Original Article

Egyptian Concept of Rational Immune Modulation: Nature-Friendly Lifestyle for Taking Athero-Protective Phenotype

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Abstract

A slightly lower rate of atherosclerosis in some tropical regions such as the Nile delta in Egypt, Saudi Arabia, Yemen and sub-Sahara Africa is associated with evidences of increased helminthic co-infection. Attempts to eradicate helminthic infections led to the shift of immune balance toward T helper 1 cells and their related cytokines. This shift is parallel with atherogenesis and its related complications. Atherosclerosis is a degenerative man-made disease which begins in early life. Thus, preventive strategies should begin at the same time. As an example to follow, living with old friends, adaption of a more nature-friendly lifestyle and 'fine immune-modulation' plans from early childhood, like Egyptians, seems a good option. Finally, a proper intentional balance between T helper 1 and 2 cells should be defended and constructed environmentally in the manner compatible with modern hygiene using a soft application of old hygiene. This needs robust understanding of atheroprotective habits in regions with lower burden of atherosclerosis.

Keywords: Atherogenesis, athero-protection, helminthes infection, immune regulation, T helper cells

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Materials and Methods

Epidemiology

A slightly lower rate of atherosclerosis in some geographic regions raises the question of the presence of atheroprotective environmental factors.[1] Environmental factors play an important role in the pathogenesis of atherosclerosis as demonstrated by immigration from rural to urban places.[2,3] Westernization is associated with smoking, hypertension, diabetes mellitus (DM) and hyperlipidemia which are the key factors in development of atherosclerosis. Other factors may have different effects, like the habitation in "wormy-world". In these regions, such as the Nile delta of Egypt, Saudi Arabia, Yemen and sub-Sahara Africa, evidence of increased co-infection with helminthes and other forms of chronic infections is seen more commonly.[1,4] Indeed, an inverse correlation has been seen between prevalence of worm-infection and coronary artery disease (CAD) in China, India and Africa. High prevalence of soil-transmitted helminthes in Flores, Indonesia, has been shown to be negatively associated with risk factors for cardiovascular diseases (CVD) and carotid intima-media thickness.[2]

The most common pattern of worm infection is a steady rise in the intensity of infection during childhood with a plateau on reaching adulthood.[5] In China, this peak is seen above 50 years of age due to the growing proportion of elderly population.[6] Decreased prevalence of death related to infectious diseases has been seen with increased death rate due to CVD.

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Pathophysiology and immune-based principals

The pathophysiology of cardiovascular diseases is related to inflammation, fat accumulation, intimal thickening and fibro-fatty changes of vessel wall which narrows vessel lumen. The presence of T-cell auto-antibodies against Ox-LDL, LDL, hsp60/65 and β2-gp-I implies the role of autoimmune entity of atherosclerosis.[7,8] The growing field of "athero-immunology" has demonstrated the T-helper 1 (TH1)-predominant balance of immune system in development and progression of atherosclerosis milieu.[9] The microenvironment provided by vessel walls attracts immune cells to recognize their appropriate antigens, the modified self-proteins; and begins the inflammation in the site of elicit.[10]

But this is quite against the pivotal TH2-based balance of immune system induced by chronic helminthes infection. In this tightly balanced system, TH1 cytokines suppress TH2 activity and vice versa. TH1- cellular and TH2- humoral immunity both participate in determining fate of the plaque: stability or rupture.[11] Identity of these cells is mainly based on their cross-talking derived cytokines, in which these two cells are working as a balance shuttle. A small shift toward TH1 cells results in hazardous chronic inflammation, as in the case of atherosclerosis.[12] TH1 cells and their atherogenic secreted cytokines are all increased in a site- and stage- dependent manner in the process of atherosclerosis.[13,14] On the other hand, most studies demonstrated the anti-atherogenic properties of cytokines secreted by TH2: IL-4, -10 and -13.[15]

People inhabiting outside developed countries, live in a partial or full commensal state with immune-modulating organisms, omitted in modern life. Helminthes are symbiotic organisms rather than mere parasites. We should change our opinions about worms. Such a perfect correlation between worms and human beings is derived from a delicate co-evolution. Helminthic eradication programs in industrialized countries in 20th century and elimination of these co-evolved organisms from human body have been accompanied by increased prevalence of auto-immune diseases.

