that increasing lymphatic flow could prevent or diminish atherosclerotic plaques. It is well-known that specific lifestyle changes like increased exercise, a diet high in fruits and vegetables, and stress modification and reduction can increase lymphatic flow [3,5,7]. Exercise can easily triple the lymphatic flow as can deep breathing [28,29]. A diet high in water, flavonoids and polyphenols can also [30-33] significantly increases lymphatic flow. Lastly stress modification, can decrease the cortisol, and epinephrine levels which can prevent lymphatic sclerosis and dysfunction and constriction.

In conclusion, perhaps the most important advice we can offer to those interested in optimizing their cardiovascular health is to improve lymphatic flow by decreasing stress, increasing exercise and eating a healthful diet.

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