ATHEROSCLEROSIS IN THE YOUNG ADULT: FEWER HYPOTHESES, MORE FACTS

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(Abstract): Several studies have reported early atherosclerotic changes in arterial wall of young adults, although they usually become symptomatic after age 40 years. Initially, some sporadic and limited data were available to document the atherosclerotic lesions in young adults; early subclinical assessment were later possible using accurate ultrasound and other imaging techniques. Our aim was to a review of eloquent studies proving different type of atherosclerotic lesion in the young adult. Long-term follow-up and further analysis of this population demonstrated important relationship with traditional and some non-traditional, risk factors. The data comprised in the reviewed studies are arguments in favor of a more refined atherosclerotic risk assessment and appropriate preventive strategy in young adult.

Keywords: Atherosclerosis, Young Adult, Cardiovascular Risk, Non-Invasive Cardiovascular Testing.

Atherosclerosis is an active systemic pathobiological process, usually clinically expressed and complicated in adulthood and elderly (1). However, previous autopsy studies (2), or, more recently clinical investigations based on the latest subclinical methods (vascular and intravascular ultrasound, coronarography, computed tomography and magnetic resonance) showed subclinical or complicated atherosclerotic lesions in young adults, or even in teenagers or children (1-3). In Bogalusa Heart Study (2), an interesting approach was developed, combining autopsy information about the extent of vascular damage, with patient’s history providing data about the presence of cardiovascular risk factors, collected prior to death. Significantly and persistently elevated blood pressure levels, adipose mass and dyslipidemia in young adults are markers of risk for progressive coronary atherosclerosis. Abdominal and visceral obesity, most commonly encountered and associated with metabolic syndrome, were strongly correlated, especially in males, with coronary atherosclerosis and, less well with aortic involvement (4, 5).

Most cardiovascular risk factors assessed in clinical studies are correlated with the initiation and progression of the atherosclerotic disease. Atherosclerotic transformation of the arterial wall is the faster the more factors such as dyslipidemia, inflammation and thrombosis are precociously activated. Smoking, sedentary lifestyle and obesity are factors increasingly
Atherosclerosis in young adults was initially studied by sporadic autopsy information and later clinical studies. One of the main limitations of the systematic interpretation of the data in the clinical studies remains the arbitrary delimitation of the age intervals defining young adult. Some of the published articles have used mixed cohorts of patients, aged under or up to 18 years, or occasionally set an upper age limit for the young adult of 35 years and even 45 years. The first anatomical observation and invasive studies reported mainly the complications of atherosclerosis such as stroke or myocardial infarction, while the modern approach is non-invasive and allows imaging assessment of subclinical atherosclerosis in several categories of young adults (1, 2, 4-6). This review outlines the most significant data published on adults aged 18 to 45 years, with emphasis on subclinical atherosclerosis beside the presence and extent of complications.

**EPIDEMIOLOGICAL APPROACH**

The epidemiological data were collected from morphological and clinical surveillance studies. Some of the earliest findings were obtained from autopsy specimens collected from young soldiers killed in war battles (7, 8). At a mean age of 22 years, 70% of them already had coronary atherosclerotic lesions (8). Post-mortem coronary angiography showed minor changes in 45% and raised lesions in 5% of 105 soldiers killed in Vietnam war (7, 8). Bogalusa Heart Study provided significant data, describing the postmortem arterial morphological findings in subjects enrolled before their death and followed-up for a period for the description of the specific cardiovascular risk factors. The study enrolled 204 patients aged 2 to 39 years. Early atherosclerotic lesions, represented by fatty streaks, were reported in 50% of subjects aged 2 to 15 years and in 85% of subjects aged 21 to 39 years (8). Advanced atherosclerotic lesions, represented by raised fibrous plaque, were mentioned in 8% of subjects aged 2 to 15 years and in 69% of subjects aged 26 to 39 years (2, 6, 8). PDAY Study (Pathobiological Determinants of Atherosclerosis in Youth) reported autopsy findings from 2876 subjects aged 15 to 34 years. Advanced atherosclerotic lesions were described in the abdominal aorta in 20% of patients aged 15 to 34 years and 40% of subjects aged 30 to 34 years. Right coronary artery showed pathological changes in 10% of subjects aged 15 to 19 years and in 30% of those 30 to 34 years (8, 9).

