The importance of the lymphatic system in vascular disease

Lemole GM *

*Professor of Surgery (Adjunct) Temple University School of Medicine, Philadelphia PA, USA

Abstract

The lymphatic system plays a significant role in atherosclerosis. Clearance of oxidized cholesterol from the large and medium-sized arterial wall is dependent upon properly functioning intramural and adventitial lymphatic vessels. This function can be severely impeded by inflammation or augmented to increase lymphatic flow and improve fluidity by lifestyle changes such as diet, exercise, stress modification and toxin avoidance. In order to optimize cardiovascular health, the cycle of oxidation, inflammation and lymphatic dysfunction in the arterial wall must be interrupted by the known and well documented lifestyle modifications. This review cites recent scientific publications that support the importance of the lymphatic system in the reverse cholesterol transport. These works, compiled with those of beneficial integrative modalities, make a strong case for support of this concept. Incorporating the lymphatic system function and those lifestyle changes that affect it, further promotes a unifying concept that includes LDL concentration and density, endothelial dysfunction, intramural inflammation and lymphatic dysfunction, spasm or sclerosis in cardiovascular disease.

Introduction

The lymphatic system is clearly recognized as the immune domain, dealing with infections, tumor cells, waste products and toxins [1-3]. It is also critical in fluid balance between the vascular bed and interstitial tissue- since about 10% of the fluid exchange at the capillary bed remains in the tissue and much be returned to the vascular system by way of the lymphatics [4]. Lastly, and often less acknowledged, is its role in returning large molecules, proteins, lipids and lipoproteins to the vascular system from the tissue space. Among other larger molecules, Apolipoprotein A (APO-A), Apolipoprotein B (APO-B), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) and their metabolites egressing the capillary bed are transported to the venous system by way of lymphatics [5].

The errant lipoproteins that randomly enter the intima of the arterial wall through dysfunctional endothelia also must be metabolized and cleared via lymph channels [6-9]. This presents a problem in the larger and midsized arteries because of the distance to lymphatics, natural barriers and impedance caused by inflammation [5]. Lymphatic function is necessary for the expeditious clearance of cholesterol from the arterial wall [10]. Cholesterol can be found throughout the entire thickness of the arterial wall, (including the adventitia where lymphatics abound) [11]. The lymphatic channels penetrate the large and medium-sized arteries in the middle to outer third of the media [12]. Cholesterol laden foam cells and HDL must penetrate the internal elastic lamina in order to reach these lymph vessels. In the past this was considered unlikely. However, recent research has shown that this indeed occurs [13-22]. Lymphatic endothelial cells express inflammation-producing proteins and peptides, augmenting the inflammatory cascade [23]. These cells are also responsive to inflammation producing molecules [24]. The lymph channels also contain autonomic nerve endings and contractile smooth muscle fibers making them intimately connected to the neuro-endoctrine systems [1].

Since the lymph system warehouses lymphocytes and is the immune cells’ conduit, it exquisitely integrates the endocrine, nervous and immune system for biofeedback, signaling and mind-body interactions [25]. The lymph vessels can dilate or constrict [26]. They have rhythmic pulsation, can go into spasm or become sclerosed [27]. Lymph fluid [4] also has great rheological variability, as it can be more fluid in the sol phase, or more viscous in the gel phase. Its fluidity may be altered by water content and the concentration of formed elements. Its volume is changed by an increase head of pressure as seen in hypertension or anoxia which causes an alteration in capillary permeability with an increase in the filtrate and proteins into the interstitium [1].

Inadequate lymphatic clearance of lipoproteins from the arterial wall as a possible cause of atherogenesis was first postulated 35 years ago [1]. Although this concept could adequately explain the positive correlation with known risk factors for coronary artery disease and the negative correlation with high density lipoproteins and lifestyle modifications, little research was undertaken in this area [14,28-30]. The confluence of drainage from the arterial wall lymph with that of the capillary interstices affects the data when measuring the lipoprotein content in lymph vessels. The pathways for LDL, HDL, nascent HDL,APO-A APO-B and other lipoprotein’s can be conflated as particles trapped in large and medium sized arterial walls and those transiting from the gut or para-capillary interstitium [31] are admixed. However, recent investigative work has clearly demonstrated the lymphatic systems involvement in reverse cholesterol transport [17-22].

