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LETTER TO THE EDITOR

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Carotid Intima-Media Thickness: When Submillimeter Differences are Important but Ignored by the Applied Methodology

Christian SALEH[a]

[a]Neurologist, Basel, Switzerland

ABSTRACT

Keywords: ultrasound, carotid artery, surrogate marker, carotid intima-media thickness, methodology.

TO THE EDITOR:

Dear Editor, in a recent issue of your journal, Singh *et al* published a study titled "Association of Adipokines and CIMT in Metabolic Syndrome in Western Uttar Pradesh Population: a Cross-Sectional Study" (1). The authors wrote that "Adiponectin enhances fatty acid oxidation, prevents foam cell formation and improves lipid metabolism. In contrast, plasminogen activator inhibitor-1 (PAI-1) possesses pro-atherogenic properties. (…) Adipose tissue products, such as adiponectin, leptin, plasminogen activator inhibitor-1 (PAI-1), resistin, inflammatory cytokines and angiotensinogen, are known to affect the systemic metabolism. (…) to evaluate the association of adipokine levels and PAI-1 with CIMT in MetS patients, including its components" (1). The cross-sectional study included 164 subjects with metabolic syndrome (MetS) (88 males and 76 females) and 100 matched controls (54 males and 46 females) (1). Serum levels of adiponectin and PAI-1 were measured using ELISA (1). Carotid intima-media thickness (CIMT) was used as surrogate marker for preclinical atherosclerosis (1). The study found lower levels of adiponectin ($p < 0.001$) but higher levels of PAI-1 and CIMT ($p < 0.001$) in patients when compared with controls (1). When the number of metabolic abnormalities increased, the levels of adiponectin decreased and those of PAI-1 increased (1). There was a strong negative

Address for correspondence:
Christian Saleh, M.D. (Neurologist)
Basel, Switzerland
Email: chs12us75010@yahoo.com

association between PAI-1 levels and those of adiponectin ($p < 0.001$) (1). "Our findings indicate that elevated PAI-1 levels are associated with a higher probability of having MetS and negatively impact MetS-related components" (1). The CIMT measurements were done at the proximal, middle and distal levels of both common carotid arteries (CCA). The mean of the maximum readings of three right and three left far walls were used to estimate CIMT. The CIMT was 0.78 mm (SD 0.17) in the case group and 0.45 mm (SD 0.09) in the control group ($p < 0.0001$). Low adiponectin levels (58.19 ng/mL, SD 3.78, $p<0.0001$) and high PAI-1 (58.19 ng/mL, SD 16.24) were associated with high CIMT. The authors drew the following conclusion: "These results suggest a potential link between PAI-1 and the prevalence of MetS; however, this association requires clarification through prospective studies. In summary, the association between adiponectin, PAI-1 and CIMT highlights the complex interplay between adipose tissue, inflammation and cardiovascular health" (1).

Some comments (points 1-5) are needed to evaluate the results of this study.

1. Location of measurement – The authors' measurements were made at three levels of the CCA (1). It remained unclear which rationale and criteria was used to select the three levels of the CCA. The international recommendations suggest that measuring should be done either at the far wall of the CCA, in proximity of the bifurcation, or (preferably, given the asymmetric nature of atherosclerosis) at multiple CA sections, *i.e.*, CCA, bifurcation and internal CA (ICA) (2, 3). It is unclear which added information Singh *et al* hoped to gain from measuring the CIMT at multiple levels instead of in only one segment (1). The role of CIMT as marker for atherosclerosis is strongly questioned when measuring solely at the CCA level (4). In this regard, Touboul *et al* report that "The general thought is that, because of its accessibility, measurement of CIMT of the common carotid artery is more reproducible than that of the internal carotid artery or the bifurcation. Yet many studies have proven this concept to be wrong. … The carotid bifurcation and internal carotid artery, next to the common carotid artery, may carry additional information on atherosclerotic disease" (5). Consequently, CIMT measurement in multiple locations may well capture more accurately the precise CIMT (i.e., reflect the atherosclerotic burden) than a single segment CIMT measurement (3, 5, 6). Therefore, it is not comprehensible why, despite the huge body of the literature and CIMT research, the authors based their measurement on multiple locations but within the same CA segment (1).

2. Plaque *versus* CIMT – Importantly, Singh *et al* did not specify if the area of CIMT measurement was free of plaque, as recommended, or if they included plaque measurement into their CIMT measurement (1, 2). Carotid intima-media thickness and carotid plaque, although inter-related, are biologically and genetically distinct phenotypes of atherosclerosis (7). If plaques were included randomly into the CIMT measures (composite measures), that may account for the higher CIMT values which were seen in the case group (1).

3. Cardiac synchronization – CIMT measurements need to be synchronized with the cardiac cycle, namely with the end-diastolic phase (2). Mean vessel diameter changes between the two cardiac cycles of 0.037 to 0.041 mm were reported (8, 9). From the methodological description it appears that no synchronization occurred in the Singh *et al*'s study (1); consequently, not solely the measures would be rendered incomparable between the subjects, but they would even be incomparable for the same subject – *e.g.*, CIMT measurement of the right CA may have occurred in systole (vessel diameter increase with CIMT reduction), while measurement of the left CA may have occurred in diastole (vessel diameter decrease with CIMT increase).

4. Manual *versus* (semi-) automated measurements – There are differences according to the applied method, manual *versus* assisted measurement by software. Secil and colleagues wrote as to manual methods: "Among the restrictions of the method, the most important are the variability between the investigators (interobserver) and variability between the studies performed by the same investigator at different times (intraobserver)" (10). Singh *et al* did not mention which method they applied and did not report on the critical issue of inter- and intra-observer variability (1).

5. Cut-offs – As there is no consensus on thresholds to define pathologically increased

CIMT, it becomes still more stringent to explain the used cut-off (11), that was not mentioned by Singh *et al* (1). The fact that the case group showed increased values [0.78 mm (SD 0.17)] in comparison to the control group can have many different reasons other than an atherosclerotic process, which may find their source, as aforementioned, in the applied methodology (1). Furthermore, CIMT values less than 0.8-1.2 mm are considered normal by some authors (4).

To summarize, the CIMT is a delicate surrogate marker for preclinical atherosclerosis. Its normal range is expressed at the submillimeter level (0.6-1.0 mm) (5, 10). Equally submillimeter differences are sufficient to categorize subjects into different CIMT groups from which important clinical and pathophysiological conclusions are deducted. A detailed measurement protocol that foremost take into account the complex asymmetric presentation of atherosclerosis needs to be in place. As on multiple issues there is no consensus regarding CIMT, it becomes of critical importance that the authors explain all their procedural steps. Only in this way the scientific community can evaluate the CIMT results and, foremost, the related conclusions. These explanations are missed by Singh *et al*'s study (1). Given these critical issues, the CIMT results and related conclusions of Singh *et al*'s study should be analyzed with caution (1). ❑

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