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Chapter 22

Assessment of Glucocorticoids – Induced Preclinical Atherosclerosis

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Additional information is available at the end of the chapter

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1. Introduction

In 1948, the US rheumatologist Philip Hench and his associates at the Mayo Clinic first administered hydrocortisone to a patient with rheumatoid arthritis and discovered its clinical benefits [1]. Two years later, Hench, together with biochemists Edward Kendall and Tadeus Reichstein, shared the Nobel Prize in Medicine. Today, glucocorticoids are among the most frequently prescribed class of anti-inflammatory medications [2]. They are part of the standard treatment for a wide range of disorders which feature inflammation and/or immune activation, such as asthma, chronic obstructive pulmonary disease, hypersensitivity reactions, autoimmune diseases, and in organ transplantation. However, even early on, the euphoria generated by the discovery of corticosteroids was rapidly tempered by the realization that clinicians were, in a sense, engaging in a Faustian pact between its impressive anti-inflammatory benefits and its potentially devastating Cushingoid side effects [3, 4].

From a cardiovascular standpoint, the propensity of glucocorticoids to produce hyperglycemia, hypertension, dyslipidemia, and central obesity has long produced concern regarding possible adverse cardiovascular events [5]. Glucocorticoids administration increases blood pressure in a dose dependent fashion. The mechanisms of glucocorticoids-mediated hypertension are incompletely understood but appear to be principally related to increased peripheral vascular resistance rather than to mineralocorticoid receptor mediated effects of increased sodium retention and plasma volume expansion [6]. Dyslipidemia in the context of long term glucocorticoids use is characterized by increased total cholesterol, low density lipoprotein cholesterol, and triglycerides. Corticosteroid treatment increases the risk of glucose intolerance in patients without known diabetes and is associated with deterioration of glycaemic control in diabetic patients [7]. Glucocorticoids treatment therefore contributes to the exacerbation of a cluster of cardiovascular risk factors that are

central to the metabolic syndrome. However, as inflammation plays a central role in the pathogenesis of atherosclerosis [8], it is also possible that glucocorticoids may exert some anti-atherosclerotic effects.

There was a significant association between ever use of oral glucocorticoids and any cardiovascular or cerebrovascular outcome. The association was stronger for current use of oral glucocorticoids than for recent or past use. Among current users, the highest odds ratios were observed in the group with the highest average daily dose, although the dose–response relation was not continuous. Current use was associated with an increased risk of heart failure, which was consistent between patients with rheumatoid arthritis, patients with chronic obstructive pulmonary disease, and patients without either of the two conditions. Also, current use was associated with a smaller increased risk of ischaemic heart disease [9].

RA population has an increased cardio-vascular mortality and premature death rate, but why does these patients have a higher incidence of atherosclerosis? There are several factors which are known risks in the development of atherosclerosis. Steroids may play a role in the increased mortality from vascular disease. Some reports have suggested that prolonged treatment with steroids accelerates the development of atherosclerosis. Steroids have atherogenic properties that are known to enhance the development of atherosclerosis and they induce vascular injury. In addition, they produce a state of hypercoagulability. In Moreland and O'Dell study, they found an increased atherosclerotic burden in the patients who were on long-term steroids. This suggests that steroid treatment may be a contributor to the higher rate of atherosclerosis seen in them [10]. Del Rincón et al. studied the carotid and lower-limb arteries in a sample of RA patients, and found that the extent of cumulative glucocorticoids dose was significantly associated with arterial incompressibility. This association displayed a gradient in which the proportion of incompressible arteries increased with higher glucocorticoids exposure. This pattern was independent of age at RA onset, sex, disease duration, CV risk factors, and manifestations of RA [11].