In order to better understand this process, it is worthwhile to review cardiovascular pathophysiology and the role that inflammation, diet, exercise, stress and environmental toxins play in the genesis of atherosclerosis. LDL is the primary transporter of cholesterol to the tissues at the capillary level. There, it is an integral component for the
and positive correlations to atherosclerosis. Lymphatic flow is clearance creates an intriguing model to explain some of the negative tissue destruction and progression of atherosclerosis [13-16,39,46,47].

If the arterial wall is exposed to these inflammation-inducing molecules, the greater the inflammation and creation of an atheroma. The longer the arterial wall and viscosity, immobility and death of the foam cells initiating greater laden HDL in the lymph then in the plasma [13-16]. Increasing wall, passes through the internal elastic lamina. This route is also shows that the majority of HDL cholesterol that entered the arterial plasticity [45]. Cholesterol clearance is also accomplished by transfer ABC A1, transporter mechanism [41]. The work of Nordestgaard [28] plasticity [45]. Cholesterol clearance is also accomplished by transfer of LDL, the extent of endothelial damage, [6-9,34] inflammation, lymphatic clearance and transit time. Upon passing into the intima, the LDL rapidly becomes oxidized [35] initiating an endothelial inflammatory process that involves selectins, vascular cellular adhesion molecules and other pro-inflammatory components thus attracting monocytes which are transformed into macrophages after migration into the intima. The inflammatory process is further enhanced by their secretion of pro-inflammatory cytokines and chemokines [10].

The inflammatory process can be initiated by other than at oxidized LDL. Radical oxygen species, infection, homocysteine and Apo-B particles are examples of these initiators [36-39]. In an attempt to minimize this inflammation, the macrophages engulf the cholesterol and unless they can transfer the cholesterol to Apo-A HDL or migrate through the arterial wall, create further inflammation and deposition of cholesterol. The efficiency of cholesterol clearance from the sub intimal space is a key factor in the development of atherosclerosis [40]. The foam cells in the inflamed arterial wall manufacturer chemokines, cytokines and enzymes which immobilizes the macrophages and increase fibroblasts and collagen matrix further slowing down the cholesterol progression to the lymphatics. The discoid HDL is not able to transfer the cholesterol from the foam cells due to myeloperoxidase that is expressed by the macrophages [41]. This egress is further delayed by the expression of neuroptides like netrin-1, Sema 3A, neuropeptide Substance P, and neuropeptide Y [42,43]. These neuroptides create inflammation and prevent cholesterol transport. Netrin-1 is a neural guidance cue, secreted by the foam cells in the atheroma and is a powerful chemotactant and smooth muscle cell recruiter and retardant to macrophage exit from the arterial wall to the lymphatics [44]. This suggests then, that foam cells play a critical but reversible role in atherogenesis [45]. Lipid laden macrophages can remove significant cholesterol amounts if unimpeded, but migration is inhibited by reactive oxygen species created by NADPH oxidase in the presence of oxidized LDL [35,44]. This creates a loss of plasticity of the macrophages cellular actin cytoskeleton. However, antioxidants like N-acetylcysteine, resveratrol and other NADPH oxidase inhibitors can restore normal plasticity [45]. Cholesterol clearance is also accomplished by transfer to nascent HDL through the adenosine triphosphate–binding cassette, ABC A1, transporter mechanism [41]. The work of Nordestgaard [28] shows that the majority of HDL cholesterol that entered the arterial wall, passes through the internal elastic lamina. This route is also supported by studies that show a higher percentage of cholesterol laden HDL in the lymph then in the plasma [13-16]. Increasing inflammation causes dysfunction of HDL, increasing tissue cellularity and viscosity, immobility and death of the foam cells initiating greater inflammation and creation of an atheroma. The longer the arterial wall is exposed to these inflammation-inducing molecules, the greater the tissue destruction and progression of atherosclerosis [13-16,39,46,47]. The vicious cycle of oxidation, inflammation and delayed lymphatic clearance creates an intriguing model to explain some of the negative and positive correlations to atherosclerosis. Lymphatic flow is increased with exercise, deep breathing, stress modification and a diet high in vegetables and is decreased with a sedentary lifestyle, a pro-inflammatory diet with reactive oxygen species, and stress [1]. These factors correlate both negatively and positively with the incidence of atherosclerosis [1,48].

