SERUM LEVELS OF NEOPTERIN IN WORKERS EXPOSED TO DUST FROM SYNTHETIC ABRASIVES

G. Prakova[1], P. Gidikova[2], G. Sandeva[2], K. Haracherova[3], E. Slavov[4]

[1]First Department of Internal Medicine, Medical Faculty, Trakia University, Stara Zagora

[2]Department of Hygiene, Epidemiology and Infectious Diseases, Medical Faculty, Trakia University, Stara Zagora

[3]Occupational Health Service "Zagora Holding", Stara Zagora

[4]Department of Molecular Biology, Immunology and Medical Genetics, Medical Faculty, Trakia University, Stara Zagora

Abstract

Neopterin is produced by the macrophage-monocyte cells (MMC) under the influence of interferon-γ and indirectly reflects its synthesis in the body, thus being an integral marker for the activation of the cellular immune response. ***The aim*** of this work was to investigate serum neopterin in subjects exposed to dust from synthetic abrasives. ***Materials and methods:*** Neopterin was measured in serum of 55 exposed to synthetic abrasive dust and 21 control group. Results were analyzed according to age, gender, smoking habits and concentrations of dust in the working environment. ***Results and discussion:*** Higher levels of neopterin were established in the exposed (1,31 ± 0,68 ng/ml) compared with the control group (1,10 ± 0,85 ng/ml). In the exposed group increased neopterin was found in smokers (1,34 ± 0,87 ng/ml) compared to nonsmokers (1,29 ± 0,55 ng/ml), and in men (1,33 ± 0,71 ng/ml) compared to women (1,28 ± 0,64 ng/ml). Higher serum levels of neopterin were observed in the group exposed to dust below the limit of 5 mg/m^3 (1,35 ± 0,72 ng/ml) versus 1,28 ± 0,66 ng/ml for the subjects exposed to dust over 5 mg/m^3. ***Conclusion:*** Exposure to dust from synthetic abrasives containing corundum and carborundum tends to activate the MMC resulting in elevated levels of serum neopterin. Smoking potentiates the effect of dust and stimulates production of neopterin in exposed workers. Further studies are needed to clarify the impact of synthetic abrasive dust on the biological response.

Keywords: *neopterin, corundum, carborundum*

Neopterin is a low molecular weight compound from the pteridine class - a heterogeneous group of substances, derivatives of guanosine triphosphate (GTP). Neopterin is a nonspecific highly sensitive marker for activation of the monocyte unit (monocytes/macrophages) of the cellular immunity under the influence of IFN-γ (Fig. 1) (1, 2, 3). According to some authors, the study of neopterin in biological materials is a way to explore the body's immune response, associated with quantification of biochemical changes induced by cytokines (4, 5, 6). Neopterin is able to enhance cell cytotoxicity through reactive oxygen species, which play an important role in the damage to vascular endothelium through induction of apoptosis. Neopterin has an active part in the formation of nitric oxide (NO) as well (7).

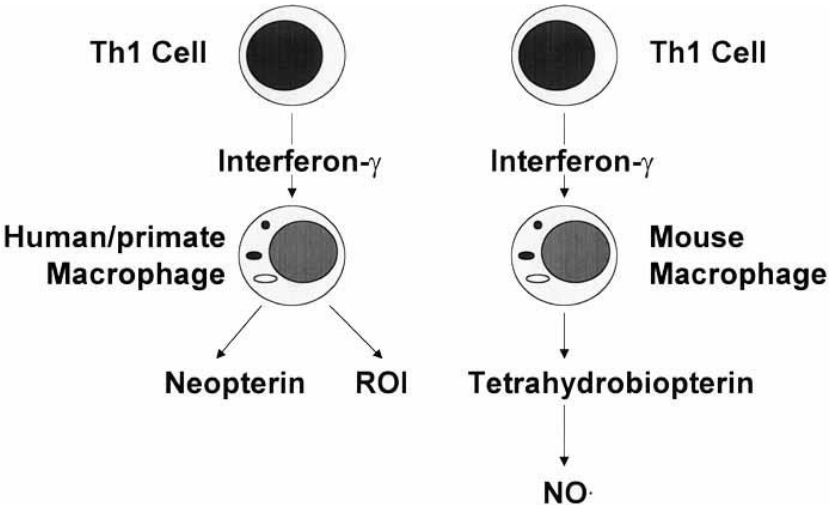


Fig. 1. Biosynthesis of neopterin derivatives in human monocyte/macrophages (8)

Recently there's been a rapid expansion in the use of neopterin in clinical practice for diagnosis, prognosis and assessment of the effect of treatment of many diseases (9, 10, 11). High levels of neopterin are an indication of activity of immunopathological processes and precede the clinical manifestations of diseases (12, 13, 14).

