Molecular and Cellular Biochemistry
https://doi.org/10.1007/s11010-021-04232-z

The potential role of neopterin in Covid-19: a new perspective

Hayder M. Al-kuraishy[1] · Ali I. Al-Gareeb[1] · Khalid J. Alzahrani[2] · Natália Cruz-Martins[3,4,5] · Gaber El-Saber Batiha[6]

Received: 1 April 2021 / Accepted: 19 July 2021

Abstract
Neopterin (NPT) is a member of pteridines group, synthesized by macrophages when stimulated by interferon gamma (INF-γ). NPT is regarded as a macrophage stimulation indicator, marker of cellular immune activation and T helper 1 (Th1) type 1 immune response. Here, we aimed to provide a view point on the NPT features and role in Covid-19. Serum NPT level is regarded as an independent prognostic factor for Covid-19 severity, with levels starting to increase from the 3rd day of SARS-CoV-2 infection, being associated with severe dyspnea, longer hospitalization period and complications. Also, early raise of NPT reflects monocytes/macrophages activation before antibody immune response, despite the NPT level may also remain high in Covid-19 patients or at the end of incubation period before the onset of clinical symptoms. On the other hand**,** NPT attenuates the activity of macrophage foam cells and is linked to endothelial inflammation through inhibition of adhesion molecules and monocytes migration. However, NPT also exerts anti-inflammatory and antioxidant effects by suppressing NF-κB signaling and NLRP3 inflammasomes. NPT can be viewed as a protective compensatory mechanism to counterpoise hyper-inflammation, oxidative stress, and associated organ damage.

Keywords Neopterin · SARS-CoV-2 infection · Covid-19 severity

Background

Coronavirus disease 2019 (Covid-19) is a global pandemic infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), having its entry through interaction with angiotensin converting enzyme 2 (ACE2) receptors, which expressed mainly in lung type II alveolar cells [1]. Moreover, the SARS-CoV-2 entry into target cells is facilitated by cellular transmembrane protein serine (TMPRSS2) through proteolytic cleaving of spike protein [2]. As a consequence, the SARS-CoV-2 binding to the ACE2 receptors expressed in lung alveolar cells, along with macrophages and endothelial cells leads to down-regulation of these receptors with induction a momentous dysregulation of renin-angiotensin system (RAS) [3]. Dysfunctional RAS with high angiotensin II (AngII) has been linked to acute lung injury (ALI) through intensification of inflammatory changes and lung vascular permeability [4]. Moreover, SARS-CoV-2 triggers a local immune response, through recruiting monocytes and macrophages to the site

✉ Natália Cruz-Martins
ncmartins@med.up.pt

✉ Gaber El-Saber Batiha
gaberbatiha@gmail.com

Hayder M. Al-kuraishy
Hayderm36@yahoo.com

Ali I. Al-Gareeb
Dr.alialgareeb78@yahoo.com

Khalid J. Alzahrani
Ak.jamaan@tu.edu.sa

[1] Department of Clinical Pharmacology and Medicine, College of Medicine, ALmustansiriyia University, Baghdad, Iraq

[2] Department of Clinical Laboratories Sciences, College of Applied Medical Sciences, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia

[3] Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

[4] Institute for Research and Innovation in Health (i3S), University of Porto, 4200-135 Porto, Portugal

[5] Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, CESPU, Rua Central de Gandra, 1317, 4585-116 Gandra, Portugal

[6] Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, AlBeheira, Egypt

Published online: 28 July 2021

of infection with activation of cellular immune response [5]. However, an abnormal immune response and high viral replication may cause pyroptosis (inflammatory program cell death) through induction of IL-1β release [6]. Likewise, severe SARS-CoV-2 and abnormal immune response may propagate to induce the development of cytokine storm (CS) [7]. At molecular level, SARS-CoV-2 infection is thoroughly analogous to that of SARS-CoV with strong inflammatory response-induced ALI, and acute respiratory distress syndrome (ARDS) [8]. In this sense, the disease severity is not solely linked to viral infection but also to an exaggerated immune response, as evident in previous SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) [9]. In the previous pandemic (SARS-CoV, in 2003) an exaggerated immune response was observed, where high neopterin (NPT) serum levels were linked to disease severity and poor clinical course [10]. In this sense, here we provide a critical view on the NPT features and its role in Covid-19.