Immunologically, atherosclerosis can be considered as an autoimmune disease directed against components of vessel wall.[16]

Chronic infection with *Opisthorchis felineus* has been found to be associated with significant attenuation of atherosclerotic wall changes and lower serum total cholesterol levels. This infectious status has been shown to be a negative predictor of atherosclerosis.[17] Mice infected with *Schistosoma mansoni* exhibit reduced atherogenesis attributed to enhanced activation of regulatory T cells (Treg).[18] In addition, decreased expression of INF-gamma in vessel walls has been shown to be associated with 60% decrease in the plaque burden in $APOE^{-/-}$ mice.[19] Worms evade the host immune system through regulation of immune responses. Chronic helminthic infections, or in other words Th2-skewing infections, regulate activation and chemotaxis of monocytes to the site of inflammation and atherosclerotic plaques.[20] Chronic worm infection down-regulates expression of major histocompatibility complexes (MHC) and adhesion molecules through over-expression of IL-10, a potent anti-inflammatory cytokine.[21] IL-10 reduces inflammation at the site of vascular damage and inhibits development of atherosclerotic plaque.[22] Interestingly, chronic worm infection is associated with stabilized atherosclerotic plaque which could be attributed to over-expression of IL-10.[20]

Despite their unpleasant nature, worms have some beneficial effects. Many years ago, earthworms were used in Far East for treatment of circulatory deficiencies. In 1980s, fibrinolytic enzyme Lumbrokinase, also known as earthworm powder enzyme (EPE) or earthworm fibrinolytic enzyme (EFE), was extracted from *Lumbricus rubellus*. Lumbrokinase was the main component of dragon heart in Korea and Japan as food supplements in order to support cardiovascular system for healthier blood state.[23]

Chronic Worm infection and risk factors of atherosclerosis

The effects of worms are partly disease specific. Dampening low grade inflammatory state in the setting of auto-immune diseases which accelerates atherosclerosis development and progression, implies to modulation of underlying disorders related to atherosclerosis. Although the influences of chronic worm infection on risk factors of atherosclerosis are not well known, some reports are in favor of beneficial effects of worms on modulation of atherosclerosis risk factors.

The concept of expanded hygiene hypothesis

It is not yet known whether chronic worm infection could outweigh the effects of genetic predisposition, over-inflammatory state, age-related changes, harmful alcohol use, obesity, postmenopausal sate, smoking and elevated Lp (a) and hemocysteine. The impact of immune-counterbalance afforded by worms on hypertension is not yet studied, but obviously involvement of renal arteries by worm infection might lead to hypertension due to thickening of renal arteries by inflammation.[24] Regarding the metabolic syndrome and DM, in cases affected with lymphatic filariasis (LF), lower prevalence rates of both type 1 (T1DM) and 2 DM (T2DM) have been seen. In LF^{+}-DM cases, lower levels of serum pro-inflammatory cytokines have been shown.[25] It demonstrates the impact of worm-induced dampened inflammation on outcomes of immune-mediated endocrine disorders. Some parts of conferred protection against atherosclerosis might derived from this endocrine protection. Indeed, the anti-atherogenesis effects of parasite-induced lowering of total blood lipid have also been demonstrated.[18]

