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REVIEW ARTICLE

The Importance of Detecting Subclinical Atherosclerosis in the Young Population and Its Prognostic Role

Gulshan Suleymanova[1*], Gulnaz Dadashova[2]

[1]*Department of Cardiology, Central Clinical Hospital, Baku, Azerbaijan*
[2]*Scientific Research Institute of Cardiology named after J. Abdullayev, Baku, Azerbaijan*

Corresponding Author: *Gulshan Suleymanova, Email: gulshansuleymanova2020@gmail.com*

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Abstract

Cardiovascular diseases (CVD) remain one of the leading causes of mortality worldwide, and their clinical manifestations typically occur years after the onset of atherosclerosis. Considering that numerous studies have demonstrated a high prevalence of atherosclerosis even among subjectively healthy middle-aged individuals, its detection at an early stage is of foremost importance. Identification of subclinical atherosclerosis enables the timely implementation of primary preventive and therapeutic interventions, thereby reducing the incidence of cardiovascular complications. In cardiovascular risk assessment, the visualization and quantification of subclinical atherosclerosis using non-invasive vascular imaging techniques play a significant role. Coronary computed tomography angiography (CCTA) provides valuable prognostic information in both symptomatic and asymptomatic coronary artery disease (CAD). Furthermore, in the absence of atherosclerotic findings, it predicts favorable long-term outcomes, whereas in patients with CAD, it facilitates accurate risk stratification. As a non-invasive imaging modality with minimal psychological burden, CCTA has particular prognostic value for detecting subclinical atherosclerosis in young adults aged 18–44 years.

Keywords: Cardiovascular diseases, Coronary artery calcium (Agatston) score, Coronary computed tomography angiography, Subclinical atherosclerosis, Young population

Introduction

Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide. The substantial socioeconomic burden of CVD necessitates the development of new, effective, and efficient preventive and therapeutic strategies. The clinical manifestations of CVD generally occur years after the onset of atherosclerosis. However, atherosclerosis, which constitutes the principal pathogenic mechanism underlying CVD, is most often detected only at advanced stages or after the occurrence of a cardiovascular event. Considering that studies have demonstrated a high prevalence of atherosclerosis even among subjectively healthy middle-aged individuals, early detection is of paramount importance [1]. Identification of subclinical atherosclerosis enables the timely implementation of primary preventive and therapeutic interventions, thereby reducing the incidence of cardiovascular complications.

The major barriers to early intervention include: (1) insufficient awareness of the need for early preventive strategies among young adults; (2) inadequate emphasis in clinical guidelines and routine practice on the high lifetime cardiovascular risk in young individuals, despite their generally low short-term cardiovascular risk; and (3) the limited number of randomized clinical trials demonstrating that intensive control of cardiovascular risk factors (CVRFs) in young adults slows the progression of atherosclerosis and consequently prevents the development of cardiovascular disease [13,14].

Atherosclerotic calcification is an ancient pathological phenomenon that was first documented based on autopsy findings from the mummy of an elderly Egyptian woman. In the nineteenth century, the pathologist Rudolph Virchow was the first to recognize the role of vascular calcification in the pathophysiology of cardiovascular disease, considering it a passive, degenerative process. However, over the past two decades, vascular calcification has increasingly been recognized as an active and tightly regulated biological process [5].

Vascular calcification involves the crystallization of calcium and phosphate in the form of hydroxyapatite within the extracellular matrix of the arterial wall. Multiple mechanisms have been proposed to explain the development of vascular calcification, and it is likely to result from several interacting processes. Based on its anatomical location and underlying pathogenesis, vascular calcification is generally classified into two major types: atherosclerotic intimal calcification and medial calcification, the latter also known as Mönckeberg's medial calcific sclerosis. The progression of atherosclerotic lesions is closely associated with the development of intimal calcification [6].

The earliest lesion associated with vascular calcification is pathological intimal thickening, in which microcalcifications first appear. These microcalcifications range in size from <0.5 to 15 μm. As atherosclerotic plaques progress, the calcific deposits enlarge, evolving into spotty calcifications (>15 μm to 1 mm), followed by fragmented calcifications (>1 mm), and ultimately sheet-like (plate) calcifications (>3 mm). Calcification of the atheromatous plaque is a hallmark of advanced atherosclerosis. It develops as a bone-like structure within the plaque and originates in inflammatory regions characterized by localized loss of collagen fibers. Coronary artery calcification complicates endovascular interventions and reduces the likelihood of adequate restoration of the arterial lumen following vascular manipulation [7,8].

