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Short Communication

Ultrasound Imaging of Subclinical Atherosclerosis: Clinical Importance of Carotid Intima-Media Thickness as a Risk Marker

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Submitted: 18 April 2016

Accepted: 02 January 2017

Published: 05 January 2017

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Keywords

- Carotid intima-media thickness
- Subclinical atherosclerosis
- Cardiovascular risk marker

Abstract

Carotid intima media thickness (IMT) has been widely utilized as an indicator of atherosclerosis in epidemiological, observational, and interventional clinical studies. It has been applied as an outcome variable in clinical investigation, and it has been employed as an exposure variable in studies on the prognostic value to predict coronary artery disease and stroke. There are different markers that can be used to determine atherosclerosis risks in the clinical trials. Although several biomarkers have been widely utilized to assess the risk of developing atherosclerosis, carotid IMT can directly visualize atherosclerosis in the vessel wall. Indeed, carotid IMT can be considered as a biomarker halfway between risk factors and organ damage that can help prevent clinical events. This approach avoids the substantial costs and lengthy follow-up required of traditional clinical randomized trials that are focused on hard clinical end points. Ultrasound measurement is a well-validated technique that has undergone in recent years substantial technical improvements in both the manner of imaging and the IMT quantification. However, it is still a limited imaging modality for assessing carotid atherosclerosis. Newer non-invasive techniques such as magnetic resonance imaging have attractive properties that may improve the assessment of atherosclerosis. Carotid magnetic resonance imaging modalities are being utilized to investigate the artery wall changes associated with pharmacological treatment. Anyway, regardless of the technique utilized to perform the assessments, carotid IMT measurements have increasingly been used in clinical studies. Indeed, the change in carotid IMT over time as an indicator for atherosclerosis progression, has predominantly served in interventional studies as a primary outcome variable aimed at assessing the effects of risk factor interventions.

INTRODUCTION

Atherosclerosis is a multifactorial disease, and the development of atherosclerotic disease involves the interaction of many genetic and environmental factors through conventional risk factors [1-3]. Carotid ultrasonography has allowed clinicians to visualize the characteristics of the carotid wall and lumen surfaces to quantify the severity of atherosclerosis. Ultrasound studies are the most common imaging procedure performed for the diagnosis of carotid disease. Carotid intima media thickness (IMT) is an echocardiography-mediated measure of early atherosclerosis and vascular remodelling that can be easily assessed with high-resolution ultrasound technique. Carotid IMT has been widely utilized as an indicator of atherosclerosis in epidemiological, observational, and interventional clinical studies. It has been applied as an outcome variable in clinical investigation, and it has been employed as an exposure variable in studies on the prognostic value to predict coronary artery disease and stroke [4-6]. The morphological changes observable in carotid IMT over time makes it a plausible tool as a marker for atherosclerosis progression and cardiovascular risk. In addition, its validity, standardization, feasibility, and reproducibility accounts for its current widespread application in randomized clinical trials [7-9]. Therefore, the ACC/AHA 2010 guidelines recommend carotid IMT as a simple and noninvasive technique for measuring atherosclerotic burden and for cardiovascular risk

assessment in appropriately selected patients. Hence, this paper aims to discuss some interesting aspects in the utilization of carotid IMT in the assessment of atherosclerosis.

There is no doubt that, recent major improvements performed in the therapeutic management of cardiovascular diseases have decreased its morbidity and mortality [10-14]. Nevertheless cardiovascular diseases still remain as the number one cause of death in the world. Therefore, there is an important necessity in public health to close the gaps that are left between risk assessment with traditional risk factors and the real clinical event. In order to close the gap, and study the efficacy of pharmacological interventions in clinical trials, drug-induced regression or slow progression in carotid IMT in the follow-up period are being used as an alternative, or surrogate clinical end point for cardiovascular morbidity and mortality [1]. In a randomized controlled clinical investigation of a certain therapeutic management for prevention of cardiovascular events, a large number of participants must be followed up for a long period of time when the occurrence of cardiovascular events is set as an end-point. Such investigation requires a significant financial support. There are different markers that can be used to determine atherosclerosis risks in the clinical trials. Although serum biomarkers have been widely utilized to assess the risk of developing atherosclerosis, carotid IMT has the additional theoretical advantage of directly visualizing the final consequence of the disease itself, namely atherosclerosis in the vessel wall. Indeed, carotid IMT can be considered as a biomarker halfway between risk factors and organ damage that can help prevent clinical events. This approach avoids the substantial costs and lengthy follow-up required of traditional clinical randomized trials that are focused on hard clinical end points such as myocardial infarction, stroke, or death [15-17]. This rapid, harmless and easy to use technique has several advantages due to the lack of invasiveness and its usefulness of repeatability which makes carotid IMT measurement an attractive biomarker, potentially useful as a therapeutic target in those patients at increased cardiovascular risk [14,18].