Autopsy studies have inherent limitations (artifacts caused during the processing of morphological samples or inconsistencies in the absence of in vivo hemodynamic conditions). Therefore, this kind of studies were followed by clinical evidence obtained with invasive or non-invasive methods. Tuzcu EM et al. (1) reported results obtained by coronary intravascular ultrasound performed within about 1 month after transplantation in 262 heart transplant recipients, the organ donors being young asymptomatic subjects (146 men and 116 women, mean age 33.4±13.2 years). Atherosclerotic lesions were present
in 136 patients (51.9%). Atherosclerosis prevalence is increasing significantly with age (17% in subjects aged under 20 years and 85% in subjects older than 50 years), without gender differences (52% in men and 51.7% in women) (1). In other studies, subclinical atherosclerosis was noninvasively assessed and it proved to be more frequent in young subjects with metabolic syndrome (5, 10), obesity and other cardiovascular risk factors (10-12). CARDIA Study demonstrated an increased incidence of coronary affection in young adults with abdominal obesity (12).

ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS

Over 20 years of research were needed to establish new methods and cardiovascular biomarkers that could be properly representative for the presence of subclinical atherosclerosis. The new methods have high applicability and maximum benefit if they prove fidelity in detection of atherosclerotic lesions, reproducibility and cost-efficiency, are non-invasive and standardized. Some of these methods have been developed more and are used to screen large populations and guide medical intervention to reduce the cardiovascular risk (13).

After 1990, accurate measurements of carotid intima - media thickness (cIMT) were possible using high - resolution B-mode ultrasonography. This imaging technique is non-invasive and accessible in large communities of all ages, gender and origin. Most of the studies demonstrated that cIMT could be correlated with aortic and coronary atherosclerosis, reflecting, at the same time, the adaptation of the arterial system to increased intravascular stress (13, 14). Accurate measurements require a standardized technique, approaching the common carotid, internal carotid and carotid bifurcation at several arterial sites. Currently, ultrasound apparatus should be equipped with a transducer greater than 8 MHz. A cIMT greater than 1 mm is considered abnormal. In term of prediction, it is important that single or average values measured for cIMT have the same power in correlation with future coronary events (13-15). Carotid atherosclerosis is an independent predictor of stroke and myocardial infarction (16, 17).

Ankle-brachial index (ABI) has started as a simple and inexpensive test for diagnosis of peripheral arterial disease (PAD). In this regard, the most used was the protocol for the determination of ABI with the Doppler method. Usually, per the American Heart Association (AHA) protocol for the determination of the ABI with Doppler method, the calculation is made for each leg with the higher of the 2 ankle pressures (determined in tibialis posterior and dorsalis pedis arteries) in relation to the highest brachial systolic blood pressure (SBP) (18). The sensitivity is ~ 90% and specificity ~ 98% in the presence of stenosis ≥ 50% in leg arteries. An ABI < 0.9 is considered abnormal. In terms of risk, the studies have reported a high incidence of cardiovascular morbidity and mortality in patients with pathological ABI values (19-21). The relevance of risk prediction is still debatable in persons ≥ 50 years old, where pathological values for ABI were more frequently found. Therefore, the importance of ABI as a predictor of atherosclerosis is more valuable in persons < 50 years old (17). Some authors have proposed a shift in the calculation of ABI, for the PAD diagnosis, and, particularly, when it is used as a general indicator of atherosclerosis and cardiovascular risk. For example, using the lower ankle
pressure instead of the higher ankle pressure between tibialis posterior and dorsalis pedis for each leg, ABI was associated with higher sensitivity, but with lower specificity in the diagnosis of PAD (22). In 831 patients who underwent coronarography, ABI was calculated using both formulas and the comparison showed that with the modified version more patients at high cardiovascular risk were identified (23).

The detection of coronary calcium by electron beam-computed tomography (EBCT) and helical computed tomography (CT) led to the identification of asymptomatic but high-risk coronary artery disease patient (17). Coronary artery calcification (CAC) score was correlated with pathological findings of atherosclerosis in coronary arteries (17, 24). Current guidelines discuss the indications for coronary CT, namely asymptomatic patients at high cardiovascular risk, stable patients with suspected coronary disease or with acute chest pain, in the preoperative evaluation of patients before noncoronary cardiac surgery and in the follow-up of cardiac transplant patients (25). CAC is an independent risk factor for the future cardiac ischemic events, stratification depending on its values. In a cohort with 4,4052 asymptomatic subjects, for a CAC reported as 0, 10-year risk of all-cause mortality was < 1% (26, 27). A CAC score ≥ 400 (Agatston units) indicate the subjects at high risk for future coronary events that should be referred for coronary angiography. However, absence of coronary calcium will not exclude the existence of noncalcified plaque (28).

Magnetic resonance is more valuable, but, at the same time, a more expensive imaging method of atherosclerosis. The use of this technique could bring new information about the remodeling of the arterial wall and vulnerable plaque in most of the arteries (coronary, carotid and peripheral arteries) and could serve as a reference point in monitoring therapy (29).

