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Editorial

Taking care of the clues already under our eyes: Early carotid plaque ultrasound detection may enlighten the age-old paradigm shift of glomerular hyperfiltration☆

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The paper by Kwon et al. published in *Atherosclerosis* [1] raises challenging questions and unearths hitherto hidden implications and benefits. From this carefully studied population, new pathways of clinical research may open. The methodology is clear, based on best-practice procedures, is reproducible, and provides sufficiently definitive results. The great healthcare awareness of this population, which self-referred to the ultrasound screening procedure, facilitated this participatory research, a merit and a feature of sustainable predictive and preventive approaches [2].

In chronic kidney disease, subclinical atherosclerosis is highly prevalent, with a greater plaque burden and more rapid progression in renal patients with diabetes: diabetes outweighs other described associated risk factors [3]. Glomerular hyperfiltration is deemed as a potential culprit of glomerular damage. This intuition is a paradigm shift [4]: decreased but also increased glomerular filtration is associated with universal atherosclerosis and vascular disease [5,6].

The concept of glomerular hyperfiltration has been long-held [7], with interpretations not widely shared [8], also for its feature of appearance and then disappearance, like sliding doors. The "osmotic work" related to urine concentration was already considered a burden for the diseased kidney almost one century ago [9]. The history of our thinking about the inexorable progression of renal disease involves years of discontinuity after the early work and vision. Interest was reawakened 40 years ago, when accurate experimental studies were carried out *in vivo* and *in vitro* [6,8] addressing a changing landscapes of mechanisms encompassing high-protein diet, obesity, diabetes mellitus and other factors. They would trigger a perverse spiral in which glomerular hyperfiltration is the critical crossroads and glomerulosclerosis the final effect [10]. Actually, valuable research groups have devoted themselves for some time to these topics, leaving key questions unaddressed or unanswered [11].

The question is still there: why is an engine running above its optimum performance? Which non-finalistic explanation for the paradox by which fewer glomeruli strive to perform a function far beyond their capabilities? It is not safe for the engine itself, i.e., the kidney, and this seems sufficiently demonstrated [5]. Is it hazardous for other organs and tissues? In this study, the answer to this last question is yes, and a very suggestive association is shown [1]. The dilemma is whether everything stops at a kind of parallel path, i.e., claiming an association, as the authors prudently do, or whether one can dare envisage and even affirm some causal interactivity. Again, we may face the chicken and egg dilemma [12]. Hyperfiltration is defined as absolute or relative. Absolute hyperfiltration is a supraphysiological elevation in the glomerular filtration rate that occurs when the single-nephron glomerular filtration rate increases in a kidney with a normal number of functioning nephrons [5]. In the subjects of the current study [1], we are conceivably facing mostly absolute hyperfiltration situations. Hyperfiltration can occur in healthy people following consumption of a high protein meal and during pregnancy, as well as in patients with obesity, latent or overt diabetes mellitus (few in this study) or autosomal-dominant polycystic kidney disease [5]. Relative hyperfiltration, differently, is present in the setting of a reduced number of functioning nephrons, in patients with a congenitally reduced number of nephrons and in those with an acquired reduction in kidney mass as a result of surgery or kidney disease. In both cases, this can result in a GFR that is within or just below the normal range. Despite the likely multifactorial effects, a melting pot of genetics, environment, behavior and much more, as reasonably it is, a speculative hypothesis is: it may be considered a bi-directional effect. That is to say, from universal atherogenesis mechanisms to glomerular hyperfiltration and vice versa. Mechanisms and factors, with reciprocal interactions,

☆ The definition of glomerular hyperfiltration is not robust, despite very meticulous research in the attenuation or elimination of confounding factors [1]. At last, the striking association of glomerular hyperfiltration with the US detection of carotid plaques outweighs the other identified differences.

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include sodium–glucose cotransporters, nitric oxide and adenosine actions on renal afferent arterioles, atrial natriuretic peptide, cyclooxygenase, renin–angiotensin–aldosterone system, and endothelin [11]. Such investigative results, even not conclusive and far from being complementary and integrated into a unified model, describe molecular and ultrastructural derangements of the glomerular machinery, that thrust forward to compete as a metaphorical "racing car".