2. Historical background

Calcification of the arterial atheroma occurs in the coronary tree as it does in the remainder of the arterial tree. Such calcified coronary arteries are occasionally noted on routine chest radiographs but are difficult to distinguish from normal mediastinal structures and are confused with calcification in the chest wall, lungs, or other intracardiac structures [12]. Calcification of the coronary arteries is a common autopsy finding and is generally present in 80 to 90% of post-mortem studies. Despite this common pathologic finding, description of coronary calcification was rare until the work of Lenk [13] in 1927, who noted calcification of the left coronary artery on a posteroanterior chest radiograph in a 61-year-old male with left ventricular aneurysm. In 1964 Beadenkopf et al. [14] reported their findings in 904 consecutive autopsies; their results indicated that as the number of coronary arteries with calcification increased, coronary artery wall thickness increased. Tampas and Soule [15] in 1965 using radiographs in 1097 patients over the age of 40 found an incidence of 15% coronary calcification with a male to female ratio of 3 to 2 that was associated with

increasing age. They suggested that coronary calcification might be an alarm signal of potential ischemic heart disease. Currently, it is generally recognized that the incidence of Coronary artery disease (CAD) was greater in patients with coronary calcification and atherosclerosis than in those without calcification [16].

3. Value of assessment of preclinical atherosclerosis

The presence of preclinical atherosclerosis increases global cardiovascular risk; therefore, it can be considered an emerging determinant in assessing such a risk. Single or multiple risk factors increase cardiovascular risk in an exponential manner, meanwhile the presence of one or more risk factors for atherosclerosis is associated with the development of cardiovascular disease. *A specific issue is defined as risk factor when it is possible, on the basis of a strong statistical association, to relate it to the incidence of new cases of disease and if it is clinically demonstrated that new disease cases can be reduced by correcting the same risk factor.*

Atherosclerosis is defined as a progressive structural remodeling of a vessel wall towards definitive plaque formation and possible related complications. According to new data, the disease begins as an endothelium functional disorder [dysfunction] inducing loss of vascular homeostasis and related functional reserve that initially can become clinically evident only in conditions in which there is a need to increase tissue metabolic requirements (as for instance effort Angina, transient Ischemic Attack, intermittent Claudication) while, after more time, they can become symptomatic at rest because even basal perfusion [blood flow] is impaired (acute coronary syndrome, stroke, critical leg ischemia, and even cardiovascular death) [12].

Coronary atherosclerosis is the leading cause of death in industrialized western countries. In up to 50% of its victims the first manifestation of CAD is sudden death or acute myocardial infarction. The cost of lost human value and approximate dollars spent ($90 billion annually) due to coronary artery disease in the western society is of great concern and is the reason for increased efforts for its prevention and its consequences as well. The detection of CAD in its asymptomatic stage is highly desirable because it is an increasingly treatable disease, but till now it has been hindered by the lack of sensitive and specific tests [13].

4. Methodology of assessment

4.1. Clinical background and limitations

In evaluating atherosclerosis the following demographic and clinical data are needed; sex, age, cigarette smoking, alcohol consumption, physical activity and life style, socioeconomic status, previous diseases, family history, BMI, WHR [waist to hip ratio] and blood pressure assessments in the standard way.

Chronic subclinical inflammation is thought to be part of the metabolic syndrome [MetSyn]. The latter is characterized by a clustering of atherosclerotic CVD risk factors. The WHO definition of MetSyn [14] requires the presence of insulin resistance plus 2 other of central

obesity, hypertension, or dyslipidemia. Insulin resistance is thought to be the most prominent pathophysiological process underlying MetSyn. Recent studies of coronary artery calcification (CAC) in asymptomatic samples have shown an association of MetSyn and insulin resistance with the burden of coronary atherosclerosis [13]. Lakka et al. [15] found a 2- to 4-fold increased risk of cardiovascular death with MetSyn in a sample of 1209 Finnish men free from diabetes and CVD at baseline. MetSyn predicted atherosclerosis progression and CVD events in 888 subjects in the Bruneck study, whereas most individual components of the syndrome were not significantly associated with CVD out-comes [16] supporting the concept that MetSyn provides information that is "more than the sum of its parts."[17].