Characteristics and role of neopterin

Neopterin (NPT) is a member of a chemical group named as pteridines, synthesized by macrophages from dihydro-NPT when stimulated by interferon gamma (INF-γ). NPT is regarded as an indicator of macrophage stimulation, marker of cellular immune activation and T helper 1 (Th1) type 1 immune response. NPT is quietly differed from biopterins, which are pterin derivative act as cofactor for endogenous enzymes mainly amino acid hydroxylase for synthesis of different molecules such as nitric oxide [11]. Briefly, NPT is an oxidized form of dihydroneopterin during antioxidant reactions, where high NPT levels in serum and other biological fluids is linked to an elevated production of reactive oxygen species (ROS) and induction of oxidative stress (OS) during intense activation of cellular immunity [12].

Different studies have shown that high NPT serum level is linked to diverse infectious diseases and immunological disorders, including autoimmune diseases [13], malignancy [14], and viral infections, like rubella, cytomegalovirus, hepatitis C, and dengue fever [15]. Also, Omma et al. [16] observed that NPT serum level is correlated with disease severity. However, El-Lebedy et al., [17] showed that NPT serum level is not correlated with the disease' severity in patients with rheumatoid arthritis. Indeed, various types of viral infections are able to activate the formation and release of INF-γ from infected cells, where INF-γ stimulates macrophages to produce and release of NPT. Therefore, NPT concentrations reflect an underlying cell-mediated immune activation [18].

Macrophages have a crucial role in innate immune response during viral infections. Two types of monocyte-derived macrophages are developed: classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 macrophages have pro-inflammatory role, are stimulated by tumor necrosis alpha (TNF-α), INF-γ, and pathogen-associated molecular patterns (PAMPs), while M2 macrophages have anti-inflammatory role and activated by IL-13 and IL-4 [19]. Specifically, NPT serum level is correlated with activation of M1 macrophages and associated hyper-inflammation-induced tissue damage [20]. Moreover, T cells through TNF-α, natural killer (NK) cells through interferon gamma (INF-γ) and viral infections through pathogen-associated molecular patterns (PAMPs) activate classical macrophage (M1) for the release of neopterin (NPT), which inhibit release of adhesion molecules [21]. As a consequence, a high release of NPT leads to the negative feedback inhibition of macrophage activity with macrophage polarization' induction from pro-inflammatory M1 to the anti-inflammatory M2 type [22].

On the other hand, NPT has a protective effect against plaque generation in patients with carotid atherosclerosis through inhibition of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemotactic protein-1 (MCP-1) to endothelial cells. Likewise, NPT derivatives improve endothelial function via activation of nitric oxide (NO) synthase. Tetrahydrobiopterin is regarded as derivative of NPT also act as a cofactor for endothelial nitric oxide synthase (eNOS) suppresses vascular injury and improve endothelial function [23]. Similarly, Shira et al. [24] observed that NPT might be conceived as a new therapeutic line in the management of ischemic heart disease and atherosclerosis through suppressing inflammation-induced endothelial dysfunction and atherogenesis. Indeed, it has been stated that elevated NPT in paraquat-induced ALI might be a compensatory mechanism due to development of OS and reduction of antioxidant capacity [25]. Therefore, there is a strong controversy regarding the potential role of NPT in cardio-pulmonary disorders. The net-effect of NPT is shown in Fig. 1.