This step of the endless quest for reliable biomarkers of atherosclerosis [13] spies on the culprit – glomerular hyperfiltration, even supposedly innocent - through the keyhole of the laboratory room. This research exercise ultimately may prove to be of practical use; nonetheless, rarely a key, chosen at random, is able to open the lock as we would like. The authors confirm this view: "*Because subclinical carotid plaque is associated with the risk of cardiovascular disease, glomerular hyperfiltration used in this study can be a useful surrogate marker for surveillance of cardiovascular disease in asymptomatic individuals*" [1]. Probably, claiming for a surrogate marker is an overstatement, but we may need it for more focus on the relationship of renal function and atherosclerosis. We could say that not only in patients with initial renal insufficiency, but also in patients with evidence of glomerular hyperfiltration, who are otherwise healthy, screening and monitoring with ultrasound the occurrence and development of carotid plaques is a rewarding exercise and an appropriate medical practice. Imaging procedures are increasingly within reach of the doctor and the patient, due to low costs, the diffusion of facilities and bedside practices, and the possibility of inclusive information on many organs or on the total body [14,15].

The patients of this study have trusted greatly in a clinical procedure, carotid ultrasound, confident that it, with a "tangible" anatomical imaging of an ongoing disease, may provide reliable information which is hopefully useful for preventive and therapeutic purposes. Data were derived from individuals who underwent self-referrals carotid ultrasound examination as part of a general health screening in a Health Promotion Center in Korea. This is an example, certainly not unique, but worthy of attention, endorsement and replication elsewhere. Actually, we are a long way from the futuristic safe algorithms that we are still trying to develop. Artificial intelligence and deep learning are more advanced approaches that may identify the algorithm that best expresses big-data meaning, in decision-making or predictive terms. Careful vetting of AI technologies is required by regulatory bodies, as well as through peer-reviewed studies and professional societies [16]. Nevertheless, the task of the doctor, when therapeutic and preventive decisions are needed, is very different. It is not surprising that even simple clinical signs, such as heart rate [17], and retinal vessel fundoscopy assessment [18] are found relevant for almost straightforward predictions of prognosis for cardiovascular disease. As a counterpart, we should distrust the compulsory guidelines and flowchart if they override the clinical skills and responsibilities of the doctor: sometimes they are the defensive surrender of reason, common sense and knowledge of the doctor to suboptimal or frankly incorrect procedures and decisions [19]. For instance, since moderate renal impairment is prevalent in the general population, with an apparent excess in females which is not explained by conventional cardiovascular risk factors, the validity of the prediction equations using renal insufficiency as an independent marker of the risk of cardiovascular morbidity and mortality, in particular in females, was found not sufficiently reliable [20].

The detection by US of carotid plaques may be, reciprocally, a sign, a "putative marker" of glomerular hyperfiltration, and therefore of the cascade of events that seem to be associated with and lead to diabetes, glomerulosclerosis, and lastly to diabetic nephropathy and renal failure. This simple US procedure, potentially in the domain of all practicing medical doctors, should become more and more widely used even at the bedside, both in general practice and in preventive medicine. Benefits, with appropriate training, as needed for all ultrasound diagnostic procedures, were and are evident for the professional qualities of doctors and for the performance of the health systems [14].

The perception of actual or possible disease is a determining element for obtaining adherence on the part of the patient [2], displaying clues easily under our eyes. Early carotid plaque ultrasound detection and the age-old paradigm shift of glomerular hyperfiltration may enlighten each other and also may ease the task of the enforcing the determination of the physician and the adherence of patients. These two early, important, inter-related and easy-to-find clues, glomerular hyperfiltration and US carotid plaque detection [1], may be useful to motivate a patient in good health and asymptomatic to follow lifestyle or drug prescriptions, suitable for lowering risk factors and counteracting obesity, diabetes mellitus, renal insufficiency and atherosclerosis. Both lend themselves to an imaginative description for the patient of the body machinery and to the acceptance of sustainable monitoring by quite basic measurements and imaging. The increasing bedside use of instrumental diagnostics such as EKG [17], ultrasound [1], retinal fundoscopy [18] is allowing the doctor to add clinical clues to traditional physical semiotics. We need signs reliable and with a powerful predictive potential, useful in anticipation of forthcoming more comprehensive machine learning data-based algorithms. The goal of AI approaches should be a sustainable increase of effectiveness, efficacy and equity of health care delivery. The results should minimize the uncertainty of choices, preserving in the meanwhile direct human and personal doctor-patient relationship, still open to receive suggestions and improvements from this practice.

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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