4.2. Laboratory methods

In more than 15 large prospective studies, C-reactive protein (CRP) has emerged as an independent predictor of an incident cardiovascular event in initially healthy subjects and outcome after acute coronary syndrome [18]. More importantly, its high levels have been demonstrated to be an even stronger predictor of cardiovascular events than LDL cholesterol levels. CRP represents only one of several new inflammatory biomarkers to be associated, independent of lipid profile, with future cardiovascular events. Among these, serum amyloid A (SAA), soluble vascular cell adhesion molecule-1 (VCAM-1), soluble intercellular adhesion molecule 1 (ICAM-1), lipoprotein associated phospholipase A2 (Lp-PLA2), homocysteine and monocyte chemoattractant protein-1 (MCP-1) are the best characterized. Interestingly, from the most recent epidemiological trials, evidence has consistently emerged that these biomarkers are independent from cholesterol levels, but also unrelated to each other. For instance, in healthy middle-aged men, CRP levels were found to correlate only marginally to Lp-PLA2 and MCP-1. The direct evidence that inflammatory biomarkers contribute to atherogenesis would be validated from the utilization of novel specific inhibitors for each of the soluble molecules which should prevent atherogenesis and coronary artery disease [18].

4.3. Sonographic modalities

Atherosclerosis is a chronic inflammatory disorder that often progresses silently for decades before becoming clinically evident. In this section we will preview sonographic noninvasive imaging of the vascular changes that occur in the atherosclerosis disease process including assessment of its inflammatory component. Because inflammation participates in plaque initiation and progression, a method capable of imaging the extent of vascular inflammation could potentially provide powerful predictive information on both early disease presence and future risk for disease progression.

4.3.1. Intima-Media Thickness (IMT) or Asymptomatic Carotid Plaque (ACP)

Echocolordoppler scanning evaluation of the carotid wall is a non invasive, low cost, and highly reproducible procedure even if, like most parts of the echographic analysis, it is strongly operator dependent. The Doppler mode permits the visualization of vessels and an

evaluation of flow disturbance that helps to quantify stenosis severity. It measures the IMT and size and number of atheromatous plaques. According to the European Society of Cardiology; 2007-Guidelines on the Management of arterial Hypertension, normal IMT is the distance between the media-adventitia and the intima-media interfaces and is interpreted as follows:

- under 0,9 mm of the entire vascular wall; normal
- between 0.9 and 1.5 mm is an increased IMT,
- While all conditions in which it is greater than 1.5 mm can be considered an ACP.

Increased IMT (or ACP) is related to the presence, number, intensity and duration of atherosclerosis risk factors as well as endothelial dysfunction [24, 25]. Also, IMT is a potent and independent predictor of future cerebro- and cardiovascular events, as proven by several studies (Finnish, American Rotterdam groups) [17].

4.3.2. Ankle Brachial Pressure Index (ABI)

Normally, ankle systolic arterial pressure (posterior or anterior tibial artery) is just a little higher than brachial pressure measurements so that their ratio always is always > 1.0. This parameter is called the Ankle-Brachial pressure Index (ABI) and can reflect altered pressure values. It is reduced < 0.90 if atherosclerosis induced arterial system impairment is present; hence the patient is considered to have an asymptomatic peripheral artery disease. It is a simple, non-expensive procedure and can also be practiced by general practitioners [17]. Several population trials evidenced an important correlation between decreased ABI, carotid or coronary atherosclerosis and future cardiac or cerebrovascular events (27).

4.3.3. Endothelial function evaluation

A new, non-invasive technique was introduced to evaluate brachial artery flow-mediated dilatation (FMD). The evaluation through a sonographic assessment of brachial artery in basal condition and after 5 minutes of occlusion using pneumonic cuff (250 mm Hg) determined a reactive hyperemia and therefore, FMD. A low FMD is a marker of multifocal atherosclerosis and severity of the disease where the progressive reduction of FMD is associated with more extensive coronary tree involvement and future cardiovascular events [28, 29].

4.3.4. Targeted Ultrasound Detection of Vascular Cell Adhesion Molecule-1 (VCAM-1)

VCAM-1 is expressed by activated endothelial cells and participates in leukocyte rolling and adhesion primarily by interacting with its counterligand VLA-4 ($\alpha 4\ \beta 1$) on monocytes and lymphocytes. VCAM-1 expression on the vessel endothelial surface or the underlying vasa vasorum plays an important role in atherosclerotic plaque development by monocyte and T-lymphocyte recruitment. It is an ideal target for molecular imaging because there is little constitutive expression and its upregulation occurs at the earliest stages of atherogenesis. It

was hypothesized that molecular imaging with *targeted contrast enhanced ultrasound* **[CEU]** could be used to evaluate the degree of vascular inflammation in atherosclerosis. CEU have multiple practical considerations; low cost, short duration [10 Minutes], good sensitivity and balance between spatial resolution and sensitivity for targeted contrast agent detection. It can potentially be useful in the early diagnosis of atherosclerosis and in monitoring the efficacy of therapeutic interventions.