At the same time, some noninvasive, reproducible and safe tests have been developed for the assessment of the functional properties of the endothelium (brachial artery flow-mediated dilatation, pulse wave and contour analysis, pulse amplitude tonometry). The analysis of pulse wave velocity (PWV) is made by a device that calculates pulse wave propagation velocity between 2 arteries (carotid and femoral or radial) (30). Carotid-femoral pulse wave velocity > 12 m/s indicates an increased risk for future cardiovascular events.

Of the serum markers, C-reactive protein (CRP) or interleukin-6 are important for the expression of systemic inflammation and were correlated with cardiovascular events (31). Particularly CRP was introduced in different risk stratification models.

**SOME PATHOGENIC HYPOTHESES**

Usually, individual characteristics known as cardiovascular risk factors will influence the progression of atherosclerosis in time. Less evidence was collected about the pathogenesis of accelerated atherosclerosis in children, adolescents or young adults under the age of 45 years. Accelerated atherosclerosis was described in case of homozygous familial hypercholesterolemia (32). The disease is characterized by a genetic heterogeneity and a phenotypic variability with impaired functionality of the low-density lipoprotein (LDL) receptor, increased levels of LDL-cholesterol and lipoprotein (a), associated with low levels of high density lipoprotein cholesterol (HDL-cholesterol) (in some patients an accelerated turnover of HDL apoA-I and a decreased
HDL-cholesterol efflux could be present) (33). The current guidelines recommend Doppler echocardiographic evaluation of the heart and aorta annually and coronary CT every 5 years for the screening of subclinical atherosclerosis in children and young adults with familial hypercholesterolemia (33).

Epidemiological and clinical studies (34) also demonstrated a cluster of cardiovascular risk factors (hypertension, obesity, hyperglycemia, smoking, family history) in relationship with unhealthy lifestyle in these patients. Some of them meet the criteria for metabolic syndrome, namely insulin resistance, associated with increased risk of developing diabetes and cardiovascular diseases (5,35). Confounding factors could be present occasionally, in patients with thrombotic complications of some hereditary or acquired systemic diseases in the absence of significant atherosclerotic lesions. Early atherosclerosis in young women was particularly related to autoimmune processes or to high levels of lipoprotein (a) (36).

**ELOQUENT STUDIES ON ATHEROSCLEROSIS IN YOUNG ADULTS**

As mentioned above, the early development of atherosclerotic lesions in children and young adults was first documented in autopsy studies (2, 7). Although the atherosclerotic changes were demonstrated after death, in the Bogalusa Heart Study the approach was because the subjects were also followed-up before death for the description of cardiovascular risk factors and, partially, for the assessment of subclinical atherosclerosis by carotid ultrasound (6, 10, 37).

Vascular ultrasound and other validated methods for detecting subclinical atherosclerosis have permitted in vivo assessment of the atherosclerotic lesions. More clinical studies were published after 2,000 year and the most eloquent are presented below (tab. I).

### TABLE I

**The main clinical studies on atherosclerosis in young adult**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population (n)</th>
<th>Age range(y)/Mean age (y)</th>
<th>Gender Male/Female (n)</th>
<th>Method for the assessment of atherosclerosis</th>
<th>Atherosclerosis outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tuzcu et al. 2001 (1)</td>
<td>262</td>
<td>NR/(33.4±13.2)</td>
<td>146/116</td>
<td>Intravascular ultrasound</td>
<td>Prevalence of atherosclerosis 52% in men and 51.7% in women, 17% in individuals &lt; 20 years, 37% in age 20-29 years and 60% in age 30-39 years</td>
</tr>
<tr>
<td>2. Lee et al. 2007 (12) CARDIA Study</td>
<td>2,951, as part of the CARDIA Study</td>
<td>18-30 at CARDIA year 0/NR</td>
<td>NR</td>
<td>Computed tomography for CAC</td>
<td>Abdominal obesity was associated with early atherosclerosis</td>
</tr>
<tr>
<td>3. Mattsson et al. 2008 (5)</td>
<td>2,163</td>
<td>NR/(32±5)</td>
<td>999/1,164</td>
<td>Ultrasound measurement of cIMT, and FMD</td>
<td>MS was associated with increased cIMT in both sexes</td>
</tr>
</tbody>
</table>
### Atherosclerosis in the young adult: fewer hypotheses, more facts