Role of neopterin in Covid-19

At present, different studies have tried to address the critical role of NPT in Covid-19 severity and clinical outcomes. In a retrospective study with 115 hospitalized patients with severe Covid-19, Bellmann–Weiler et al. [26] illustrated that NPT serum levels above 45 nmol/L at time of admission predict both severity and the need for mechanical ventilation at intensive care unit (ICU), since high NPT serum levels reflect exaggerated T cells activations-induced ALI and ARDS in SARS-CoV-2 pneumonia [27]. Similarly, Robertson et al. [28] showed that NPT serum levels are regarded as an independent prognostic factor for Covid-19 severity. Besides, in SARS patients, the NPT level started to increase

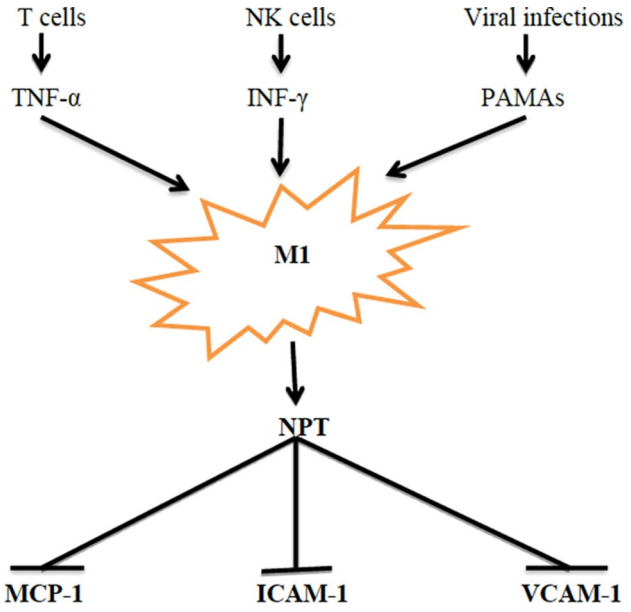

Fig. 1 Activation of neopterin release and inhibition of adhesion molecules: T cells through tumor necrosis alpha (TNF-α), natural killer (NK) cells through interferon gamma (INF-γ) and viral infections through pathogen-associated molecular patterns (PAMPs) activate macrophage (M1) for release of neopterin (NPT), which inhibit release of adhesion molecules, monocyte chemoattractant protein-1 (MCP-1), intracellular adhesion molecule-1(ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1)

from the 3rd day of infection and was linked to severe dyspnea, longer hospitalization period and associated complications. Thus, early increase of NPT reflects monocytes/macrophages activation before antibody immune response [10]. In a prospective study, Ozge et al. [29] confirmed that NPT serum level has higher sensitivity (100%) and specificity (76%) in severe Covid-19 patients compared to mild ones. Thus, NPT serum level can be a helpful biomarker to recognize Covid-19 patients at an elevated risk of a deteriorated outcome. In addition, it has been reported that NPT serum level may be a diagnostic biomarker in viral infections of lower respiratory tract as it increased more than 10 nmol/L in 96% of patients. Also, NPT serum level can be able to differentiate a viral infection of lower respiratory tract from that of bacterial one, being stated an increase two times higher in case of viral when compared to bacterial infection. Also, in viral infections, elevation of NPT serum level is associated with high CRP as compared with bacterial infection, in which C-reactive protein (CRP) is slightly increased [30, 31]. In addition to this, NPT serum level is correlated with viral load, infectivity, and mortality in infected patients with HIV [32], hepatitis C and B [33]. Indeed, NPT level in cerebrospinal fluid (CSF) is elevated in patients with severe SARS-CoV-2 infection with neurological disorders suggesting a remarkable pattern of CSF inflammation and central nervous system (CNS) pathobiology in Covid-19-induced brain injury [34].

Despite these findings confirmed strong associations between NPT serum level and Covid-19 severity, none of studies follow NPT level at the end course of Covid-19 severity. The NPT level may remain high in patients with Covid-19 or elevated at the end of incubation period before the onset of clinical symptoms, but none of the studies follow NPT level at the end course of Covid-19 severity [35, 36]. In addition, severe cases of Covid-19 have been linked to a high-risk of acute kidney injury (AKI) in about 50% of cases [37]. In AKI, NPT level is correlated with elevated blood urea and serum creatinine levels [38]. Furthermore, the correlation between NPT level and blood urea and/or serum creatinine levels was not evaluated in most studies that concern NPT level in Covid-19. Therefore, linking NPT level with Covid-19 severity seems to be a compensatory protective mechanism against SARS-CoV-2 rather than a causal factor. In fact, during viral infection, macrophages synthesize dihydro-NPT upon IFN-γ activation, which oxidized to form NPT. Therefore, NPT is an oxidized form of dihydro-NPT during macrophage-induced inflammatory changes and OS. Free radicals, ROS and other oxidants agents during OS increase conversion of 7,8-dihydro-NPT to NPT. Therefore, measurement of total NPT (NPT plus dihydro-NPT) is a more accurate measure than NPT alone in assessment of macrophage activity [15]. It has been shown that the generated 7,8-dihydro-NPT during macrophages activation exert antioxidant activity against local oxidizing inflammatory environment [39]. Undeniably, NPT is not always a reflex of the disease activity and severity, as shown by a systematic review and meta-analysis, illustrating that NPT level has no any role or substantial effect on disease activity and severity of RA [40].