4.4. Radiological modalities

4.4.1. Fluoroscopy

The detection of coronary calcification on chest films is not easy and the accuracy is only 42% compared with fluoroscopy, which itself is not sensitive. Fluoroscopy has frequently been used to detect calcification in the coronary arteries [31]. Data from the Duke registry of 800 patients by Margolis et al. [32] showed that patients with fluoroscopic evidence of calcium in the coronary arterial tree had a remarkably high prevalence of significant disease (94%). Only 6% of patients with coronary calcification had normal coronary angiograms. Among those without demonstrable calcification, 87% survived for more than 5 years compared to 58% with coronary calcification. Hence the latter implies a greater risk of future cardiac events. Fluoroscopy is widely available but it has several disadvantages [18]:

1. Although it can detect moderate to large calcifications; its ability to identify small calcifications is low.
2. Fluoroscopic detection of calcification is dependent on the skill and experience of the operator as well as the number of views studied.
3. Other important factors include variability of the equipment, patient's body habitus, and calcifications in other structures such as valves and vertebrae and overlying anatomic structures.
4. Finally with fluoroscopy, quantification of calcium is not possible and film documentation is not commonly obtained.

4.4.2. Computed tomography (CT)

Conventional CT is extremely sensitive in detecting vascular calcification. CT showed 50% more calcified vessels than did fluoroscopy. Its limitations are slow scan times resulting in motion artifacts, breathing misregistration, and inability to quantify amount of plaque. *Helical CT* has considerably faster scan times than conventional CT and overlapping sections improves calcium detection. *Double-helix CT scanners* appear to be more sensitive and now termed *electron beam (EBCT)* to distinguish them from conventional CT scanners.

Only *EBCT* can quantitate the amount or volume of calcium. The absence of calcific deposits on an EBCT scan implies the absence of significant angiographic coronary narrowing; however, it does not imply the absence of atherosclerosis, including unstable plaque. One of the most appealing features of EBCT is the potential to detect progression or regression of

coronary atherosclerotic disease non-invasively and quantification with the use of calcium-volume score. Although the ACC/AHA [American College of Cardiology (ACC) and the American Heart Association (AHA)] guidelines affirm the strong negative predictive value of a normal EBCT they are not supportive for its widespread use in asymptomatic patients [18].

4.4.3. Magnetic Resonance Imaging [MRI]

Imaging techniques are needed that allow earlier and more refined diagnosis, guide targeted treatment in individual patients and monitor response to that treatment. MRI is well-suited to these tasks as it can provide anatomical, structural, and functional data of the arterial wall. Its capabilities are further enhanced by the use of a range of increasingly sophisticated contrast agents that target specific molecules, cells, and biological processes. Currently, it is considered to identify biologically relevant targets involved in the pathogenesis of atherosclerosis along its different stages [33].

For assessment of lesions that encroach on the vessel lumen inducing ischemia as in angina; angiography provides excellent resolution for the affected vascular territory with possible therapeutic intervention. However, atherosclerosis commonly develops within the walls of arteries without impinging on the vessel lumen; even established disease can be concealed from lumenographic methods. Unfortunately, even these non-stenotic lesions can rupture or erode precipitating intra-arterial thrombosis and acute ischemic events.

Distinct from alternative imaging modalities, MRI can provide data on a large range of vascular parameters that includes measures of vascular physiology (compliance, pulse wave velocity, and flow-mediated vasodilatation), cellular imaging, molecular imaging [adhesion molecule expression (VCAM-1), fibrin and platelets targeting] and functional anatomical data such as wall sheer stresses and density of neovascularization [33].

