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DOCTORAL SCHOOL

Abstract of the PhD thesis

Role of new imaging-derived markers in assessing cardiovascular risk in patients with peripheral arterial disease

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Cardiovascular diseases are the main cause of death globally. Coronary artery disease (CAD), cerebrovascular disease and peripheral arterial pathology are the most prevalent manifestations. Due to the fact that peripheral arterial disease (PAD) increases the risk of global and cardiovascular mortality and morbidity, it is of major importance to develop new screening tools that can assess both local atherosclerotic burden and global cardiovascular risk. Although atherosclerotic biomarkers determined by non-invasive techniques, such as carotid intima-media thickness and coronary calcium score are routinely used to determine cardiovascular risk, data is scarce regarding their usefulness in peripheral arterial examinations of the lower limb.

The research, which comprised of three studies, aims to bring new information about the role of the new imaging-derived biomarkers, iliac calcium score (ICS) and femoral intima-media thickness (f-IMT) in predicting global atherosclerotic burden and cardiovascular risk and to shed light on their associations with traditional risk factors and severity of peripheral arterial disease.

The first study was a prospective, non-randomized computed-tomographic angiography (CTA) evaluation of the role of iliac calcium score in determining the severity and complexity of peripheral arterial lesions defined by clinical and angiographic criteria (Fontaine and Rutherford stages and TASC class) and its correlations with traditional cardiovascular risk and novel markers, such as iliac-intima-media thickness (i-IMT). Patients were divided into high and low ICS groups based on the median value for ICS of 3934 HU. There was a significant increase in ICS with age (66.2 ± 8.0 vs. 62.8 ± 11.2 years, $p < 0.0001$) and diabetes was more prevalent among the high ICS group (61.9 vs. 38.1% , $p = 0.04$). ICS was significantly higher in Rutherford stages 5-6 compared to stages 1-2 ($p = 0.03$) and in TASC C or D classes vs. TASC B class ($p = 0.01$). Mean i-IMT was also significantly increased in the high ICS group compared to the low ICS group (1.3 ± 0.2 vs. 0.9 ± 0.2 , $p < 0.0001$). Linear regression analysis between ICS and i-IMT proved a good correlation between the two parameters, significant for left, right and for both iliac arteries averaged ($r = 0.59$, $p < 0.0001$, $r = 0.57$, $p < 0.0001$ and $r = 0.67$, $p < 0.0001$ respectively). Compared to the low ICS group, left ventricular ejection fraction (LVEF) was

significantly lower in the high ICS group (45.3 ± 4.3 vs. $53.8 \pm 4.8\%$, $p < 0.0001$). Linear regression analysis also showed a significant inverse correlation between LVEF and ICS ($r = -0.54$, $p < 0.0001$). These data suggest that an increase of ICS, the new CTA-derived vascular biomarker is associated with an increased severity and complexity of peripheral arterial disease and a more depressed function of the left ventricle. Higher i-IMT is also correlated to ICS and both vascular parameters may become new surrogate markers of atherosclerotic burden.

The second study was aimed at investigating the correlations between femoral IMT, measured by ultrasound at the common femoral artery, traditional markers of risk and the degree of left ventricular function impairment in a group of patients with stable CAD. Mean f-IMT significantly correlated with total cholesterol levels ($r = 0.383$, $p = 0.048$), ankle-brachial index (ABI) ($r = 0.623$, $p = 0.005$) and was associated with a decrease in systolic pressure of the anterior and posterior tibial artery ($r = 0.450$, $p = 0.018$, $r = 0.418$, $p = 0.029$ respectively). Analysis of the groups with low (< 0.9 mm) and high (> 0.9 mm) f-IMT revealed a significant difference between minimum anterior tibial artery pressure (95.57 mmHg vs. 63.5 mmHg, $p = 0.0011$), the lowest ABI of the two limbs (0.85 vs. 0.5, $p = 0.015$) and femoral IMT ($p = 0.0001$). In the group with increased f-IMT (> 0.9 mm), ABI and f-IMT were significantly correlated ($r = -0.710$, $p < 0.0001$). The results are proof that f-IMT measured at the common femoral artery has the potential of becoming a new marker for evaluating systemic atherosclerosis and could help to stratify global cardiovascular risk in patients with CAD.

The third study investigated the relationship between femoral intima-media thickness measured at the superficial femoral artery, traditional risk factors and inflammatory markers in patients with a history of cardiovascular involvement (CAD, hypertension or stroke). In the group with low f-IMT, a significant, reverse correlation was established between f-IMT, uric acid ($r = -0.483$, $p = 0.042$), reflecting a low inflammatory status and right ABI ($r = -0.730$, $p = 0.0006$). Increased f-IMT was significantly associated with age ($r = 0.408$, $p = 0.031$), fasting glucose ($r = 0.407$, $p = 0.034$), total cholesterol ($r = 0.429$, $p = 0.02$), HDL-cholesterol ($r = -0.56$, $p = 0.0019$), triglycerides ($r = 0.45$, $p = 0.01$), hs-CRP ($r = 0.45$, $p = 0.01$) and left ABI ($r = -0.71$, $p < 0.0001$) in the group of patients with f-IMT > 0.75 mm. Associations in the high f-IMT group between traditional markers of cardiovascular risk and f-IMT in a population with coronary and peripheral vascular pathology reflects that these patients exhibit a malignant vascular phenotype, with more pronounced atherosclerosis even in the asymptomatic vessels. Correlations between hs-CRP and f-IMT in the same group is an indicator that inflammation plays a key role in the atherosclerotic process of the lower limbs, even if asymptomatic. f-IMT measured at the superficial femoral artery, similarly to c-IMT, may become a marker of cardiovascular risk in high-risk population or established cardiovascular disease.

In conclusion, based on the correlations with traditional biomarkers, these new imaging-derived vascular parameters – iliac calcium score and femoral intima-media thickness – are related to global and local peripheral atherosclerotic burden and could become useful tools as systemic markers of atherosclerosis.