Worms derive cholesterol from their hosts rather than synthesizing it *de novo*.[26] Cholesterol precursors are required for stimulation of egg production by female parasites.[27] Since HMG-CoA reductase activity plays a fundamental role in helminthic egg production, statins lead to developmental arrest.[28] Male and female worms incorporate and convert host cholesterol to its metabolites.[29] Indeed, metabolites released from *Schistosoma mansoni* decrease synthesis and release of lipid particles from host hepatic tissue. Therefore, this proposed statin-like action of worms is achievable through both lowering lipid levels and directing immune balance toward TH2 cells. Helminthes exert species specific effects on lipid metabolism which could be considered as an athero-protective mechanism. In contrast with mammals, which do not possess the ability to convert omega-6 to omega-3 fatty acids due to the lack of its genetic code, the worm has this capability. *In vitro* experiments demonstrated that mice with heterogeneously expressed *Caenorhabditis elegans* fat gene found capability of this beneficial conversion.[30] In people afflicted with Schistosoma hepatic fibrosis (SHF), reduced prevalence of atherosclerosis has been seen.[31] Helminthic infection is considered to counteract the effects of atherogenic diet by reducing total cholesterol and modulation of lipid metabolism.[32] Mice infected by *Schistosoma mansoni* demonstrated low serum cholesterol level due to the released metabolites of worms. The ability of worms to reduce serum cholesterol increases during their paring. Paired worms lose up to 65% of their cholesterol. Bi-directional cholesterol transfer in worm pairs is mediated through physical contact between juxtaposed membranes of paired worms and tegmental turnover of molecules.[33] Indeed, cholesterol stimulates survival of larvae. In the presence of Ascaris worms in their larval stage, lipid metabolism is seriously disturbed.[34] Reduced high density lipoprotein (HDL), triglyceride and total cholesterol are seen in guinea pigs infected with Ascaris worms which is suggested to be due to the decreased synthesis of HDL in the gut of larvae by the presence of inflammation and toxins.[34,35] Among Peruvian Shipibo inhabitants, an inverse correlation was seen between hookworm egg excretion and serum HDL level.[36,37] Tapeworms absorb serum cholesterol in a carrier-dependent manner. Indeed, Ancylostoma worms survive better in culture tissues enriched by worms.[37,38] Decrease in LDL levels by worms is not only due to the impairment in host nutrition, but also by regulating antibodies directed against cholesterol.[20] A putative LDL-receptor is known on the gut tegument of *Schistosoma japanicum* and *Schistosoma mansoni*.[30,40] Receptor mediated LDL endocytosis is another mechanism developed in schistosomes.[41] A beneficial increase in ratio of HDL to LDL cholesterol was also seen in $APOE^{-/-}$ mice.[42] IL-4 secreting TH-2 cells are resistant to hyperlipidemia and chronic TH2 activation is in parallel with decreased LDL level.[43]

Chronic Worm infections and umbrella of cardiovascular diseases

Influence of worms on different types of cardiovascular involvement, such as peripheral vascular diseases and cerebrovascular diseases, is not yet investigated. Interestingly, the 2.5% prevalence of significant atherosclerotic carotid artery diseases has been found to be much lower in Egypt than developed countries in America, Europe and Asia.[44] Worms have been used successfully in the treatment of diabetic foot ulcers.[45] For the first time, Larrey noted that during the Napoleonic war, those soldiers infested by larvae (maggots) had improved prognosis.[46] Interestingly, abdominal aortic aneurysm is a cardiovascular disease

which is accelerated by TH-2 related cytokines. [47] Reported cases with etiology of helminthic infection of aneurysm are rare in human beings (although frequent in animals). Verminous aneurysm caused by Filaria has been reported in a male from Marcilio Dias Naval Hospital, Rio de Janeiro, Brazil.[48] Thus, direct invasion of abdominal aorta by worms might be associated with destruction of vessel wall and dilation of aorta but again, the effects of chronic worm infection in a focus far from abdominal aorta are not evaluated yet.