4.5. Radionuclide evaluation

4.5.1. Tc-99m sestamibi lower extremity muscle scan

Amin et al. [34] stated that Tc-99m sestamibi lower extremity muscle scan is a technique that can be effectively used to diagnose preclinical atherosclerosis in rheumatoid arthritis disease by measuring the so called perfusion reserve [PR]. They reported that it has a place as a screening tool considering the fact; whenever the diagnosis, the better it is the result, however, it could be used for detecting preclinical atherosclerosis even in apparently healthy subjects.

4.5.2. Technique

Prior to the administration of Tc-99m sestamibi for measurement of PR in lower limbs, each subject moved her right foot to produce maximal dorsal and plantar flexion 30–40 times in the sitting position (exercising side). 185 mBq of Tc-99m sestamibi was injected through

intravenous line at least 10 sec before exercise termination. Posterior images of each calf were obtained 10 min post-injection. The processing phase was carried out by drawing symmetrical and equal regions of interest (ROI) over both exercising and resting calves. The total counts (Cts) in each (ROI) were obtained through a closed program inherent to the computer system [figure 1]. The percentage of increase of Cts in the exercising right calf was calculated, and the percentile increase obtained was considered as the perfusion reserve using the following formula [normal PR is approx. 50%]:

Perfusion reserve (%) =

[Cts in the exercising calf - Cts in the resting calf/ Cts in resting calf] x 100

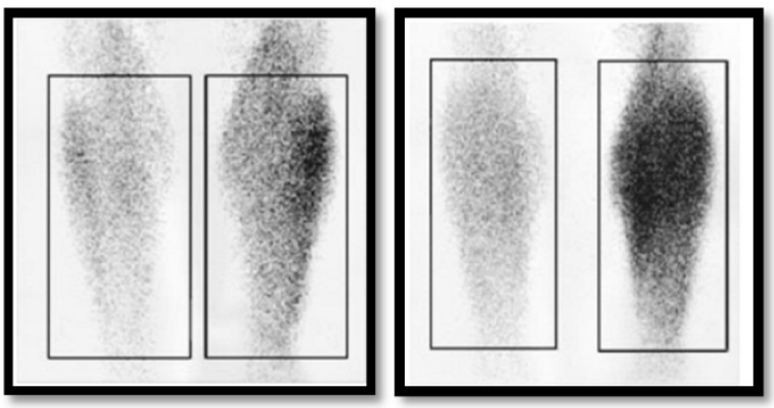

Figure 1. Tc-99m sestamibi muscle scans of an RA patient (PR 29.4%) [Left panel] and a control subject (PR 85%) [Right panel]

4.5.3. Myocardial sestaMIBI Gated-SPECT

Also, in our center a study was designed to evaluate usefulness of Dipyridamole pharmacological stress test in conjunction with Tc-99m sestamibi Gated-SPECT to screen the prevalence of subclinical coronary vascular dysfunction [SCED] in asymptomatic Egyptian Behçet's disease patients and to identify those at higher risk for the presence of such abnormalities as a predictor for preclinical atherosclerosis [*data are not published yet*]. Dipyridamole is an indirect coronary vasodilator that works by increasing intravascular adenosine through inhibition of phosphodiesterase that prohibits reuptake of endogenously produced adenosine into endothelial and red blood cells leading to arteriolar vasodilatation. This increases coronary arterial flow to approximately three times resting values in healthy endothelial state, however it is attenuated in diseased coronary arteries that cannot further dilate in response to adenosine. So, Dipyridamole infusion produces relative flow heterogeneity throughout coronary arteries, resulting in relatively more coronary blood flow in healthy arteries compared with the diseased-arteries inducing ischemia via a "*coronary steal phenomenon*" with subsequent perfusion defects ± abnormal left ventricular

wall motion during radionuclide imaging. Hence, we used Dipyridamole stress in conjunction with Tc-99m sestamibi Gated-SPECT as a screening tool for SCED [Figure 2 and 3].

