

Letter to the Editor

Gernot P. Tilz*, Gerald Höfler, Sabine Suppan, Marianne Leitner and Jutta von Auersperg

The non-inflammatory vascular diseases: hyalinosis, inhibition, and the role of neopterin – a medical hypothesis

<https://doi.org/10.1515/pteridines-2025-0057>

Published online December 31, 2025

Our scientific journey into the field of immune-mediated inflammation and vascular pathology began in 1969, when one of us collaborated with Sir Richard Bayliss and John Hobbs of Westminster Medical School in presenting work on inflammation and graft rejection. Both investigators expressed great enthusiasm for the pioneering studies of Wachter, Fuchs, and their colleagues in Innsbruck, who had demonstrated a decisive correlation between the newly identified molecule neopterin and graft failure [1]. This discovery provided a crucial conceptual anchor point for distinguishing immune-based inflammation from degenerative vascular decay. Research expanded rapidly. The association between human leukocyte antigen (HLA) incompatibility and elevated neopterin levels helped establish neopterin as a marker of T-cell-driven, macrophage-derived type 1 immune activation [2]. This distinguished neopterin from the broader and less specific C-reactive protein (CRP) axis, whose synthesis – occurring in the liver, but to a far less extent extrahepatically also in macrophages, activated T cells, and adipocytes – reflects a more generalized inflammatory response. Across autoimmunity, cancer, transplantation, viral diseases such as HIV, and many other clinical conditions, neopterin has proven invaluable for diagnosis, prognosis, and monitoring immune activation [3, 4].

***Corresponding author: Gernot P. Tilz**, Former Jean Dausset Laboratory Graz and Clinical Immunology Unit Graz, Clinical Rheumatology and Clinical Immunology, Medical University of Graz, Graz, Austria, E-mail: gernot.tilz@medunigraz.at

Gerald Höfler, D&F Institute of Pathology, Medical University of Graz, Graz, Austria, E-mail: gerald.hoefler@medunigraz.at

Sabine Suppan, Institute of Information Technology and Digitalization, Medical University of Graz, Graz, Austria, E-mail: sabine.suppan@medunigraz.at

Marianne Leitner, Central Apothecary Pharmacies, Graz, Austria, E-mail: marianne.leitner@kages.at

Jutta von Auersperg, Scientific consultant, Graz, Austria, E-mail: gernot.tilz@medunigraz.at

The seminal work of the Innsbruck group laid much of the foundation for applying neopterin to vascular research and aging [5–8]. Over decades, our investigations progressed along two major lines: (1) defining the clinical utility of inflammatory markers in vascular disease, and (2) proposing provocative concepts designed to stimulate future research and innovation.

Clinicians are repeatedly confronted with the heterogeneity of vascular pathology. Some patients present with substantial peripheral atherosclerosis while maintaining remarkably intact cognitive performance. Conversely, others who are physically fit may show profound cognitive decline. At autopsy, conventional plaques are often identified in the coronary and peripheral arteries, yet in the central nervous system and kidneys, one frequently encounters an “amyloid-like” thickening of small arteries – what we have termed inhibition and hyalinosis. These changes, unlike classical atherosclerosis, appear to reflect the accumulation of small, often non-degradable molecules within vessel walls.

Given the enormous literature on inflammatory atherosclerotic lesions, we focus here on the less explored mechanisms of hyalinosis and inhibition. Earlier work from our group [9, 10] proposed that small protein molecules migrating electrophoretically in the pre-albumin fraction may infiltrate the vascular wall and induce thickening. Amyloid transthyretin (ATTR) amyloidosis provides a striking example: a mutated transthyretin that resists catabolism accumulates in the walls of small arteries, leading to cardiomyopathy and multi-organ involvement. Analogous accumulation processes may involve microbial, viral, or autologous antigens modified by antibiotics or cytostatics. More than 30 such molecular candidates have been described, including free light chains in paraproteinemias and degradation products arising after chemotherapy.

The identification of these non-degradable hyaline deposits requires further morphological, immunochemical, and clinical investigation. Presently, such lesions remain difficult to detect with imaging modalities such as MRI and rely largely on biopsy. Advances in capillary electrophoresis

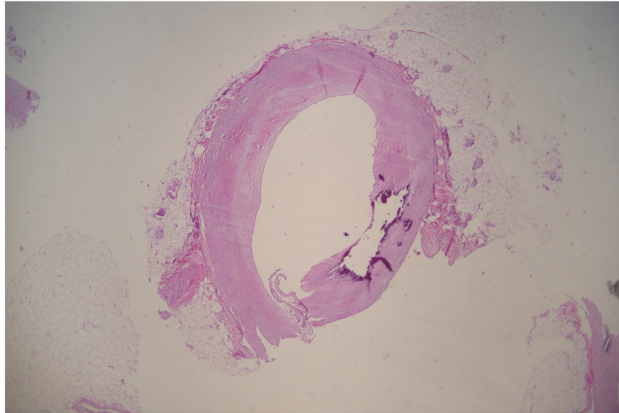


Figure 1: Illustration of inflammatory inhibition, arterial wall thickening, and capillary rupture. The image depicts hyalinosis of a renal artery, obtained from the Graz university tissue bank (MS), serving as a representative example of renal arterial hyaline sclerosis.

and immunoelectrophoresis may help characterize the pre-albumin peak and elucidate its immunogenic components.