Desired chronic worm infection

The appropriate life stage in which chronic worm infection might be beneficial is not well known. But it seems that worm infection in childhood brings most positive effects of worm-borne immune balance. In some life stages, worm infection could be harmful. Maternal worm infection during pregnancy might results in low-birth weight which could be considered a risk factor for hypertension in adulthood.[49] Worm infection during the first months of stent implantation might raise the risk of in-stent restenosis due to increased secretion of TH-2 related cytokines as transforming growth factor-β (TGF-β) which is a pro-fibrotic cytokine. This could be interpreted conversely as decreased rate of stent thrombosis due to decreased inflammation in the setting of chronic worm infection at the period of stent implantation. The influence of media provided by chronic worm infection in this clinical situation has not been investigated yet but theoretically it seems to act as a double-sword. The focus of chronic worm infection is also very important. Worm infection in the heart leads to vessel wall thickening and myocarditis. Opisthorchiasis infects all cardiac cells especially cardiomyocytes and might progress gradually to cardiosclerosis. It may manifest as ischemic heart disease or myocarditis.[50] Myocardial infection with *Trichinella spiralis* manifests as electrocardiographic changes and decreased ejection fraction.[51] Thus, the site of chronic helminthic infection imposes a great impact on the cardiovascular system. Direct infection of the cardiovascular system by worms is potentially dangerous, while chronic worm infection as intestinal helminthic infection, in a focus far from cardiovascular system, could be beneficial. Indeed, not all worm infections are safe. Currently, safe therapeutic worms include *Necator americans* (human hookworm), *Trichuris suis* (pig whipworm) and Trichuris trichiura (human whipworm). Non-human species (*Trichuris suis*) are preferred for clinical applications in order to modulate or block diseases related to immune dysregulation.[52] Of course, therapeutic worm infection could be beneficial if other risk factors are modified. In the presence of uncontrolled underlying risk factors, worm-based therapies might not be beneficial.

Suggested animal model

For comprehensive evaluation of atheroprotective properties of worms, lack of experimental models is a great obstacle. By transferring worm-modulated B-cells to sensitized recipients as atherosclerosis prone animals and following the fate of atherosclerosis, the impact of chronic worm infection in pathogenesis of atherosclerosis could be well studied as an experimental model.

Clinical pearls

Cardiovascular diseases fall in the category of "man-made degenerative diseases". Did over-health care issues lead to the human-made skewness of immune system? There is no explicit evidence; however, the idea of voluntary immune skewness sounds intriguing. This therapeutic option has captured attentions previously for the treatment of some disorders, especially auto-immune diseases. Larva therapy or being stung by honey bees/mosquitoes are among these natural weapons for voluntary immune modulations. Worm therapy has been applied in treatment of auto-immune disease as type-I DM, asthma, allergic disorders, eczema, hay fever and inflammatory bowel diseases.[52–54] Protection against atherosclerosis or treatment of cardiovascular diseases could be added to the list of applications of worm-based therapies. Atherosclerosis seems eligible for this kind of therapy as a disease with possible autoimmune nature. Nevertheless, it is evident that atherosclerosis is a silent killer due to its gradual progression and identification of the early stages of disease is not easily achievable. By the time when atherosclerosis manifests, the opportunity for initiation of immune modulation is lost. Since atherosclerosis is a disease beginning in early childhood, "fine immune-modulation" plans should be sought much earlier. Decreased microbial burden in childhood due to Westernization leads to missed immune responses and pathogen specific polarization of TH1 to TH2 profile. This untrained immune system is in parallel with increased prevalence of allergic disorders and CVD.[4] Currently there is no way to predict the immune balance signature of an individual from childhood to decide if he/she is eligible for such immune modulation cares before disease initiation. The simplest option which precludes these insurmountable mountains is the allowance of wild-type life and achieving a better nature-friendly phenotype. Appreciating the seminal works of Strachan and applying Darwinian medicine, evolutionary adaptation to "old-friends" seems practical for maintenance and promotion of vascular health. But certainly, current hygiene must be held at intermediate stages between past and modern hygiene states due to the complexity of modern life. Fortunately, rational immune modulation is achievable through various ways as exposure to cowsheds, endotoxins, environmental saprophytic bacteria as lactobacilli, probiotics, helminthes, hepatitis A virus, bees, mosquitoes, etc.[1,55–57] So, is it possible to render environmentally missed "old-friends" to reconciled "vessel-friends"? Someday, the concept of "nothing is nonsense in nature" may help to the improvement of cardiovascular hygiene of humans who changed the environment to great extent during ages. A dose-range study should be performed to identify the amounts of larva of eggs/gram of feces which are both safe and effective. If worms down-regulate inflammatory conditions leading to atherosclerosis (Figure 1), it may be benefical if physicians do not treat mild stages of childhood infection with safe worms (after diagnosis of the worm type). Thus, routine dehelmintization should not be advised. Perhaps timely helminthic eradication plans would be developed in future in order to initiate dehelmintization after recognizing that enough athero-benefits have been derived from worm infection. It is obvious that chronic worm infection is not always safe and this chronic infection might predispose the host to various disease states such as malnutrition, iron deficiency anemia, portal hypertension, chronic diarrhea, seizure, increased morbidity and mortality, etc.[58–59] Thus, if alive worms should be certainly eradicated by the physician diagnosis, is it possible to afford host or even high risk patients for cardiovascular disease, with desired athero-protective immune state using dead worm eggs or dried components of dead worms? The true answer is still obscure, but if it is possible, addition of dried worm components could be used as food supplements for enhancement