Although the incidence of atherosclerotic cardiovascular disease among older adults has decreased worldwide, a similar trend has not been observed in young and middle-aged populations. Epidemiological data indicate an increasing incidence of acute coronary syndrome (ACS) among patients aged 35–54 years, particularly in women, especially those with early-onset menopause [10]. Identifying the risk of coronary artery disease (CAD) in young and middle-aged adults remains challenging because of the limitations of currently available risk prediction models, the relatively low sensitivity of existing screening methods, and the limited availability of observational data for this age group. Furthermore, the 10-year CAD risk assessment tools used to determine eligibility for statin therapy do not include individuals younger than 40 years, resulting in delayed initiation of preventive treatment in this population [14]. The YOUNG-MI study primarily evaluated patients younger than 50 years who were hospitalized with acute myocardial infarction (AMI). The study demonstrated that, before the cardiovascular event, statin therapy had not been prescribed in accordance with contemporary guideline recommendations [10].

Identification of high-risk individuals at an early age is essential for improving the prediction and prevention of cardiovascular disease. Currently available cardiovascular risk scores have limited accuracy and may lead to unnecessary lifelong pharmacological treatment in individuals who are unlikely to develop disease, while simultaneously failing to identify high-risk individuals who would benefit from timely preventive therapy. Moreover, despite their widespread use in clinical practice, the effectiveness of these risk prediction models has not been sufficiently validated by evidence from randomized clinical trials [1].

Several authors have proposed recommendations aimed at identifying high-risk conditions and facilitating early intervention in young adults aged 20–39 years [12]. These include both modifiable and non-modifiable cardiovascular risk factors, such as cigarette smoking, elevated blood pressure (BP) or hypertension, a family history of premature cardiovascular disease (CVD), severe hypercholesterolemia (e.g., familial hypercholesterolemia), diabetes mellitus, metabolic syndrome, and others. In women, a history of preeclampsia or menopause before the age of 40 is also considered a cardiovascular risk factor. It should also be noted that the prevalence and severity of atherosclerosis in young men and women within these age groups remain incompletely understood. Risk factors such as dyslipidemia are valuable for estimating long-term cardiovascular risk. Current approaches to lipid-related risk assessment, including triglycerides, high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, and lipoprotein(a), continue to evolve [12]. In addition, recent studies have explored novel risk stratification strategies in this age group, including coronary artery calcium (CAC) scoring and polygenic risk assessment. Although these approaches appear clinically promising, their optimal implementation in routine practice has yet to be clearly established [12].

Visualization and quantification of subclinical atherosclerosis using non-invasive vascular imaging techniques play a pivotal role in cardiovascular risk assessment. Coronary computed tomography angiography (CCTA) provides important prognostic information in both symptomatic and asymptomatic coronary artery disease (CAD). In the absence of atherosclerotic findings, CCTA predicts favorable long-term outcomes, whereas in patients with established CAD, it enables accurate risk stratification [1]. Because CCTA is a non-invasive imaging modality associated with minimal psychological burden, it has particular prognostic value for detecting subclinical atherosclerosis in young adults aged 18–44 years.

Studies have demonstrated that the higher the coronary artery calcium score, the greater the future risk of acute coronary events [6]. In addition to quantifying coronary artery calcium, contrast-enhanced CCTA is a highly valuable imaging modality because it enables the detection of fibrotic plaques and even subtle fibrotic irregularities of the arterial wall associated with early atherosclerosis. The coronary artery calcium (CAC) score is calculated using the Agatston method, which remains the reference standard for