Nonetheless, most studies that confirmed the potential benefit of NPT as a biomarker of Covid-19 severity did not discuss why it increases and do it exert harmful or protective effects during the clinical course in Covid-19 patients. It has been revealed that SARS-CoV-2 infection leads to endotheliitis which provoke the release of pro-inflammatory cytokines [41]. As a consequence, endothelial inflammation activates the production of IL-6 and adhesion molecules, like ICAM-1, MCP-1, and VCAM-1 that encourage T cells and monocyte adhesions and infiltrations into vascular neointima with secretion of TNF-α [42]. Yan et al. [43] illustrated that NPT attenuates the activity of macrophage foam cells and is linked with endothelial inflammation through inhibition of adhesion molecules and monocytes migration. Therefore, high NPT levels in Covid-19 patients can display a protective effect to counteract the SARS-CoV-2-induced endotheliitis and endothelial dysfunctions. Into the bargain, SARS-CoV-2 infection is associated with macrophage activation with acquisition of pro-inflammatory phenotype

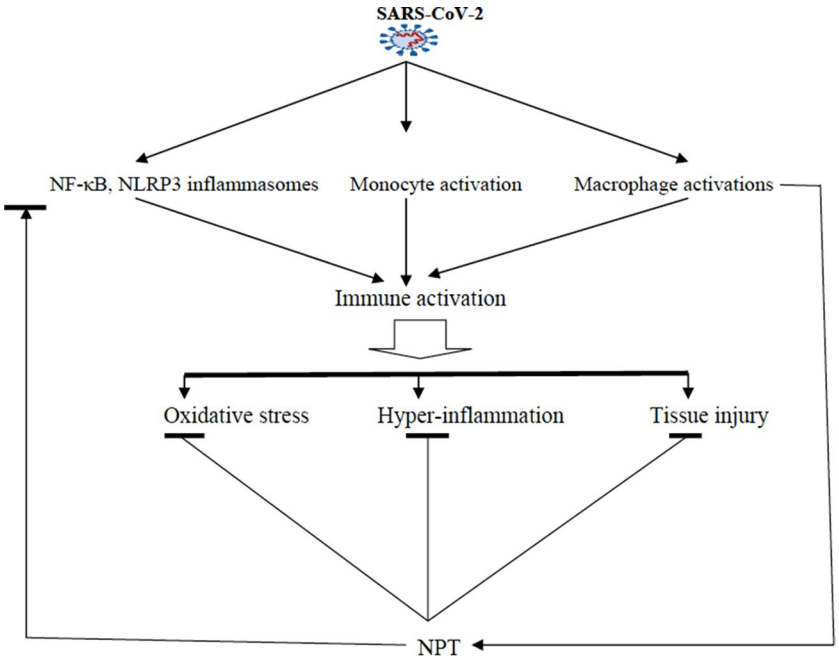

Fig. 2 The potential role of neopterin in SARS-CoV-2 infection: Neopterin (NPT) inhibits tissue injury, hyperinflammation and oxidative stress that are induced by SARS-CoV-2-mediated immune activation

(M1) and activation of NF-κB and nods like receptor pyrin 3 (NLRP3) inflammasomes leading to hyper-inflammatory status [44]. Different studies have shown that NPT exert anti-inflammatory effects through suppressing NF-κB signaling and NLRP3 inflammasomes [22]. The inhibitory effect of NPT on the NLRP3 inflammasomes is mediated through activation of anti-inflammatory IL-10 and nuclear translocation of transcription factor-2 (Nrf-2). As well, a prolonged NPT effect accelerates the development of M2 over M1 leading to an anti-inflammatory status to counterbalance the M1-mediated pro-inflammatory response [45].

