BMC Nephrology

MATTERS ARISING

Open Access

Carotid intima-media thickness, fibroblast growth factor 23, and mineral bone disorder in children with chronic kidney disease. Knowing the limitations of the applied methodology for a better understanding of the clinical results

Christian Saleh[1*]

Dear Sir,

Palupi-Baroto et al. published in the recent issue an article titled, "Carotid intima-media thickness, fibroblast growth factor 23, and mineral bone disorder in children with chronic kidney disease" [1]. The study aimed to 1- identify factors associated with high carotid intima-media thickness (CIMT), high fibroblast growth factor 23 (FGF23) and poor mineral and bone disorders (MBD) control and 2- analyze the relationship between cIMT, FGF 23, and MBD control in children with chronic kidney disease (CKD) [1]. The authors write, "Mineral and bone disorders (MBD) are complications of CKD, contributing to vascular calcification and accelerated atherosclerosis. Increased fibroblast growth factor 23 (FGF23)—the earliest detectable serum abnormality associated with CKD-MBD—has been linked with cardiovascular disease in patients with CKD" [1]. The study included 42 children aged 2–18 years old with CKD stages 2 to 5D [1]. No significant correlations between CIMT and factors including advanced CKD, use of dialysis, body mass index, hypertension, anemia, MBD, FGF23 levels, and left ventricular mass index (LVMI) were found [1]. The authors write, "This may have been caused by the uniformity of CIMT measurements we found across the CKD stages, and may be attributable to a few limitations in our CIMT measurement" [1]. Some comments are needed to evaluate the results of this study. The authors should be lauded investigating the influence of the above-mentioned important but less studied factors on pre-clinical atherosclerosis. However, to use CIMT as surrogate marker for preclinical atherosclerosis several long-standing debated issues need to be known and mentioned to allow the reader for a full evaluation of the results and the related conclusions. The use of CIMT as a surrogate marker for pre-clinical atherosclerosis dates back to 1986, to the pioneering work of the Italian group lead by Pignoli and colleagues [2]; since then a major attention was based on the different measurement protocols and their quality to capture atherosclerotic changes. Bots and colleagues wrote in 2003 "When a randomized intervention study with CIMT as a primary outcome measure is designed, a number of features may have considerable effects on the conduct and size of the study. These include, in particular, the choice of the primary outcome CIMT measure (segments, near/far wall, angles of interrogation), reproducibility of CIMT measurement, expected CIMT progression rate,

*Correspondence:
Christian Saleh
chs12us75010@yahoo.com
[1]Basel, Switzerland

and expected effect of the intervention on the progression rate. At present, carotid ultrasound protocols differ considerably across studies" [3]. Palupi-Baroto et al. mentioned several limitations as to their CIMT evaluation, e.g. "only one blinded examiner performed single anterior and posterior measurement, while several large-scale pediatric cIMT studies used averages from 5 to 6 consecutive measurements undertaken by three examiners", "…reproducibility and operator dependency," lack of "…performing the CIMT measurement at one point in time,…" [1]. Although, these are important limitations, the most critical limitation the authors [1] did not consider: *their own measurement protocol.* Measurements were made in the Palupi-Baroto et al. study in a pre-determined single segment of the common carotid artery (CCA) [1]. Hereby the authors [1] missed a critical topographical aspect of atherosclerosis: its asymmetric presentation [4, 5]. Tajik et al. write in their excellent paper, "Asymmetrical distribution of atherosclerosis in the carotid artery: identical patterns across age, race, and gender" the following, "…the measurement protocols should not be limited to just the single 'nicest double line pattern' view. Our findings show that depending on the angle of carotid interrogation, the absolute CIMT measurement differs and when evaluating individual risks based using the absolute value of CIMT, all measurable sites of the both sides should be interrogated [4]."

A single-location measurement may coincide with a normal segment of a still atherosclerotic altered vessel, therefore multi-site measurements are recommended by some of the pioneers in the field [3, 6]. A further crucial methodological and universally recommended aspect was ignored (unfortunately seen in many studies [7, 8]), namely, cardiac synchronization [9, 10]. Therefore, it remains unclear, which measurements in the Palupi-Baroto et al. study [1] were made in systole (lower CIMT values) and which measures in diastole (higher CIMT values); that leads to the inevitable situation that for the *very same patient* CIMT measurements were potentially made in two distinct cardiac phases, e.g. right CCA in systole, left CCA in diastole, with mean differences reported of 0.037 to 0.041 mm between the two cardiac phases [11, 12]. That renders measurements incomparable, by introducing an important *intra- and inter-individual variability*. The authors state further, "Although increased CIMT has been noted in pre-dialysis CKD patients, no correlations have been found between increased CIMT and decreased eGFR or CKD progression" [1], by citing three studies from Schaefer et al. [13], Brady et al. [14], and Lopes et al. [15]. The major mistake Palupi-Baroto et al. [1] made is to compare the CIMT results of these studies with their own, without comparing first the methodologies upon which the results are based: the cited studies [13–15] cannot be compared as they differ significantly for the applied CIMT methodology. Schaefer et al. [13] based their cIMT measurement on the Mannheim CIMT consensus paper [9] which recommends cardiac synchronization and use of edge-tracking semiautomated devices. Brady et al. [14] performed manual measurements by a point-to-point method with 6 values (3 each site) averaged; a point-to-point is not recommended [10]; Cardiac synchronization is not described therefore likely not performed rendering the obtained results incomparable. Lopes et al. [15] equally performed manual measures without cardiac synchronization rendering their CIMT results unreliable.