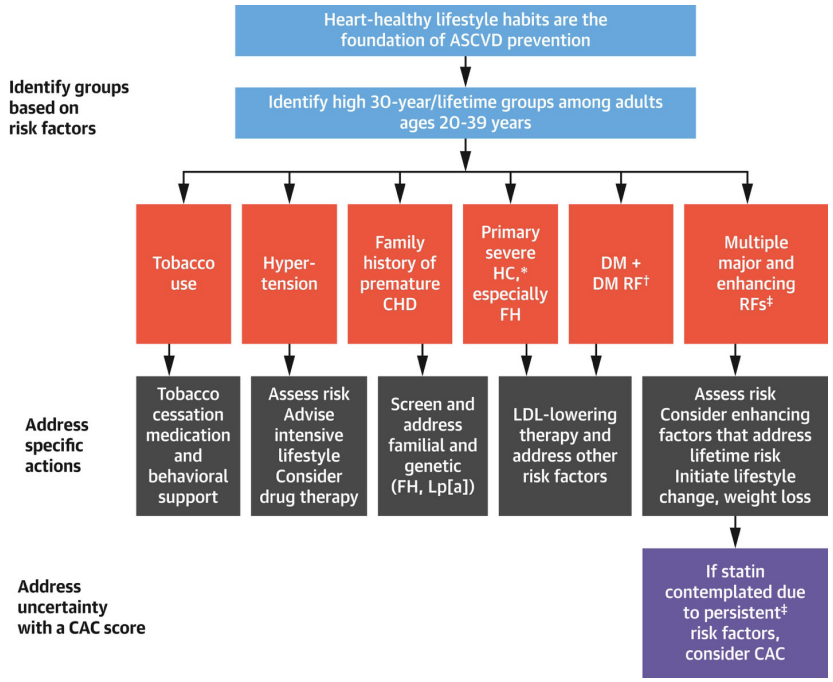

Figure 1: Identifying High 30-Year/Lifetime Risk Groups Among Young Adults 20-39 Years

assessing the risk of coronary artery disease. Owing to its simplicity and broad clinical applicability, CAC scoring may be particularly useful for cardiovascular risk stratification in young individuals, especially those at intermediate or high cardiovascular risk.

The coronary artery calcium (CAC) score is widely used for cardiovascular risk prediction and enables incremental outcome stratification beyond traditional cardiovascular risk factors [2,9]. However, it is not sufficient for detecting atherosclerosis at its earliest stages or for comprehensive long-term disease monitoring. Because plaque calcification develops relatively late in the natural history of atherosclerosis, CAC scoring cannot identify early non-calcified plaques [15]. Furthermore, although recent studies have shown that progression of CAC is associated with increased all-cause mortality, increasing calcification may also reflect plaque stabilization rather than disease progression. Consequently, the prognostic value of CAC progression may be reduced, particularly in patients receiving lipid-lowering therapy [3,4]. Therefore, the use of more advanced contrast-enhanced non-invasive imaging techniques should be considered for the comprehensive detection and characterization of coronary atherosclerotic plaques.

Identifying high 30-year/lifetime risk groups in young adults aged 20-39 years focuses on 6 groups that can be easily identified and for which there are specific actions for clinicians to pursue. If risk factors are persistently elevated and statin therapy contemplated, a CAC score may be useful (see Discussion). ∗Hypercholesterolemia defined as LDL-C ≥190 mg/dL or 160 mg/dL with risk factors. †Duration (type 1 >20 years, type 2 >10 years) and either 1 or more major risk factors or complications such as diabetic microangiopathy including albuminuria or an ankle brachial index <0.9. ‡No progress in 2-5 years depending on severity of risk factor burden. CAC = coronary artery calcium score; CHD = coronary heart disease; DM = diabetes mellitus; FH = familial hypercholesterolemia; HC = hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); RF = risk factor.

Despite numerous studies conducted worldwide, no universally accepted screening algorithm or differentiated management strategy for various cardiovascular risk groups has yet been established. Most published studies have focused either on patients with confirmed symptoms of cardiovascular disease or on the evaluation of individual cardiovascular risk factors.

In view of the increasing mortality and hospitalization rates associated with cardiovascular disease, the early detection of atherosclerosis in the young population aged 18–44 years should be prioritized. Timely identification and evaluation of subclinical atherosclerosis, particularly through non-invasive imaging modalities, may provide substantial prognostic value while minimizing the psychological burden associated with diagnostic testing in this population.

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