New Concepts for the Management of Atherosclerosis From Persian Medicine

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Abstract

Objectives: Atherosclerosis is the basic pathology of most cardiovascular diseases which are the most common non-communicable diseases in the world. Recently, inflammation in the arterial wall has been proposed for the initiation of atherosclerosis although there is no specific anti-inflammatory treatment for atherosclerosis. Persian medicine (PM) with at least 7000 years of practice background may help in atherosclerosis management. The aim of this study was to describe atherosclerosis according to the teachings of PM to find better methods for its management.

Materials and Methods: To this end, several data were searched, including current medical literature and published articles on PM, as well as Avicenna's main medical textbook, the Canon of medicine for creating the hypothesis of the mechanism of atherosclerosis in PM.

Results: Avicenna has implied *Waram* in the arterial wall. The features of *Waram* in PM accommodate inflammation, and *Waram* in the artery is compatible with atherosclerosis. The natural history of atherosclerosis is highly similar to humoral evolutions in *Waram*. PM has a wide range of therapeutic drugs and treatment plans for warm, and many of the applied drugs in this regard have documented anti-inflammatory effects in the current medicine. New risk factors for prevention and new treatment modalities are recommended based on this hypothesis.

Conclusions: The new hypothesis that emerged from PM for atherosclerosis is compatible with the newest hypothesis of the mechanism of atherosclerosis in current medicine. Moreover, PM introduces new preventive and treatment modalities for atherosclerosis which is unknown in current medicine and their application may reduce disease burden and mortality of atherosclerosis-related diseases.

Keywords: Persian medicine, Atherosclerosis, Inflammation

Introduction

"Atherosclerosis" derives from Latin words "*athero*" and "*sclerosis*" meaning plaque and hardening, respectively. It is a pathologic description in arteries, which was first used by Jean Lobster, a French pathologist and surgeon in 1826 (1). Atherosclerosis has been described in humans, as well as other nonhuman primates, mammals, and birds. The evaluation of Egyptian mummies has shown that ancient people's atherosclerotic lesions are not different from present time atherosclerotic lesions (2). In pathologic examinations, the intimal and inner sides of the medial layer of the artery are involved by lipid accumulation, calcium deposition, fibrosis, necrosis, and inflammatory cell infiltration (3).

The etiology and pathogenesis of atherosclerosis are not clearly understood. Carl von Rokitansky and Rudolf Virchow were two pathologists in the 19th century and both noticed that atherosclerosis is an inflammatory process (4). Later, with evidence on lipid accumulations in atherosclerotic plaques by Anitschkow and Chaltow in 1913, the lipid accumulation theory emerged in this

respect (5). During the last decades of the 20th century, two hypotheses were proposed, namely, "response to injury" and "inflammation" (6). Although Rudolf Virchow in his book, "*Cellular Biology*" described the inflammatory origin of atherosclerosis, it was considered as lipid precipitation for more than a century. Recent scientific findings again confirmed the inflammatory origin of atherosclerosis (4).

In spite of the increasing knowledge of mechanism and management approaches to this disorder, it is still one of the unsolved health problems in all societies. Overall, cardiovascular diseases are the leading cause of disease burden and mortality worldwide (7), consisting of the coronary artery, cerebrovascular, peripheral arterial, and aortic-related diseases such as hypertension. Atherosclerosis is the basic pathology in these diseases. A previous study showed that diabetes, hyperlipidemia, hypertension, cigarette smoking, obesity, old age, male gender, and family history are major atherosclerotic risk factors (8). Lifestyle modifications and risk factor management, as well as drug, and interventional and surgical therapies have been only partially effective in