In summary: CIMT is a surrogate marker that has advantages (low-cost, not-invasive, fast procedure) and significant disadvantages. The disadvantages should not deter from using CIMT as surrogate marker, but if applied its pros and cons and that of the applied methodology need to be discussed. The critical issue of CIMT as surrogate marker is that it is expressed at a sub-millimeter range (e.g. thresholds 0.6–0.9 mm [10]), consequently smallest imprecisions or due to measurement or due to a suboptimal defined methodology will translate easily in inaccuracies equally within a sub-millimeter range, which suffice to classify subjects into different CIMT categories. High precision measurements and a detailed measurement protocol that considers the specific pattern of atherosclerotic distribution, need to be in place. Only in this way and by *knowing and mentioning the limitations of the applied methodology* the results can be evaluated in a balanced way. Given these important methodological flaws in the applied CIMT measurement in the Palupi-Baroto et al. study [1] the CIMT data and related conclusions of this study [1] need to be analyzed with caution.

Author contributions
Christian Saleh wrote manuscript, revised final version.

Funding
N/A.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
N/A.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

Received: 26 October 2024 / Accepted: 10 February 2025
Published online: 20 February 2025

References

1. Palupi-Baroto R, Hermawan K, Murni IK, Nurlita T, Prihastuti Y, Puspitawati I, et al. Carotid intima-media thickness, fibroblast growth factor 23, and mineral bone disorder in children with chronic kidney disease. BMC Nephrol. 2024;25(1):369.
2. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation. 1986;74(6):1399–406. https://doi.org/10.1161/01.cir.74.6.1399.
3. Bots ML, Evans GW, Riley WA, Grobbee DE. Carotid intima-media thickness measurements in intervention studies: design options, progression rates, and sample size considerations: a point of view. Stroke. 2003;34(12):2985–94.
4. Tajik P, Meijer R, Duivenvoorden R, Peters SAE, Kastelein JJ, Visseren FJ, et al. Asymmetrical distribution of atherosclerosis in the carotid artery: identical patterns across age, race, and gender. Eur J Prev Cardiol. 2012;19(4):687–97.
5. KolaszyŃSka O, Lorkowski J. SYMMETRY AND ASYMMETRY IN ATHEROSCLEROSIS. Int J Occup Med Environ Health 36(6):693–703.
6. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) Study, 1987–1993. Am J Epidemiol. 1997;146(6):483–94.
7. Saleh C. Letter by Saleh regarding article, carotid atherosclerosis evolution when targeting a low-density lipoprotein cholesterol concentration < 70 mg/dL after an ischemic stroke of atherosclerotic origin. Circulation. 2021;143(12):e790–1.
8. Saleh C. Carotid intima-media thickness, primary aldosteronism, and target organ damage in untreated hypertensive patients. J Clin Hypertens (Greenwich). 2024;26(10):1201–2.
9. Touboul P-J, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290–6.
10. Simova' 'Iana. Intima-media thickness: appropriate evaluation and proper measurement [Internet]. [cited 2024 Aug 12]. Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-13/Intima-media-thickness-Appropriate-evaluation-and-proper-measurement-described
11. Polak JF, Johnson C, Harrington A, Wong Q, O'Leary DH, Burke G, et al. Changes in carotid intima-media thickness during the cardiac cycle: the multi-ethnic study of atherosclerosis. J Am Heart Assoc. 2012;1(4):e001420.
12. Polak JF, Meisner A, Pencina MJ, Wolf PA, D'Agostino RB. Variations in common carotid artery intima-media thickness (cIMT) during the Cardiac cycle: implications for Cardiovascular Risk Assessment. J Am Soc Echocardiogr. 2012;25(9):1023–8.
13. Schaefer F, Doyon A, Azukaitis K, Bayazit A, Canpolat N, Duzova A, et al. Cardiovascular phenotypes in children with CKD: the 4 C study. Clin J Am Soc Nephrol. 2017;12(1):19.
14. Brady TM, Schneider MF, Flynn JT, Cox C, Samuels J, Saland J, et al. Carotid intima-media thickness in children with CKD: results from the CKiD Study. Clin J Am Soc Nephrol. 2012;7(12):1930.
15. Lopes R, de Morais MB, Oliveira FLC, Brecheret AP, Abreu ALCS, de Andrade MC. Evaluation of carotid intima-media thickness and factors associated with cardiovascular disease in children and adolescents with chronic kidney disease. Jornal De Pediatria. 2019;95(6):696–704.

Publisher's note