There is much evidence for the cardiovascular protective effect of a diet high in fruits and vegetables [49-52]. Plants contain the lymph stimulating polyphenols and flavonoids. Lymphogenic products are essentially compounded flavonoids like Dafillon, a combination of two flavonoids – hesperidin and Diosmin. These flavonoids reduce the expression of the ICAM-1, L-Selectin and VCAM-1 besides increasing the intensity and frequency of lymphatic contraction and increasing the total number of lymphatic capillaries. This results in the decrease of adhesion, migration, and activation of leukocytes, leading to lowering of prostaglandin’s PGE2 and PGF2a and the reduction of radical oxygen species [53-58]. Vitamin D down regulates the inflammation of macrophages and monocytes and slows the ingress of monocytes and dendritic cells into the intima [59-60].

Exercise is essential for optimum cardiovascular health. Exercise considerably increases lymphatic circulation, positively affects anti-inflammatory markers and reduces pro-inflammatory ones [61,62]. On its way to the venous system, the majority of lymph flows through the thoracic duct in the chest. Lymph flow through the chest cavity is significantly increase by rapid deep breathing [1] which creates larger diaphragmatic excursions, increases the negative intrathoracic pressure and stimulates lymphatic flow [63]. Changes of physical activity maximize lipid clearance and circulating dendritic T cells which have been shown to be increasingly significant in cardiovascular disease [64-67]. Physical and mental stress are significant in the production of inflammation and atherosclerosis [25,68]. Stress increases the epinephrine and cortisol levels and chronic stress can lead to lymphatic sclerosis [68,69].

Incorporating the importance of the clearance of cholesterol and inflammatory metabolites in the arterial wall by the lymphatic system can adequately explain how lifestyle changes such as diet, exercise, stress modification and environmental toxin clearance can significantly improve cardiovascular health [70,71]. It also helps explain how mind-body interactions and biofeedback can also be of benefit through immuno–neuro-endocrine pathways. Incorporating the lymphatic system into this paradigm allows us to forward “The Unifying Concept of Atherosclerosis” [72] (Figure 1). This concept proposes that atherosclerosis is begun by initiating agents in the blood. These can

---

**Figure 1. Unifying concept of Arteriosclerosis.**

---

Lemole GM (2016) The importance of the lymphatic system in vascular disease
be oxidized cholesterol, oxidized apoprotein A-I, homocysteine, bacterial and viral infections (i.e. Helicobacter Pylori, dental caries, Chlamydia or Cytomegalic Inclusion Virus) [35-38] that enter the intima through a dysfunctional endothelial lining (e.g. elderly, hypertensives, diabetics). These create an inflammatory milieu which is countered by anti-inflammatory homeostasis which includes the recruitment of antioxidants, anti-inflammatory, and enzymes (glutathione peroxidase, catalase and superoxide dismutase). Lymphatic clearance ensues and can be enhanced by positive lifestyle changes or impeded by neuropetide production and persistent, unresolved chronic inflammation. Including the lymphatic system in an overview of atherogenesis can help us understand the disease process. More importantly, have greater confidence in recommending and incorporating positive lifestyle changes for improved outcomes in cardiovascular disease (Figure 1).

References

1. Lemole G (2014) The role of lymphstasis in atherogenesis. Ann Thoracic Surg 31: 290-294.

2. Reed R, Rolf K, Ruben K (2010) Trans capillary exchange: role and importance of the lymphatic system in an overview of atherogenesis can help us understand the disease process. More importantly, have greater confidence in recommending and incorporating positive lifestyle changes for improved outcomes in cardiovascular disease (Figure 1).

