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Chapter

Atherosclerosis: A Journey around the Terminology

Oladimeji Adebayo and Abiodun Moshood Adeoye

Abstract

The term atherosclerosis underwent a tedious pathway to arrive at its current status and interpretation. Furthermore, terms such as atherosclerosis, arteriosclerosis, and arteriolosclerosis appear similar and are misused interchangeably. This chapter highlighted the various terminologies linked with atherosclerosis. This chapter highlighted how the terminology of atherosclerosis evolved and, also, the various classifications, e.g., atherosclerosis, Monckeberg calcific sclerosis and arteriolosclerosis, and gave mention to the differences among them.

Keywords: atherosclerosis, arteriosclerosis, arteriolosclerosis

1. Introduction

The understanding of atherosclerosis evolved uniquely in terms of terminology, aetiology, structural features or pathophysiology over the last 300 years [1]. Furthermore, the three terms, atherosclerosis, arteriosclerosis and arteriolosclerosis, with lethal implications and similar terminologies affecting the arterial vessels, however, can easily be confused or just used interchangeably indiscriminately [1–5]. There is evidence in the literature that these terms are mistakenly interchanged [3, 4, 6]. This confusion was not helped by the key stakeholders like the pathologists and clinicians who over the years failed to reach a consensus to delineate them [7].

A remarkable example of such confusion is that emanating from the American Heart Association (AHA) who publishes journals titled Arteriosclerosis, Thrombosis, and Vascular Biology and Hypertension. While the Arteriosclerosis, Thrombosis, and Vascular Biology journal publishes mainly articles related to the experimental, clinical and epidemiological facets of atherosclerosis, the Hypertension journal has a prominent section on “arteriosclerosis” [6].

Interestingly the confusion around the nomenclature appears to be age-long. Hueper, WC’s writing in the Archives of Pathology and Laboratory Medicine in 1945 titled “Arteriosclerosis” suggests the term atherosclerosis was extensively used concerning the pathology related to cholesterol metabolism [8]. Rabson a medical doctor while writing a letter to the editor of the American College of Clinical Pathology expressed his alarm at the confusion of the degenerative disease [8, 9]. This alarm was stemmed from the observation of an article titled arteriosclerosis, but the article did not use any of such nomenclature rather than atherosclerosis [9].

As recent as 1995, the AHA Report from the Committee on Vascular Lesions of the Council Arteriosclerosis interchanged arteriosclerosis and atherosclerosis [11].
Not that there are no prominent attempts to delineate these terms, especially for arteriosclerosis and atherosclerosis. As far back as 1963, George Pickering, one of the fathers of modern cardiology, highlighted the similar confusion between arteriosclerosis and atherosclerosis in his lecture at The University of Alabama, published in the article “Arteriosclerosis and Atherosclerosis: The Need for Clear Thinking” which stated the definition in clear terms [6, 7]. He believed the confusion might be as a result of affection of the arterial system by the two entities although they affect different arterial sizes. He, however, delineated them by defining atherosclerosis as a complex inflammatory process associated with the presence of oxidized low-density lipoprotein (LDL) cholesterol in the intima and media of the arterial wall and arteriosclerosis as the functional depletion of large artery elasticity [6].

Also, notable observation is that arteriosclerosis [10] serves two functions, an overarching term for other sub-terms and merely a term that can be inter-used with atherosclerosis [2, 11]. Besides, there is poor agreement on the terms related to arteriosclerosis.

Also, over the years, other terms such as Mönckeberg medial calcific sclerosis (MCS) and arteriolosclerosis gained popularity [1]. There was a feeble attempt for clear terms and classification as related to atherosclerosis.

The chapter will also highlight recommendations on possible reclassification based on gross and histopathologic features, among others. In summary, the chapter will extensively discuss the key terms related to arteriosclerosis and the historical evolution of these terms and highlight recommendations on possible reclassification as having been previously recommended and published.

2. Arteriosclerosis

Arteriosclerosis is derived from the Greek word arteria, meaning artery, and sclerosis, meaning hardening, and “osis” is a Greek suffix that means a diseased condition [14]. Much literature appears to refer to arteriosclerosis as the overarching term that includes three different lesions, atherosclerosis, arteriolosclerosis and Mönckeberg medial calcific sclerosis (Figure 1) [2, 12]. The three lesions are underpinned by the resultant hardening and thickening of the arterial wall [2]. However there appears not to be any consensus document by any significant cardiovascular or pathology organization on such division rather than such classification emanated from classic textbooks of pathology [1]. Many articles also carry this classification [13].