On the other hand, SARS-CoV-2 infection-induced complications are linked to OS induction, resulting from an overproduction of ROS from neutrophils and activated monocytes/macrophages axis [46]. Laforge et al. [47] illustrated that ROS and OS in SARS-CoV-2 infection led to high neutrophil–lymphocyte ratio, dysfunction of red blood cell, thrombosis, and tissue damage. Thus, antioxidants, like vitamins C, D and E may attenuate Covid-19 severity through modulation of glutathione level, immune response and tissue oxygenations [48]. It has been documented that NPT and 7,8-dihydro-NPT have antioxidant effects comparable to that of melatonin [49]. Similarly, high NPT level reflects a poor endogenous antioxidant capacity and deregulated immune response [50]; herein, NPT may attenuate Covid-19-associated inflammatory and OS-derived disorders as well as tissue damage (Fig. 2).

Furthermore, the NPT level is also increased in patients with type 2 diabetes mellitus (T2DM) [51], cardiovascular disorders [52] and in elderly [53] due to OS and depletion of antioxidant capacity. In a recent study, old age patients with T2DM and cardiovascular disorders were regarded as high-risk group for Covid-19 severity [54]. In this sense, NPT level in those risk groups with Covid-19 should be reevaluated, despite high NPT level in patients with Covid-19 seems to be a protective compensatory mechanism to counterbalance the hyper-inflammatory response, OS, and associated organ damage through its anti-inflammatory and antioxidant effects. Furthermore, the development of NPT agonist agents either drugs or analogues of phytomedicine may be of a great value in the management of Covid-19.

Conclusion

An elevated NPT serum level in Covid-19 patients is regarded as a protective compensatory mechanism to counterpoise the hyper-inflammatory response, OS, and associated organ damage through its anti-inflammatory and antioxidant effects. Thus, prospective and randomized, controlled clinical trials should be warranted to confirm and reevaluate the association between serum NPT level and Covid-19 severity mainly in high-risk patients.

Acknowledgements This work was supported by Taif University Researchers Supporting Program (Project Number: TURSP-2020/128), Taif University, Saudi Arabia.

Author contributions Study design: HMAK, GESB; Investigation: HMAK, AIAG, KJA; Supervision: GESB; Validation: NCM, GESB; Writing—original draft: HMAK, AIAG; Writing—review and editing: NCM, GESB.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that there are no conflict of interest.