References

1. Lemole G (2014) The role of lymphstasis in atherogenesis. Ann Thoracic Surg 31: 290-294.

2. Reed R, Rolf K, Ruben K (2010) Trans capillary exchange: role and importance of the lymphatic system in an overview of atherogenesis can help us understand the disease process. More importantly, have greater confidence in recommending and incorporating positive lifestyle changes for improved outcomes in cardiovascular disease (Figure 1).

References

1. Lemole G (2014) The role of lymphstasis in atherogenesis. Ann Thoracic Surg 31: 290-294.
Lemole GM (2016) The importance of the lymphatic system in vascular disease

44. Van Gils JM, Derby MC, Fernandes LR, et al. (2012) The neuroimmune guidance cue netrin-1 promotes atherosclerosis by inhibiting the emigration of macrophages from plaques. Nat Immunol 13: 136-143.

45. Llodrä J, Angeli V, Liu J, et al. (2004) Emigration of monocyte-derived cells from atherosclerotic lesions characterizes regressive, but not progressive, plaques. Proc Natl Acad Sci USA 101: 11779-11784.

50. Willett WC (1994) Diet and health: what should we eat? Am J Clin Nutr 78: 357-358.

51. Ginter E, Simko V (2015) Recent data on Mediterranean diet, cardiovascular disease, cancer, diabetes and life expectancy. Bratisl Lek Listy 116: 346-348.

52. Chainani-Wu N, Weidner G, Purnell DM, Frenda S, Merritt-Worden T, et al. (2011) Changes in emerging cardiac biomarkers after an intensive lifestyle intervention. Am J Cardiol 108: 498-507. [Crossref]

53. Vogel G, Ströcker H (1966) The effect of drugs—especially flavonoids and aescin—on low-density lipoprotein and albumin uptake in the rabbit aortic wall. Circ Res 79: 532-540.

54. Shaikemeleva US (1983) Effect of rutin on the cholesterol content of the lymph, blood and tissues of the dog] Biull. Eksp Biol Med 95: 35-37.

55. Friesenecker B, Tsai AG, Intaglietta M (1995) Cellular basis of inflammation, edema and the activity of Daflon 500 mg. Int J Microcirc Clin Exp 15 Suppl 1: 17-21. [Crossref]

56. Labrid C (1995) Lymphagogue and pulsatile activities of Daflon 500 mg on canine thoracic lymph duct. Int Angiol 8: 15-18. [Crossref]

57. Labrid C (1994) Pharmacologic properties of Daflon 500 mg. Angiology 45: 524-530. [Crossref]

58. Takeda M, Yamashita T, Sasaki N, et al. (2010) Oral administration of an active form of vitamin D3 (calcitriol) decreases atherosclerosis in mice by inducing regulatory T cells and immature dendritic cells with tolerogenic functions. Arterioscler. Thromb Vasc Biol 30: 2495-2503.

60. Riek AE, Oh J, Sprague JE, et al. (2012) Vitamin D suppression of endoplasmic reticulum stress promotes an antiatherogenic monocyte/macrophage phenotype in type 2 diabetic patients. J Biol Chem 287: 38482-38494.

62. Desai P, Williams AG Jr, Prajapati P, Downey HF (2010) Lymph flow in instrumented dogs varies with exercise intensity. Lymphat Res Biol 8: 143-148. [Crossref]

65. Reiss AB, Wan DW, Anwar K, et al. (2009) Enhanced CD36 scavenger receptor expression in THP-1 human monocytes in the presence of lupus plasma: linking autoimmunity and atherosclerosis. Exp Biol Med 234: 354-360.

67. Marcondes MC, Zhukov V, Bradlow H, et al. (2011) Effects of chronic mental stress and atherogenic diet on the immune inflammatory environment in mouse aorta. Brain Behav Immun 25: 1649-1657.

69. Selby H (1975) The Stress of Life. Revised Edition, McGraw-Hill, New York 22-23.

70. Ramanathan G, Yin F, Speck M, Tseng CH, Brook JR, Silverman F, et al. (2016) Effects of urban fine particulate matter and ozone on HDL functionality. Part Fibre Toxicol 13: 26.

72. Lemole GM (2000) Unifying concept of atherosclerosis (table 4.14) an integrative approach to cardiac care. Medtronic 46.