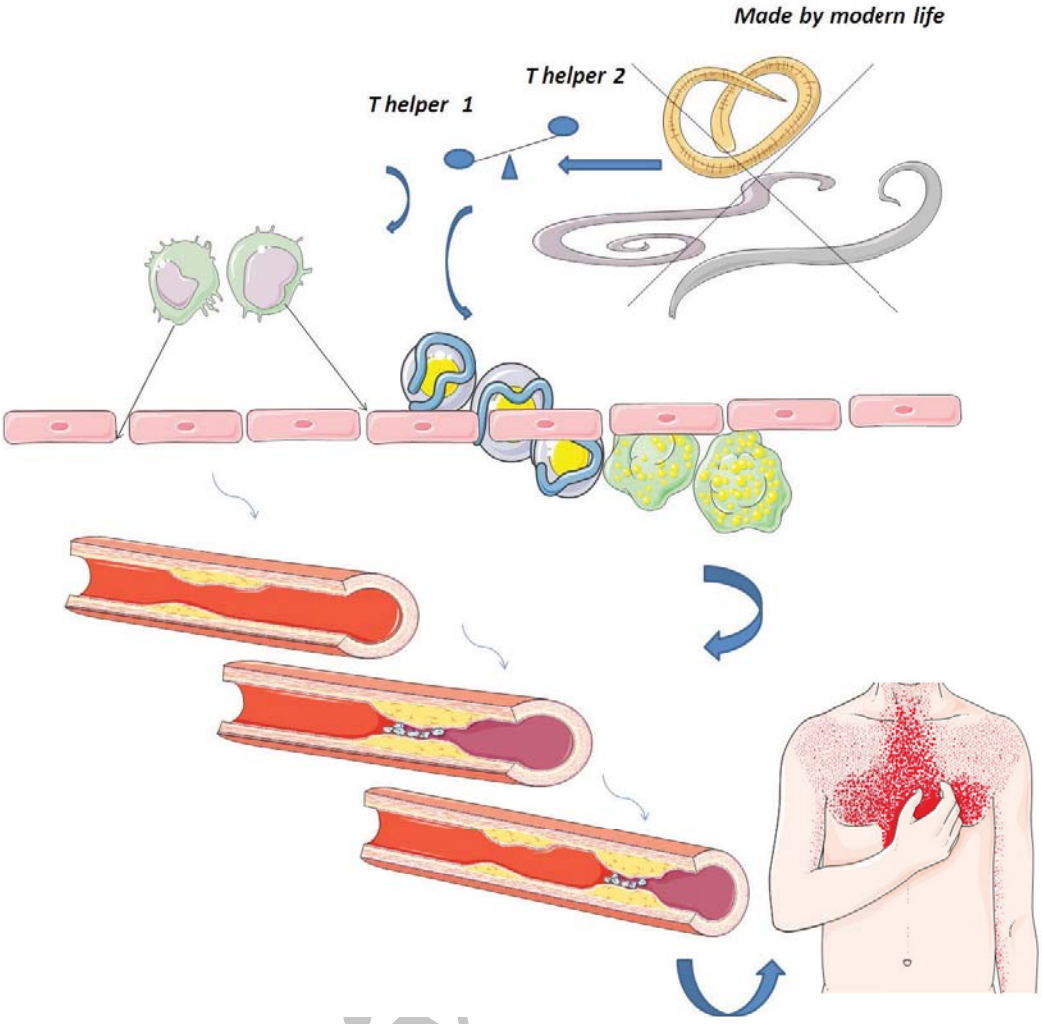

Figure 1. In modern life, through strong attempts for eradication of helminthes infections, balance of T helper cells shifts toward T helper 1 cells and related cytokines which cause imitation, development and progression of atherosclerosis and its complication.

of cardiovascular system as omega-3 fatty acids. I speculate that this Egyptian diet could be used beneficially like heart healthy Mediterranean diet which relies on basic healthy eating of food materials enriched with anti-oxidants plus flavorful olive oil or dragon heart food supplement used in past Korean and Japanese diet.[23,60] Of course, further and future surveys should clarify possible beneficial effects of this speculated Egyptian diet. Wormy products can also be used in their living state as probiotics in natural yogurts enriched with safe worms or worm eggs. We can imagine that worms could be helpful in non-pharmaceutical secondary prevention of atherosclerosis. If worms lose their tendency for transmigration in human body or destruction of the host tissue, chronic worm infection could provide a therapeutic immunomodulatory focus far from atherosclerotic plaque in human body. Thus, the idea for pills filled with genetically modified worms that can be released in the acidic environment of the stomach is excellent. The idea of vaccination by worm elements for prevention of atherosclerosis may be considered as a future innovation that becomes applicable by identifying the athero-protective parts of safe helminthes.