References

1. Al-Kuraishy HM, Al-Naimi MS, Lungnier CM, Al-Gareeb AI (2020) Macrolides and COVID-19: an optimum premise. Biomed Biotechnol Res J 4(3):189
2. Al-Kuraishy HM, Hussien NR, Al-Naimi MS, Al-Buhadily AK, Al-Gareeb AI, Lungnier C (2020) Renin-Angiotensin system and fibrinolytic pathway in COVID-19: one-way skepticism. Biomed Biotechnol Res J 4(5):33
3. Al-Kuraishy HM, Al-Gareeb AI, Qusty N, Cruz-Martins N, Batiha GE (2021) Sequential doxycycline and colchicine combination therapy in Covid-19: the salutary effects. Pulm Pharmacol Ther 67:102008
4. Al-Kuraishy HM, Al-Niemi MS, Hussain NR, Al-Gareeb AI, Al-Harchan NA, Al-Kurashi AH (2020) The potential role of renin angiotensin system (RAS) and dipeptidyl peptidase-4 (DPP-4) in COVID-19: navigating the uncharted. In: Kibel A (ed) Selected chapters from the reninangiotensin system. IntechOpen, London, pp 151–165
5. Al-Kuraishy HM, Al-Gareeb AI, Alblihed M, Cruz-Martins N, Batiha GE (2021) COVID-19 and risk of acute ischemic stroke and acute lung injury in patients with type II diabetes mellitus: the anti-inflammatory role of metformin. Front Med 8:110
6. Lugnier C, Al-Kuraishy HM, Rousseau E (2021) PDE4 inhibition as a therapeutic strategy for improvement of pulmonary dysfunctions in Covid-19 and cigarette smoking. Biochem Pharmacol 185:114431
7. Al-Kuraishy HM, Al-Gareeb AI, Cruz-Martins N, Batiha GE (2021) Hyperbilirubinemia in Gilbert syndrome attenuates Covid-19 induced-metabolic disturbances: a case-report study. Front Cardiovasc Med 8:71
8. Al-kuraishy HM, Al-Gareeb AI, Alqarni M, Cruz-Martins N, Batiha GE (2021) Pleiotropic effects of tetracyclines in the management of COVID-19: emerging perspectives. Front Pharmacol 12:136
9. Zou L, Dai L, Zhang Y, Fu W, Gao Y, Zhang Z, Zhang Z (2020) Clinical characteristics and risk factors for disease severity and death in patients with Coronavirus disease 2019 in Wuhan, China. Front Med 7:532
10. Zheng B, Cao KY, Chan CP, Choi JW, Leung W, Leung M, Duan ZH, Gao Y, Wang M, Di B, Hollidt JM (2005) Serum neopterin for early assessment of severity of severe acute respiratory syndrome. Clin Immunol 116(1):18–26
11. Michalak Ł, Bulska M, Strząbała K, Szcześniak P (2017) Neopterin as a marker of cellular immunological response. Postepy Hig Med Dosw 71(1):727–736
12. Goyal N, Kashyap B, Singh NP, Kaur IR (2017) Neopterin and oxidative stress markers in the diagnosis of extrapulmonary tuberculosis. Biomarkers 22(7):648–653
13. Arshadi D, Nikbin B, Shakiba Y, Kiani A, Jamshidi AR, Boroushaki MT (2013) Plasma level of neopterin as a marker of disease activity in treated rheumatoid arthritis patients: association with gender, disease activity and anti-CCP antibody. Int Immunopharmacol 17(3):763–767
14. Melichar B, Spisarová M, Bartoušková M, Krčmová LK, Javorská L, Študentová H (2017) Neopterin as a biomarker of immune response in cancer patients. Ann Transl Med 5(13):280
15. Koç DÖ, Özhan Y, Acar ET, Bireroğlu N, Aslan F, Keğin M, Sipahi H (2020) Serum neopterin levels and IDO activity as possible markers for presence and progression of hepatitis B. Pteridines 31(1):91–99