reducing disease burden and mortality. Moreover, it is estimated that cardiovascular diseases will cause more than 30% of mortalities in 2030 (7). Atherosclerotic disease morbidity, mortality, and treatment have impressive financial issues, especially in low- and medium-income societies. The development of new prevention and treatment methods for reducing the prevalence and mortality of atherosclerosis-related diseases are welcomed accordingly. Traditional and complementary systems of medicine are considered as one of the sources that are rooted in history to find new approaches regarding treating and preventing diseases. In this regard, the World Health Organization recommends using traditional medicines in countries for treatment (9). Persian medicine (PM) is one of the oldest traditional systems of medicine, dating back to at least 7000 years ago (10). PM was born in ancient Persia thousands of years ago and developed through time by the collaboration of other nations such as Greeks and Egyptians. It was the main paradigm of medicine in the West and the Middle East for centuries, at least until the 17th century (11). Nowadays, it is practiced as an alternative medicine all over the world from Asian countries such as China to African Arabic countries such as Egypt and even in North America (12). This medical system is based on the humoral theory and has a holistic approach to health and disease. The humoral theory denotes that all body functions act through four liquid substances called humors (*Akhlat*). According to the principles of PM, ingested food harbors four steps of digestion in the body including stomach, liver, vessels, and tissue digestion. Food converts to four types of humors by liver digestion. Humors are nourishing fluids with different temperaments and are called "*Dam*" (sanjuine), "*Balgham*" (phlegm), "*Safra*" (yellow bile), and "*Sauda*" (black bile). It is believed in PM that the imbalance of humors or abnormal humors in collaboration with *Tabiate Modabbere* (the healing power of the body) causes diseases (13). *Tabiate Modabbere* is a force that manages all body functions.

The most famous Persian physician, Avicenna, collected past medical experiences and categorized the principles of medical practice in his five-volume medical encyclopedia, the Canon of the medicine (*Al-Qanon fi-al-Tibb*). This book has been described as the bible of medicine (11). In spite of the development of new drugs and technologies, atherosclerosis has remained number one killer of mankind. Although current medicine has proposed a new inflammation theory for atherosclerosis, there are no effective drugs yet. This gap could be filled with PM.

Thus, this study aimed to combine this ancient medical system with the current concepts of medicine to find new hypotheses and approaches to manage atherosclerosis.

Materials and Methods
In this study, cardiovascular reference texts and papers (1930-2018) were searched in data centers of the Web of Science, PubMed, Scopus, and Google Scholar using the keywords of 'atherosclerosis', 'inflammation', 'coronary artery', 'humor', 'Unani system of medicine', and 'Persian medicine'. Avicenna's Canon of the medicine (Arabic edition) was studied word by word and any statement regarding atherosclerosis was noted as well. Any findings were compared to the current knowledge of medicine. Then, the narration was conducted and recommendations were proposed regarding atherosclerosis prophylaxis and treatment in the PM.

Results
Inflammation is the last proposed mechanism of atherosclerosis in the literature and inflammatory biomarkers are increasingly used in the diagnosis and risk stratification of coronary artery atherosclerotic diseases (6). Well-known coronary atherosclerotic disease risk factors are hypertension, diabetes, hyperlipidemia, cigarette smoking, obesity, and physical inactivity and all are related to inflammation (5). There is no specific anti-inflammatory treatment for atherosclerosis in the current medicine although evidence exists regarding the anti-inflammatory effects of the applied drugs in alternative medicine for atherosclerotic-related diseases. For example, Chinese drugs against atherosclerosis have anti-inflammatory effects (14). Further, Uyghur medicine, which is related to the northwest of China, presents drugs for heart diseases with anti-inflammatory properties (15). There is no basic and detailed theory and description in ancient traditional medicines regarding atherosclerosis (it was first introduced in 1826) thus drugs and other treatment modalities used in the treatment of atherosclerosis-related diseases in alternative medicine should be interpreted with known scientific findings of current medicine. Therefore, the study aimed to hypothesize the mechanism of atherosclerosis based on PM according to new scientific findings in current medicine and tried to explore basic mechanisms of treatment modalities for atherosclerosis in PM. The most complete academic textbook of PM, the Canon of medicine was used for analyzing ancient concepts.