It, however, appears that the term is also used to describe the functional diminution of large artery elasticity marked by pulse wave velocity [14]. It, however, brings to fore another dimension of intermix with atherosclerosis.

![Figure 1](image.png)

*The classification of arteriosclerosis.
3. Atherosclerosis

Atherosclerosis is derived from the Greek word “athero”, meaning gruel or paste, and sclerosis, meaning hardening, and “osis” is a Greek suffix that describes a diseased condition [15]. It merely is the hardening of an artery precisely due to an atheromatous plaque. Atherosclerotic lesions otherwise called atheromata are asymmetric focal

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1575</td>
<td>Fallopius wrote about “a degeneration of arteries into bone,” and anatomists of that era commonly mentioned ossified arteries [2]</td>
</tr>
<tr>
<td>1740</td>
<td>Johann Friedrich Crell described this as the hardening of the vessels instead of bony arteries [17]</td>
</tr>
<tr>
<td>1755</td>
<td>von Haller described this hardening as thickening as “atheroma” [1, 37, 38]</td>
</tr>
<tr>
<td>1833</td>
<td>Frenchman Jean Frederic Martin Lobstein first used the term “arteriosclerosis” to describe calcified arterial lesions [1]</td>
</tr>
<tr>
<td>1868</td>
<td>George Johnson limited the term arteriosclerosis to “noncalcified, non-atheromatous stiffening of small vessels” [2]</td>
</tr>
<tr>
<td>1881</td>
<td>Jean Frederic Martin Lobstein first used the term arteriosclerosis in the second volume of his book titled <em>Traité d’Anatomie Pathologique</em> [17, 39]</td>
</tr>
<tr>
<td>1903</td>
<td>Mönckeberg arteriosclerosis was first described and named after Johann Georg Mönckeberg using details from 130 patients. It was also called “Mönckeberg media sclerosis” or “Mönckeberg media calcinosis” [38, 40]</td>
</tr>
<tr>
<td>1904</td>
<td>Félix Marchand introduced the term “atherosclerosis” and suggested it is responsible for obstructive processes in the arteries [2, 33, 41]</td>
</tr>
<tr>
<td>1908</td>
<td>A.I. Ignatowski demonstrated that rabbits experimentally develop atherosclerosis by feeding on cholesterol-rich food of egg and meat [33, 34]</td>
</tr>
<tr>
<td>1910</td>
<td>Adolf Windaus demonstrated that atheromatous plaque has a concentration of cholesterol [33, 42]</td>
</tr>
<tr>
<td>1914</td>
<td>Anitschlow described the role of cholesterol accumulation in the development of atherosclerosis [35]</td>
</tr>
<tr>
<td>1912</td>
<td>Faber differentiated calcification in the coronary arteries which are atherosclerotic in origin from Mönckeberg sclerosis [4]</td>
</tr>
<tr>
<td>1913</td>
<td>Nikolai N. Anichkov showed that cholesterol alone caused the atheromatous changes in the vascular wall [33, 43]</td>
</tr>
<tr>
<td>1954</td>
<td>Rabson SM noted that arteriosclerosis lacked specificity, uniformity and consistency. He suggested how the term would be used [2]</td>
</tr>
<tr>
<td>1961</td>
<td>Sir George Pickering, one of the fathers of modern cardiology in his lecture at the fourth Tinsley Randolph Harrison lecture at The University of Alabama, clearly differentiated arteriosclerosis and atherosclerosis</td>
</tr>
<tr>
<td>1965</td>
<td>Eggen and other workers demonstrated atherosclerotic coronary artery calcification [4]</td>
</tr>
<tr>
<td>1971</td>
<td>Russell Ross and Seymour J. Klebanoff using electron microscopy demonstrated that the atherosclerosis lesions are characterized by an accumulation of smooth muscle cells associated with abundant connective tissue matrix [44]</td>
</tr>
<tr>
<td>1972</td>
<td>Ross and colleagues showed that vascular smooth muscle cells proliferate and synthesize and secrete all three major constituents of connective tissue: collagen, elastic fibre microfibrils and elastin</td>
</tr>
<tr>
<td>1975</td>
<td>Watanabe heritable hyperlipidaemic rabbits were discovered and subsequently used in most experimental settings for lipid disorder and atherosclerosis [45]</td>
</tr>
<tr>
<td>1985</td>
<td>Brown and Goldstein discovered the role of low-density lipoprotein (LDL) receptors which won them the 1985 Nobel Prize</td>
</tr>
<tr>
<td>1992</td>
<td>The AHA started to release a series to define the intima of human arteries and its atherosclerosis-prone regions</td>
</tr>
</tbody>
</table>

Table 1.