This is prudent to say that lower prevalence of atherosclerosis among habitants of the Nile Banks is just due to living with co-evolved organisms. Despite its lower prevalence in Egyptians, it is still the predominant driver of death in this nation. Interestingly, atherosclerosis has been linked to mummies longevity. Athermanous deposits were found in the aorta of the Egyptian king Menephta in 1909. Atherosclerosis and calcified vessels have been found to be commonplace in ancient Egyptian mummies (Ramesses II, III, Sethos I, Ramesses V and Ramesses VI), attributed to a diet rich in saturated fat confined to these elite population compared with the general vegetarian population.[61–63] In these mummies, calcified vascular patches and atherosclerotic vessels were found to be equal in both males and females but it was more commonly seen in mummies with older age at the time of death.[64,65] But Egypt, as a country in transition for development of atherosclerosis, could be scrutinized more for lower prevalence of atherosclerosis. Most Egyptians are concentrated in the Nile Banks, notably in Alexandria and Cairo. Despite emerging risk factors of atherosclerosis in younger Egyptians such as overweight and reduced physical activity, the first Cairo imigrants in recent years were ex-farmers with lower prevalence of overweight, but seeking for hidden factors that brings lower frequency of CVD should be sought.[44] In this regard, Cairene lifestyle, Egyptian commensal state, their nature-friendly habits and adherence to such conceivable Egyptian diet might be those speculated hidden factors. Many lessons remain to be learned yet from ethnic differences in

the prevalence of cardiovascular diseases.

Conflict of Interest:

none declared.

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