Hypothesis
Based on PM teachings, arterial stenosis could be due to intraluminal ethnologies (e.g., viscous humors), intramural problems (e.g., spasm), and extraluminal

factors due to pressure effects. Avicenna in the Canon of the medicine denotes *Waram* in arteries and mentions that its treatment is difficult (16). Moreover, he notes *Waram* as one of the mechanisms of a lumen narrowing and obstruction. We hypothesized that *Waram* in the artery in PM is in accordance with inflammation inside the intimal layer of arteries in current medicine.

Waram

Waram is a bulging (edema) in the tissue with the distortion of its architecture (16). During four stages of food digestion, some waste products are produced which must be eliminated from the body. Defecation eliminates stomach waste byproducts through feces, urination often excretes liver waste materials, perspiration is usually for vessel cleaning, and skin dead layers and hair are mostly for the tissue removal of waste products (16). Waste products are related to each humor with respective temperament. If these wastes are not excreted, they accumulate in the body. The accumulation of waste products including humoral wastes, *rih* (gaseous wastes), and extra water in the body causes them to accumulate in the lumen and the tissue matrix of organs. *Waram* may ensue if accumulations take place inside the tissue. Based on the temperament of precipitated humoral waste materials, *Wram* is classified into cold (i.e., *Balgham*, *Sauda*, long-standing warm substance) and warm (i.e., *Dam*, *Safra*, and *ofunat* as the infected material). *Waram* has usually acute manifestations but cold *Waram* has mostly chronic features. *Waram* undergoes one of the four pathways during the time. More precisely, it may become dense and cold through time and cause tumors such as masses, dissolved with body powers and disappeared, infected with *Hararate gharibe* (infection) or healed with producing and discharging pus (16). A natural history of *Waram* induction and healing has each of the four stages of initiation, acceleration, steady-state, and resolution. All manifestations of *Waram* comes from the interaction of wastes with the body power of healing, namely, *Ttabiate Modabberehe* (16).

Discussion

The pathology and the natural history of *Waram* are highly similar to inflammation in current medicine. Both *Waram* and inflammation are pathologic findings in body tissues with edematous configuration and distortion. Inflammation results from the immune system combating foreign, noxious, or abnormal agents (17). *Waram* also results from interacting humoral wastes with *Tabiate Modabbere*. There are systemic signs and symptoms, along with inflammatory markers in inflammation. Abnormal humors and wastes are also present in the blood, urine, or other body discharges in *Waram* and are clues to the identification of the etiology of *Waram*. Both *Waram* and inflammation have the same natural history

with induction, acceleration, steady state, and finally, resolution. Based on these findings, it can be hypostatized that abnormal humors are related to inflammation. They initiate inflammation in tissues such as arteries and their presence in blood or other body fluids are the markers of inflammation. We could classify inflammation into four major types according to four humors.

Atherosclerosis is a chronic silent inflammatory process in the arterial wall. It is exactly unknown what induce inflammation is in the intimal layer at first. There are four pathologic stages in atherosclerosis. These are (*a*) endothelial inflammation and activation, (*b*) lipoprotein accumulation, modification, and foam cell formation, (*c*) plaque growth, fibrosis, thrombosis, and necrosis, and (*d*) the activation of a plaque with acute events (18). Foam cells are monocytes recruited to the intima and changed to macrophages and engulfs deposited lipids. Other immunity cells such as T-lymphocytes and plenty of inflammatory mediators are present in plaques. A plaque is surrounded by a fibrous capsule made by migrated smooth muscle cells from the media. A capsule may be weakened in active inflammation and ruptures and causes acute events due to chronic and silent nature (19).