Key milestone which refined the term atherosclerosis and related terms.
Atherosclerosis, Arteriosclerosis and Arteriolosclerosis

<table>
<thead>
<tr>
<th>Atherosclerosis [18]</th>
<th>Arteriolosclerosis</th>
<th>Mönckeberg arteriosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidaemia</td>
<td>Dyslipidaemia</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Genetic risk factors</td>
<td>Genetic risk factors such as ABCC9 gene variant</td>
<td>Genetic diseases such as Keutel syndrome</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Chronic inflammatory disease such as systemic lupus erythematosus, etc.</td>
<td></td>
</tr>
<tr>
<td>Ageing</td>
<td>Ageing</td>
<td>Disturbances of calcium metabolism</td>
</tr>
<tr>
<td>Obesity</td>
<td>Chronic kidney disease</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Family history of early heart disease or coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking and other tobacco use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High level of CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
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<tr>
<td>Sleep apnoea</td>
<td></td>
<td></td>
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<tr>
<td>Sedentary lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A personality type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air pollution</td>
<td>Blood-brain barrier dysfunctions</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. The risk factors associated with atherosclerosis, arteriolosclerosis and Mönckeberg’s arteriosclerosis.

<table>
<thead>
<tr>
<th>Atherosclerosis</th>
<th>Arteriolosclerosis</th>
<th>Mönckeberg arteriosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key processes</td>
<td>Lipid accumulation</td>
<td>Protein accumulation and fibromuscular proliferation of the intima</td>
</tr>
<tr>
<td>Type of process</td>
<td>Pathologic</td>
<td>Pathologic</td>
</tr>
<tr>
<td>Vessels affected</td>
<td>Large and medium arteries</td>
<td>Concentric media thickening of muscular arteries</td>
</tr>
<tr>
<td>Part of the vessel affected</td>
<td>Intima and underlying smooth muscle</td>
<td>Media</td>
</tr>
<tr>
<td>Pathomorphological</td>
<td>Plaque-forming degenerative changes of the large elastic arteries such as the aorta</td>
<td>Thickening of the vessel walls that narrows the lumen</td>
</tr>
<tr>
<td>Effect on vessel dimension</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Calcification</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Some key differences in atherosclerosis, arteriolosclerosis and Mönckeberg arteriosclerosis.
thickenings of the intima which is the innermost layer of the artery [16]. While arte-
riosclerosis is a chronic pathological disease concept which refers to arterial lesions
characterized by intimal thickening, stiffening and remodelling of the arterial walls [2].
Atherosclerosis is a generic term used to describe a general term describing a hardening
of medium or large arteries [1, 2] and also referred to as atherosclerotic vascular disease.
The atheroma principally blocks large- and medium-sized elastic and muscular
arteries leading to ischemia in the heart, brain or extremities, thereby causing infarction
[17]. The most critical risk factor for atherosclerosis is dyslipidaemia due to high plasma
concentrations of cholesterol, especially low-density lipoprotein (LDL) cholesterol or
high-density lipoprotein. While dyslipidaemia is a key risk factor, it can be found at age
(Tables 1–3) [17]. The critical step in atherosclerosis formation includes (i) fatty streak
formation, (ii) atheroma formation and (iii) atherosclerotic plaque formation [18].

4. Arteriolosclerosis

Arteriolosclerosis is simply the hardening and loss of the elasticity of the small
arteries and arterioles due to the progressive increase in the elastic and muscular
components of the wall of those vessels. It is simply the small vessel disease and prin-
cipally affects the brain and the kidneys [19, 20]. In the brain, it is associated with
the lacunar infarcts, vascular cognitive impairment and diffuse white matter lesions
[19]. The key predisposing factors include hypertension, ageing, ABCC9 gene vari-
ant, diabetes mellitus and blood-brain barrier dysfunctions (Tables 2 and 3) [21].
The sub-types include hyaline arteriolosclerosis and hyperplastic arteriolosclerosis.