In a meta-regression analysis evaluating carotid IMT changes using a wide range of cardiovascular therapies, it was demonstrated a statistically significant relationship between mean changes in carotid IMT over time and the risk of developing nonfatal myocardial infarction [19]. Nevertheless, these findings were not consistent across some subgroups and in sensitivity analyses. Indeed, in those clinical trials of this meta-analysis that evaluated statin therapy, they found no relationship between changes in carotid IMT over time and nonfatal myocardial infarction in patients with high carotid IMT at baseline [19]. Those investigations that have primarily relied on measurements of carotid IMT at baseline found out that it may be a valid surrogate end point for coronary atherosclerosis, drug efficacy, and clinical outcomes such as myocardial infarction [4-6,11,20-22]. It was demonstrated a strongly good association in those clinical trials that evaluated antihypertensives [23]. However, their findings were less consistent for statin therapy despite the fact that prior studies have suggested a reduction of carotid IMT and the unparalleled cardiovascular benefits of statin therapy. These findings may be related to the concept that the clinical benefits of statin therapy likely works by mechanisms other than their effect on carotid IMT. There are potential mechanistic reasons why the clinical benefit of statin therapy in clinical trials may be independent of their effect on carotid IMT [24]. The efficacy of these drugs is primarily related to their pleiotropic effects on vascular remodeling, inflammation, and plaque composition [25,26]. It should be considered that statin therapy was largely evaluated in clinical trials with patients who had high carotid IMT values at baseline. Goldberger ZD et al., found a strong association between changes in carotid IMT and clinical outcomes in clinical trials enrolling patients with low carotid IMT values at baseline, but less so in clinical trials where patients had higher values of carotid IMT at baseline [19]. This findings raise the probable assumption and strongly suggest that changes in carotid IMT over time that occur during the incipient stages of disease may be more predictive of future events than changes that occur in patients with more extensive atherosclerosis at baseline [19]. On the other hand, it is very important to emphasize also the need to better identify potential limitations caused by the type of drug under investigation. Even when a pharmacological therapy leads to improvements in atherosclerotic burden within the carotid artery, clinical outcomes may still worsen due to potential harmful effects at other vascular and non-vascular sites.

In a meta-regression analysis that pooled 41 clinical studies of carotid IMT involving a total of 18,307 patients followed for a mean of 2.4 years, it was found that regression or slowed progression of carotid IMT induced by cardiovascular drug therapies does not reflect reduction in cardiovascular events [27]. However, they found that very few coronary events occurred, only 635 (3.1%). This small number of events limits the statistical power of the meta-regression, and it is probably related to the fact that many of the included studies had short term follow-up, and were performed in trial populations at low risk of clinical cardiovascular disease. In disagreement with these findings, the meta-regression analysis performed by Goldberger ZD et al. [19], demonstrated that change in carotid IMT was associated with the risk of nonfatal myocardial infarction. The short-term follow-up of many of these trials may have mitigated the ability to assess many of the outcomes. Clinical outcomes are typically apparent for many drug agents only after longer follow-up. Therefore, care should be taken in the interpretation of data obtained from a meta-regression analysis of numerous small, short-term trials in which a variety of different study designs and methodological approaches were used to assess the measurements of carotid IMT. In placebo controlled, clinical pharmacological interventional trials the event curves often do not begin to diverge until after several years of treatment. Therefore, trials with short term follow-up duration may yield weak correlations in their analysis. There are other several limitations in the interpretation of the data from regression analysis related to age distribution of patients, and different carotid segment analysis which was not uniform [28].

Ultrasound measurement is a well-validated technique that has undergone in recent years substantial technical improvements in both the manner of imaging and the IMT quantification. However, it is still a limited imaging modality for assessing carotid atherosclerosis. A drawback of the ultrasound IMT measures includes poor inter- and intra-subject reproducibility. Therefore, it looks attractive the utilization of newer non-

invasive techniques such as magnetic resonance imaging to improve the assessment of atheroma burden in the vessel walls [29]. Carotid magnetic resonance imaging has already begun to be used for evaluating the artery wall changes associated with pharmacological treatment [30-33]. Despite the greater cost compared to ultrasound, the proper utilization of carotid resonance imaging may lead to more accurate quantification of atherosclerotic burden and improve the correlation of IMT changes with clinical events. Anyway, regardless of the technique utilized to perform the assessments, carotid IMT measurements have increasingly been used in observational and interventional clinical studies. There has been an enormous effort to improve the diagnostic and therapeutic management of atherosclerosis and its complications with positive results [34-40]. Indeed, carotid IMT has been applied as an outcome variable in studies on the determinants of atherosclerosis, and it has been employed as a biomarker in order to predict coronary artery disease and stroke. Change in carotid IMT over time as an indicator for atherosclerosis progression, has predominantly served in interventional studies as a primary outcome variable aimed at assessing the effects of risk factor interventions.

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Cite this article

Centurión OA (2017) Ultrasound Imaging of Subclinical Atherosclerosis: Clinical Importance of Carotid Intima-Media Thickness as a Risk Marker. JSM Atheroscler 2(1): 1020.