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<tr>
<td>4. Knoflach et al. (2009) (36)</td>
<td>205</td>
<td>18-22/ 20.6±1</td>
<td>0/ 205</td>
<td>Ultrasound measurement of cIMT</td>
<td>Autoimmune processes, high lipoprotein (a), environmental exposure to tobacco smoke accelerated early atherogenesis in young women</td>
</tr>
<tr>
<td>5. Skilton et al. 2014 (38), Cardiovascular Risk in Young Finns Study</td>
<td>696</td>
<td>24-45/ 31.9±5</td>
<td>320/ 376</td>
<td>Ultrasound measurement of cIMT, and FMD</td>
<td>cIMT was increased in people with larger versus normal birth weight</td>
</tr>
<tr>
<td>6. Spring et al. 2014 (39), CARDIA Study</td>
<td>3,538, as part of the CARDIA Study</td>
<td>18-30 at CARDIA year 0/NR</td>
<td>1,535/ 2,003</td>
<td>Ultrasound measurement of cIMT, computed tomography for CAC</td>
<td>Healthy lifestyle changes during young adulthood are associated with decreased risk for subclinical atherosclerosis in middle age</td>
</tr>
<tr>
<td>7. Bhuiyan et al. 2015 (40), Bogalusa Heart Study</td>
<td>461, as part of the Bogalusa Heart Study</td>
<td>24-43/ 35.6</td>
<td>0/461</td>
<td>Ultrasound measurement of cIMT</td>
<td>cIMT was same in early menarcheal age (&lt; 11 yrs.) vs normal menarcheal age (≥11yrs.) in white women but higher in black women</td>
</tr>
<tr>
<td>8. Eikendal et al. 2015 (41), USE-IMT initiative</td>
<td>3,067</td>
<td>NR/ 32-42</td>
<td>1,828/ 1,239</td>
<td>Ultrasound measurement of cIMT, recording of the new cardiovascular disease events</td>
<td>55 first-time myocardial infarctions or stroke occurred during a follow-up of 16.3 years and the events were related to cIMT</td>
</tr>
<tr>
<td>9. Reis et al. 2015 (42), CARDIA Study</td>
<td>4,061, as part of the CARDIA Study</td>
<td>18-30 at CARDIA year 0/NR</td>
<td>2,043/ 2,018</td>
<td>Recording of the new cardiovascular disease events</td>
<td>During a 24.8 year, median period of observation, were 125 incidents cardiovascular disease, 62 coronary heart disease and 33 heart failure events</td>
</tr>
<tr>
<td>10. Gidding et al. 2016 (43), CARDIA Study</td>
<td>3,008, as part of the CARDIA Study</td>
<td>18-30 at CARDIA year 0/NR</td>
<td>NR</td>
<td>Computed tomography for CAC and AAC</td>
<td>During the follow-up period, the CAC increased from 3 to 5 and AAC remain 2 between the age 35±3.6 to 40.2±3.6</td>
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<tr>
<td>11. Hartiala et al. 2016 (44), Cardiovascular Risk in Young Finns Study</td>
<td>589, as part of the Cardiovascular Risk in Young Finns Study</td>
<td>39-45/NR</td>
<td>NR</td>
<td>Computed tomography for CAC</td>
<td>Mean levels of LDL-C, total cholesterol, Apo-B, and SBP levels across the 27-year period were significantly higher among those with CAC vs. those without</td>
</tr>
<tr>
<td>12. Eikendal et al. 2016 (45) The Atherosclerosis Risk in Young Adults (ARYA) Study</td>
<td>736</td>
<td>NR/28.4±0.9</td>
<td>344/392</td>
<td>Ultrasound for carotid intima-media echogenicity quantified as gray-scale median and for cIMT</td>
<td>Adolescent BMI related to cIMT and echogenicity in young adults; SBP only related to cIMT</td>
</tr>
</tbody>
</table>

AAC - abdominal aortic calcium, Apo-B - apolipoprotein B, BMI - body mass index, CAC - coronary artery calcification, cIMT - carotid artery intima-media thickness, FMD - brachial artery flow-mediated dilatation, LDL-C - low density lipoprotein cholesterol, MS - metabolic syndrome, NR - not reported, SBP - systolic blood pressure

**CONCLUSIONS**

Our review has demonstrated an increased incidence of subclinical atherosclerosis in young adults. Based on the main selected studies, early atherosclerosis was related to a cluster of traditional risk factors (hypertension, obesity, hyperglycemia, smoking, dyslipidemia) and some non-traditional risk factors (birth weight), or more particular for the young women (lipoprotein (a), autoimmune processes). Further improvement in the methods of subclinical atherosclerosis assessment will consistently contribute to a better prediction of future cardiovascular morbidity and of outcome following the therapeutic strategies.

**REFERENCES**

Atherosclerosis in the young adult: fewer hypotheses, more facts