Hyalinosis and inhibition represent clinically significant processes capable of producing organ damage – dementia, renal insufficiency, coronary disease, and other small-vessel pathologies. Their study calls for a conceptual framework reminiscent of early immune-complex pathology, shaped by von Pirquet, Dixon, and others, who emphasized the importance of identifying and removing pathogenic molecular entities with the greatest possible specificity. This ethos – akin to the precision of classical bacteriology – remains relevant as we search for the origins of these circulating molecules.

Inspired by the pioneering efforts of Wachter, Fuchs, and their colleagues, we have also considered a speculative but intriguing second avenue: the modulation of the immune milieu through small quantities of amino acids or modest immunostimulatory agents. As an example, tryptophan – an essential amino acid important for sleep, behavior, cognition, and overall mental status – deserves further exploration with respect to its clinical applications [11]. Such interventions may influence the milieu intérieur, as envisioned by Claude Bernard, and offer gentle supportive strategies for individuals with metabolic or immunological vulnerabilities.

Taken together – and in tribute to our esteemed colleagues who have guided and inspired this work – we advocate a broader perspective on inflammatory and non-inflammatory vascular processes, from immune-mediated injury to hyalinosis. By refining diagnostic approaches and exploring physiologically sympathetic therapeutic concepts, we hope to contribute to future strategies for recognizing and managing these often-overlooked forms of vascular disease.

Non-inflammatory vascular diseases, partly attributable to hyalinosis and inhibition of the vascular wall (Figure 1), give rise to the medical hypothesis of hyalinosis versus sclerosis. In this context, neopterin is of irreplaceable importance for the assessment of true vascular inflammation as opposed to inhibition, representing a provocative and forward-looking concept.

Funding Information: Authors state no funding involved.

Conflict of interest: Authors state no conflict of interest.

Data Availability Statement: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

References

1. Margreiter R, Fuchs D, Hausen A, Huber C, Reibnegger G, Spielberger M, u. a. Neopterin as a new biochemical marker for diagnosis of allograft rejection. Experience based upon evaluation of 100 consecutive cases. *Transplantation* 1983;36:650–3.
2. Huber C, Fuchs D, Hausen A, Margreiter R, Reibnegger G, Spielberger M, u. a. Pteridines as a new marker to detect human T cells activated by allogeneic or modified self major histocompatibility complex (MHC) determinants. *J Immunol* 1983;130:1047–50.
3. Murr C, Widner B, Wirleitner B, Fuchs D. Neopterin as a marker for immune system activation. *Curr Drug Metabol* 2002;3:175–87.
4. Fuchs D, Zangerle R, Artner-Dworzak E, Weiss G, Fritsch P, Tilz GP, u. a, et al. Association between immune activation, changes of iron metabolism and anaemia in patients with HIV infection. *Eur J Haematol* 1993;50:90–5.
5. Innerhofer P, Tilz G, Fuchs D, Luz G, Hobisch-Hagen P, Schobersberger W, u. a, et al. Immunologic changes after transfusion of autologous or allogeneic buffy coat-poor versus WBC-reduced blood transfusions in patients undergoing arthroplasty. II. Activation of T cells, macrophages, and cell-mediated lympholysis. *Transfus* 2000;40:821–7.
6. Nasonov EL, Samsonov MI, Shtutman VZ, Gekht BM, Gurkina GT, Tilz GP, u. a, et al. [Neopterin: marker of cellular immunity activation in idiopathic inflammatory myopathy]. *Klin Med Mosk* 1997; 75:47–51.
7. Weiss G, Willeit J, Kiechl S, Fuchs D, Jarosch E, Oberhollenzer F, u. a, et al. Increased concentrations of neopterin in carotid atherosclerosis. *Atherosclerosis* 1994;106:263–71.
8. Fuchs D, Samsonov M, Tilz GP, Reibnegger G, Belenkov JN, Nasonov EL, u. a. Stimulated cellular immune system in patients with congestive heart failure. *Eur J Clin Chem Clin Biochem* 1993;31:111–4.
9. Tilz GP, Diez-Ruiz A, Baier-Bitterlich G, Demel U, Wachter H, Fuchs D. Soluble receptors for tumor necrosis factor and neopterin as parameters of cell-mediated immune activation. *Hematology* 1996;1:141–54.
10. Tilz GP, Domej W, Diez-Ruiz A, Weiss G, Brezinschek R, Brezinschek HP, u. a, et al. Increased immune activation during and after physical exercise. *Immunobiology* 1993;188:194–202.
11. Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. *Clin Chim Acta* 2006;364:82–90.