In PM's view, *Waram* in the arterial wall correlates with atherosclerosis, thus four types of *Waram* or four stages of atherosclerosis could be considered in the arterial wall. *Waram* due to *Balgham* and *Sauda* are chronic with a long-standing history of accumulation and both have the cold temperament. *Waram* due to *Balgham* is soft while *Sauda*-type *Waram* is dense and hard (20). *Balgham*-type of *Waram* is correlated with early atherosclerotic lesions with extreme fatty components such as fatty streaks. During the time, it becomes denser with calcification and fibrosis and *Sauda*-type *Waram* may ensue accordingly. This correlates with cold, calcified, and chronic plaques. *Waram* may develop a necrotic core "rim" and ruptures and evacuates its contents. This happens in acute events due to the rupture of the capsule of the plaque. The dissolution of *Waram* may equal the regression of atherosclerosis. The activation of the atherosclerotic plaque with the enlargement of the plaque, the thinning of the capsule, and changing to a hot plaque may correlate with infection (*Ofunat khelt)*. Any condition resulting in waste product accumulation, especially with *Balgham*- or *Sauda*-like quality in the body exacerbates inflammation in tissues such as arteries. These may be considered atherosclerotic risk factors from PM's view of point. In this regard, there are four types of risk factors. Type one atherosclerotic risk factors are from the ingestion of foods producing more wastes. These include overeating, incomplete chewing, eating without true hunger, drinking much while eating, returning to work immediately after eating, sleeping or sexual intercourse with a full stomach, eating mainly *Balgham* or *Sauda* producing food, eating bad processed foods such as fried food or reheating of refrigerated food,

eating incompatible foods such as meat with dairy, and eating in a hurry. Type two risk factors are from excess waste production due to abnormal digestion. Gastric mal-digestion, liver disease, and vessel and tissue weak metabolism can increase waste products. Toxic materials from the environment, extreme climate changes, psycho-spiritual stress, sleep disturbance, drinking cold while the body is warm after exercise or bathing, old age after sixty years, and the hereditary weakness of metabolism impair digestion and increase waste production. Type three risk factors are excess waste accumulations from their incomplete excretion. Constipation, incomplete urination or renal disease, inadequate perspiration, lack of medical bathing, physical inactivity, *Sodde* (obstruction in body transit channels), and an increase in the viscosity of body humors (*Ghelzat* and *Lozojat*) cause the incomplete removal of wastes. When waste materials increase in the body, they precipitate in weak susceptible tissues (21). Type four risk factors are local or generalized factors which increase the arterial tendency for waste accumulations. Susceptibility may be hereditary or acquired. Constitutionally weak arteries have a tendency to *Waram*. This may be to the abnormal constitutional temperament of the artery. It may correlate with genetic susceptibility. Locally, bifurcation and branching points of arteries tolerate extreme damage and become weak during the time, thus atherosclerosis is more frequent at these points (18). There are some foods and drugs with booster effects in PM that may increase arterial resistance to *Waram* (16). The treatment of the long-standing atherosclerotic lesions requires eliminating the modification (*Nozj*) of waste materials. According to (16), dense substances must be softened and then excreted with feces (*Es-hal*), urine (*Ed-rar*), or sweet (*Tarig*). Some drugs with a dissolving effect (*Mohallel*) may reduce *Waram* and may be used for atherosclerosis regression. Many applied drugs for the treatment of *Waram* have antioxidant and anti-inflammatory effects (19). This hypothesis derived from ancient PM obviously confirms new scientific findings showing that classic and traditional medicines are two faces of a coin. Each medical system refers to a human body with its own language and both can be complementary to each other. The topic of this paper should be better coined "new ideas about humoral medicine". This article is the first one to call abnormal humors as inflammatory systems, thus we could have four major inflammatory pathways. This new idea opens a wide area of research and new methods of treatment. Nonetheless, the major weakness of this study was the absence of detailed clarification regarding these four inflammatory pathways, which needs another extensive laboratory study.

Conclusions

PM explores more risk factors and broad lifestyle components compared to current medicine. This could complete and intensify the lifestyle modification plan in current medicine (13). It also introduces a novel and different therapeutic approach to atherosclerosis which is based on medications with anti-inflammatory effects. Current drugs used in atherosclerotic diseases are anti-lipid, anti-thrombotic, and vasodilators. Based on the new inflammatory mechanism of atherosclerosis, the PM approach may light the innovation of new drugs in classic medicine and could also reduce the ever-increasing burden and mortality of the cardiovascular disease. More investigations are required to assay their effects and appreciate this hypothesis in atherosclerosis management.

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