5. Mönckeberg medial calcific sclerosis (MCS)

Monckeberg medial calcific sclerosis (MCS), Mönckeberg arteriosclerosis, or
Mönckeberg sclerosis is a degenerative and noninflammatory disease in which the
media of medium-sized and small muscular arteries becomes calcified independent
of atherosclerosis [22]. It is also considered as atherosclerotic medial calcification [4].
It is a ringlike calcification of the vascular media of small- to medium-sized vessels
without associated intimal thickening [22, 23]. It is a form of arteriosclerosis or ves-
sel hardening, where calcium deposits are in the muscular middle layer of the walls
of arteries (the tunica media). It usually causes damage to the kidney and heart.
Mönckeberg arteriosclerosis is commonly mixed up with calciphylaxis and prob-
ably is the most controversial type of arteriosclerosis [4, 24].

6. Historical background of atherosclerosis

Atherosclerosis or other related nomenclatures are not new disease entities
(Tables 2 and 3). There was, however, some emerging insight into what was later
termed as atherosclerosis. Hippocrates (469–377 BC), the father of modern medicine,
described the sudden cardiac death, while approximately 300 BC, Erasistratus
described the typical claudication intermittent symptoms of peripheral arterial
disease [25].
Egyptian mummies were noted to have evidence of atherosclerosis; although this
was not yet named atherosclerosis [8, 26–28]. In the earlier times, due to the lack of
sophisticated equipment to help the understanding, degenerative and nondegenera-
tive arteriopathy was also lumped together and poorly delineated. However, the
understanding of atherosclerosis increased exponentially in the last seven decades,
even though it was earlier thought to be a mere accomplishment of ageing and dodged for many years with controversies surrounding its link with cholesterol [27].

Albrecht von Haller, a Swiss biologist and the father of experimental physiology, used the Latin term “atheroma,” in 1755, to describe the plaque deposited on the innermost layer of systemic artery walls [29]. However it appears that Celsius may have used the same word about 2000 years ago while describing a fatty tumour [30].

In 1575, Fallopius wrote about “a degeneration of arteries into bone” suggestive of the presence of calcified atherosclerotic lesions in the arteries. Furthermore, ossified arteries were commonly mentioned by anatomists of that era [2]. By the eighteenth century, it was apparent that some progress has been made in understanding albeit rudimentary on what we call atherosclerosis today. For example, in 1799, Parry suggested the relationship between coronary lesions and the symptoms of angina pectoris [25].

Also, in 1815, J. Hodgson defined the fatty arterial degeneration as atheromatosis [30].

Frenchman Jean Frederic Martin Lobstein first used the term “arteriosclerosis” to describe calcified arterial lesions in his main body of work, a four-volume work on pathological anatomy written in French titled *Traité d’Anatomie Pathologique* (Treatise on Pathological Anatomy), based upon his vast personal experience [1, 25]. The work was unfinished at the time of his death in 1835.

The first mention of nondegenerative arteriopathy in the textbook was by Maurice Raynaud’s in *De l’Asphyxie Locale et de la Gangrene Symetrique des Extremites* (1852) and Leo Buerger’s “Thromboangiitis obliterans” [31]. While in 1879, more than 80 years later, Potain interpreted the relationship Parry found to arise from myocardial ischemia [25].

From 1900 onwards, the most significant progress in the understanding of atherosclerosis was made. At the beginning of the twentieth century, Aschoff introduced atherosis and atherosclerosis to describe morphologically different intimal lipid deposits of children and adults as early and late stages, respectively [32].

By 1904, Félix Marchand suggested that “atherosclerosis” should be better instead of “atheroma” as earlier described by Haller [29]. He had combined two Greek root words: *athéré*, which meant gruel or porridge, and *sclerosis*, which signifies hardening [29]. He did not only gave a nomenclature currently in use, but he also did justice to the pathologic process involving the association of fatty degeneration and vessel stiffening. He believed that atherosclerosis was responsible for almost all obstructive processes in the arteries [33]. In 1910, Adolf Windaus demonstrated that aortic “atheromatous lesions” contained six times as much as free cholesterol and 20-fold of esterified cholesterol compared to normal aortic wall [27, 33]. A.I. Ignatowski demonstrated that rabbits experimentally develop atherosclerosis by feeding on cholesterol-rich food of egg and meat [33, 34].