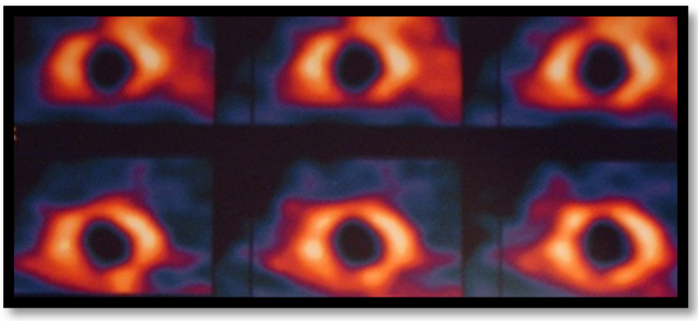

Figure 2. A 35-year-old male with stress induced reduced flow in LAD [anterior wall] and RCA vascular territories [inferior wall] with Complete recovery in the rest phase Coronary angiography was normal; [Stress; Upper row and Rest; Lower row- Short axis slices]

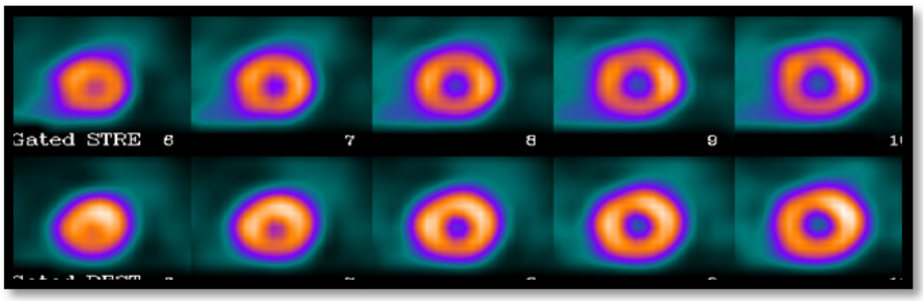

Figure 3. A 33-year-old negative Case for SCED [Stress; Upper row and Rest; Lower row-Short axis slices]

5. Special consideration

5.1. Premature lower limb atherosclerosis

Symptomatic lower extremity arterial occlusive disease in young adults is presumably rare provided that atherosclerosis is a natural consequence of ageing process. Several factors contribute to the "neglect" of premature lower extremity atherosclerosis (*PLEA*) among young population in clinical practice; including low public health awareness of this pathology, absence of large-scale epidemiologic studies, and overall low index of suspicion for vascular etiology of effort-induced lower extremity symptoms. A number of small clinical studies published in the last decade have strongly suggested that PLEA is the major cause for peripheral arterial disease (PAD) in young patients [35].

Levy report in 2002 identified 3 major clinical presentations of PLEA; the majority of patients had typical symptoms of effort-induced claudication, frequently misdiagnosed and attributed to arthritides, muscle spasms, and trauma. Approximately 20-25% present with "blue toe syndrome" caused by atheromatous embolization, most frequently originating

from a segmental aortoiliac atherosclerotic lesion. The rest of patients presents with rapidly progressive symptoms of limb-threatening ischemia secondary to atherothrombosis. Also, they observed that many younger patients with isolated aortoiliac atherosclerotic disease had prolonged lower back pain on ambulation involving the spinal muscles who have been treated for several years for chronic low back pain by orthopedic surgeons, or neurosurgeons and some of them even had "unsuccessful" laminectomies before the diagnosis of PAD. In PLEA patients, clinical atherosclerotic disease was present in more than one anatomic location in approximately 60% including the coronary tree. Noninvasive studies are a mainstay of the PLEA diagnosis including ABI measurement and standardized lower extremity treadmill testing that has been developed to assess hyperemic blood flow response to exercise with repeat ABIs compared to the resting ABI with pulse-wave recordings. Also, Tc-99m sestamibi lower extremity muscle scan is suggested as a diagnostic test in PLEA patients [35].

6. Summary and conclusions

In summary, improved understanding of atherogenesis allowed the identification of a large number of molecules and processes. This will provide functional insights to aid diagnosis and to guide treatment with the introduction of new molecular imaging approaches that hold much promise for translation to the clinical practice. In fact, inflammatory biomarkers and imaging will combine structural and functional information to provide a comprehensive evaluation of vascular status at an early stage; hoping to be reversible.

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