16. Omma A, Colak S, Can Sandikci S, Yucel C, Erden A, Sertoglu E, Ozgurtas T (2019) Serum neopterin and ischemia modified albumin levels are associated with the disease activity of adult immunoglobulin a vasculitis (Henoch-Schönlein purpura). Int J Rheum Dis 22(10):1920–1925
17. El-Lebedy D, Hussein J, Ashmawy I, Mohammed AM (2017) Serum level of neopterin is not a marker of disease activity in treated rheumatoid arthritis patients. Clin Rheumatol 36(9):1975–1979
18. Pizzini A, Kurz K, Santifaller J, Tschurtschenthaler C, Theurl I, Fuchs D, Weiss G, Bellmann-Weiler R (2019) Assessment of neopterin and indoleamine 2, 3-dioxygenase activity in patients with seasonal influenza: a pilot study. Influenza Other Respir Viruses 13(6):603–609
19. Orecchioni M, Ghosheh Y, Pramod AB, Ley K (2019) Macrophage polarization: different gene signatures in M1 (LPS+) vs. classically and M2 (LPS–) vs. alternatively activated macrophages. Front Immunol 10:1084
20. Prebble H, Cross S, Marks E, Healy J, Searle E, Aamir R, Butler A, Roake J, Hock B, Anderson N, Gieseg SP (2018) Induced macrophage activation in live excised atherosclerotic plaque. Immunobiology 223(8–9):526–535
21. Watanabe T (2020) Neopterin derivatives–a novel therapeutic target rather than biomarker for atherosclerosis and related diseases. Vasa. https://doi.org/10.1024/0301-1526/a000903
22. de Paula MR, Ghisoni K, Lim CK, Aguiar AS Jr, Guillemin GJ, Latini A (2018) Neopterin preconditioning prevents inflammasome activation in mammalian astrocytes. Free Radic Biol Med 115:371–382
23. Farghaly HS, Metwalley KA, Raafat DM, Saied GM, Gabri MF, Algowhary M (2021) Association between vascular endothelial dysfunction and the inflammatory marker neopterin in patients with classic congenital adrenal hyperplasia. Atherosclerosis. https://doi.org/10.1016/j.atherosclerosis.2021.05.017
24. Shirai R, Sato K, Yamashita T, Yamaguchi M, Okano T, Watanabe-Kominato K, Watanabe R, Matsuyama TA, Ishibashi-Ueda H, Koba S, Kobayashi Y (2018) Neopterin counters vascular inflammation and atherosclerosis. J Am Heart Assoc 7(3):e007359
25. Toygar M, Aydin I, Agilli M, Aydin FN, Oztosun M, Gul H, Macit E, Karslioglu Y, Topal T, Uysal B, Honca M (2015) The relation between oxidative stress, inflammation, and neopterin in the paraquat-induced lung toxicity. Hum Exp Toxicol 34(2):198–204
26. Bellmann-Weiler R, Lanser L, Burkert F, Seiwald S, Fritsche G, Wildner S, Schroll A, Koppelstätter S, Kurz K, Griesmacher A, Weiss G (2021) Neopterin predicts disease severity in hospitalized patients with COVID-19. InOpen forum infectious diseases, vol 1. Oxford University Press, Oxford, p ofaa521
27. Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, Dejnirattisai W, Rostron T, Supasa P, Liu C, Lopez-Camacho C (2020) Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat Immunol 21(11):1336–1345
28. Robertson J, Gostner JM, Nilsson S, Andersson LM, Fuchs D, Gisslen M (2020) Serum neopterin levels in relation to mild and severe COVID-19. BMC Infect Dis 20(1):1–6
29. Ozger HS, Dizbay M, Corbacioglu SK, Aysert P, Demirbas Z, Tunccan OG, Hizel K, Bozdayi G, Caglar K (2020) The prognostic role of neopterin in COVID-19 patients. J Med Virol 93(3):1520–1525