In 1914, Anitschkow, influenced by Ignatowski’s work, gave the first description of the role of cholesterol accumulation in the development of atherosclerosis while emphasizing the cardinal role of cholesterol in atheromatous changes in the vascular wall [35]. He had used a cholesterol-fed rabbit model while working at the Military Medical Academy in St. Petersburg to demonstrate that the extent of atherosclerosis was proportional to the absolute amount of and length of exposure to high blood cholesterol [27, 35]. His discovery was a defining moment in the study of this disease entity, although not without scepticism. While the rabbit model develops atherosclerosis after being fed high amounts of meat, eggs and milk, the dog and rat model did not [33]. This finding by later workers almost torpedoed this discovery attributable to Anitschkow [27]. It was also a blow to the lipid hypothesis due to these later species relative resistance to diet-induced hypercholesterolemia. Other factors that may have eroded the most unequivocal link of
cholesterol and atherosclerosis as enunciated by Anitschkow was the prevailing senescence hypothesis as a plausible reason for the development of atherosclerosis when he made the discovery [27]. Anitschkow also first described the *cholesterinesterphagozyten*, which today commonly is known as foam cells, derived from macrophages [25, 35].

The discussion of lipid hypothesis generally in the first 50 years of the twentieth century was also dodged with controversy, particularly the role of high blood cholesterol levels to the causal relationship of atherosclerosis and coronary heart disease, and that atherosclerosis was a reward of ageing as espoused by senescence hypothesis [27, 36].

With the improvement in morphological, immunohistological and molecular methods and advanced investigative techniques, LDL receptor and its roles in the development of atherosclerosis were discovered by Brown and Goldstein [25]. By 1958, there was enough information to make classification of atherosclerosis by the World Health Organization and described the sequences as a fatty streak, atheroma, fibrous plaque and complicated lesions [32]. The American Heart Association (AHA) starting from 1992 proposed a new morphological classification based on eight lesion types designated by Roman numerals which indicate the usual sequence of lesion progression [32].

Jian-Jun Li and Chun-Hong Fang’s writing in *Medical Hypotheses* journal suggests that atheroscleritis is a more rational term for atherosclerosis [29].

We now know the pathological processes that underpin atherosclerosis, which entails (1) endothelial injury, (2) intimal cholesterol accumulation and monocyte invasion with subsequent foam cell formation, (3) migration and proliferation of smooth muscle cells with expression of extracellular matrix, (4) local thrombus formation with secondary organization, (5) calcification and/or plaque rupture and (6) final occlusion due to plaque rupture/thrombus formation [25].

### 7. Challenges with terms

Gregory et al. pointed out the difficulty with terms which they notice: (i) it has an inconsistent naming convention, (ii) it fails to use terms that accurately describe the lesions, (iii) significant sclerotic arterial lesions are absent from the classification, and (iv) interchangeability of arteriosclerosis and atherosclerosis [2]:

1. **Naming convention.** The three authors noticed that the arteriosclerosis, atherosclerosis and Mönckeberg medial sclerosis are defined by their gross and histopathologic attributes while arteriolosclerosis was defined by vessel dimension [2]. Furthermore, “arteriolo” is a descriptive pathologic term.

2. **Description of lesion.** This term poorly describes the terms [2]. The Mönckeberg medial sclerosis as described by Mönckeberg, ironically, may not be described, and the lesion may involve the arterial intima rather than the arterial media [2]. Furthermore, arteriolosclerosis, which is a hardening of the vessel, does not describe the lesion since the process involves both protein accumulation and fibromuscular proliferation of the intima [1].

3. **Absence of crucial lesion from the classifications.** Restenosis lesions after balloon angioplasty and stenting, transplant arteriopathy, intimal nonatherosclerotic proliferative lesions in arterial vessels larger than arterioles, and a variety of disorders associated with vascular calcification are not yet included in the current classification.
Although Gregory et al. highlighted the problems with terms, they retained the classifications which do not have all the necessary inclusion [2]. They suggested atherosclerosis, primary arterial calcification, fibromuscular intimal hyperplasia, hyalinosis, and miscellaneous categories which include amyloidosis and oxalosis, among others [1].

8. Conclusion

Atherosclerosis, arteriosclerosis and arteriolosclerosis are not only confused; they are also associated with some controversies. However, while the current classifications and description of terms have been developed over the centuries, there are possible better ways to classify the terms.
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