30. Ip M, Rainer TH, Lee N, Chan C, Chau SS, Leung W, Leung MF, Tam TK, Antonio GE, Lui G, Lau TK (2007) Value of serum procalcitonin, neopterin, and C-reactive protein in differentiating bacterial from viral etiologies in patients presenting with lower respiratory tract infections. Diagn Microbiol Infect Dis 59(2):131–136
31. Coster D, Wasserman A, Fisher E, Rogowski O, Zeltser D, Shapira I, Bernstein D, Meilik A, Raykhshtat E, Halpern P, Berliner S (2019) Using the kinetics of C-reactive protein response to improve the differential diagnosis between acute bacterial and viral infections. Infection 2019:1–8
32. Wirleitner B, Schroecksnadel K, Winkler C, Fuchs D (2005) Neopterin in HIV-1 infection. Mol Immunol 42(2):183–194
33. Abdelaziz HG, El-Tantawy TM, Attia HA, Hamed MM (2020) Neopterin as a predictor of response to pegylated interferon therapy in Egyptian patients with chronic hepatitis C virus. Asian J Res Biochem 6:43–52
34. Edén A, Kanberg N, Gostner J, Fuchs D, Hagberg L, Andersson LM, Lindh M, Price RW, Zetterberg H, Gisslén M (2020) CSF biomarkers in patients With COVID-19 and neurologic symptoms: a case series. Neurology 96(2):e294–e300
35. Eisenhut M (2013) Neopterin in diagnosis and monitoring of infectious diseases. J Biomark. https://doi.org/10.1155/2013/196432
36. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062
37. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD, Abate M, Andrade HP (2020) Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 98(1):209–218
38. Enger TB, Pleym H, Stenseth R, Greiff G, Wahba A, Videm V (2017) A preoperative multimarker approach to evaluate acute kidney injury after cardiac surgery. J Cardiothorac Vasc Anesth 31(3):837–846
39. Gieseg SP, Amit Z, Yang YT, Shchepetkina A, Katouah H (2010) Oxidant production, oxLDL uptake, and CD36 levels in human monocyte–derived macrophages are downregulated by the macrophage-generated antioxidant 7, 8-dihydroneopterin. Antioxid Redox Signal 13(10):1525–1534
40. Hejrati A, Taghadosi M, Alizadeh-Navaei R, Hosseinzadeh S, Bashash D, Esmaili M, Zafari P (2020) Neopterin serum level does not reflect the disease activity in rheumatoid arthritis: a systematic review and meta-analysis. IUBMB Life 72(12):2563–2571
41. Thacker VV, Sharma K, Dhar N, Mancini GF, Sordet-Dessimoz J, McKinney JD (2020) Rapid endothelial infection, endothelialitis and vascular damage characterise SARS-CoV-2 infection in a human lung-on-chip model. bioRxiv. https://doi.org/10.1101/2020.08.10.243220
42. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko AV, Orekhov AN (2017) Mechanisms of foam cell formation in atherosclerosis. J Mol Med 95(11):1153–1165
43. Yan JQ, Tan CZ, Wu JH, Zhang DC, Chen JL, Zeng BY, Jiang YP, Nie J, Liu W, Liu Q, Dai H (2013) Neopterin negatively regulates expression of ABCA1 and ABCG1 by the LXRα signaling pathway in THP-1 macrophage-derived foam cells. Mol Cell Biochem 379(1):123–131
44. van den Berg DF, Te Velde AA (2020) Severe COVID-19: NLRP3 inflammasome dysregulated. Front Immunol 11:1580
45. Yang CA, Huang ST, Chiang BL (2015) Sex-dependent differential activation of NLRP3 and AIM2 inflammasomes in SLE macrophages. Rheumatology 54(2):324–331
46. Schönrich G, Raftery MJ, Samstag Y (2020) Devilishly radical NETwork in COVID-19: oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression. Adv Biol Regul 77:100741
47. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, Benoliel JJ, Becker C (2020) Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat Rev Immunol 20(9):515–516
48. Qin M, Cao Z, Wen J, Yu Q, Liu C, Wang F, Zhang J, Yang F, Li Y, Fishbein G, Yan S (2020) An antioxidant enzyme therapeutic for COVID-19. Adv Mater 32(43):2004901
49. Girgin G, Sabuncuoğlu S, Ünal AZ, Baydar T (2017) Assessment of antioxidant and cytotoxic activity of known antioxidants compared to neopterin. Multidiscip Digit Publ Inst Proc 1(10):1071
50. Murr C, Winklhofer-Roob BM, Schroecksnadel K, Maritschnegg M, Mangge H, Böhm BO, Winkelmann BR, März W, Fuchs D (2009) Inverse association between serum concentrations of neopterin and antioxidants in patients with and without angiographic coronary artery disease. Atherosclerosis 202(2):543–549
51. Rasheed HA, Al-Kuraishy HM, Al-Gareeb AI, Hussien NR, Al-Nami MS (2019) Effects of diabetic pharmacotherapy on prolactin hormone in patients with type 2 diabetes mellitus: bane or boon. J Adv Pharm Technol Res 10(4):163
52. Al-Kuraishy HM, Al-Gareeb AI, Al-Buhadilly AK (2018) Rosuvastatin improves vaspin serum levels in obese patients with acute coronary syndrome. Diseases 6(1):9
53. Abdul-Hadi M, Hussian N, Rasheed H, Al-Kuraishy H, Al-Gareeb A (2020) Subclinical hypothyroidism and erectile dysfunction: the potential nexus. Urol Sci 31(2):56
54. Al-kuraishy H, Al-Gareeb AI, Guerreiro SG, Cruz-Martins N, Batiha GE (2021) COVID-19 in relation to hyperglycemia and diabetes mellitus. Front Cardiovasc Med 8:335