The purpose of this work was to investigate serum neopterin in workers exposed to dust from synthetic abrasives.

Material and methods: Concentrations of synthetic abrasive dust in the air of the working environment (containing primarily corundum and carborundum) were measured in mg/m^3. Neopterin was defined in serum of 55 workers exposed to dust and 21 control group. The study of neopterin was performed by ELISA kit for quantitative determination in human serum, manufactured by DRG Instruments GmbH, Germany. The analysis was performed according to the manufacturer's protocol. As physiological limits were adopted serum neopterin levels between 0,3 and 3,0 ng/ml. The results were analyzed according to the age, gender, smoking habits of the subjects and the concentration of dust in the working environment. Statistical analysis of the results was performed using SPSS package version 10.

Results and discussion: Higher levels of neopterin were found in workers exposed to dust from synthetic abrasives (1,31 ± 0,68 ng/ml) compared to the control group - 1,10 ± 0,85 ng/ml (Fig. 2).

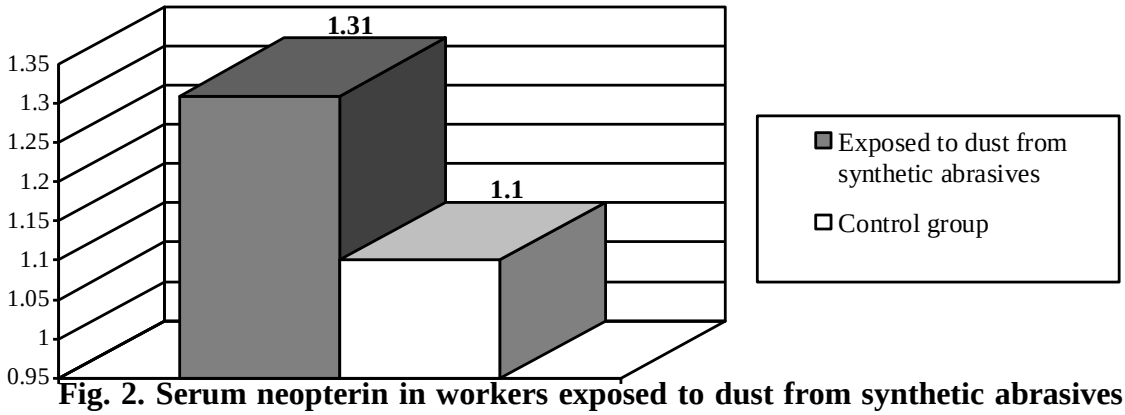
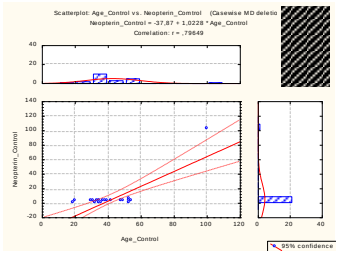


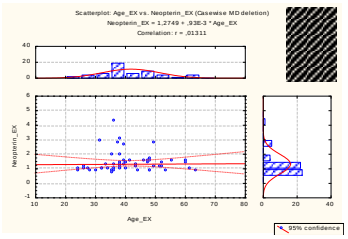
Fig. 2. Serum neopterin in workers exposed to dust from synthetic abrasives and in a control group.

The lack of significant difference in serum neopterin levels from the two groups is probably a result of the dust's chemical composition. The dust from synthetic abrasives, to which the surveyed workers were exposed, contained predominantly corundum and carborundum. No free silica was detected, which exhibits fibrogenic properties and leads to significant activation of macrophage-monocyte cells and release of biological substances, including neopterin. Our studies in this area have found significantly higher levels of neopterin in workers exposed to dust containing free silica compared with a control group (15). The results of the present study showed macrophage activation and release of neopterin in values close to those of the control group, which is a result of the absence of silica in synthetic abrasive dust. In the exposed workers increased neopterin was measured in men (1,33 ± 0,71 ng/ml) compared to women (1,28 ± 0,64 ng/ml). According to Wachter, H. et al., and Fuchs, D. et al., 1989, reference values of neopterin in healthy individuals between 19-75 years were 5,3 ± 2,7 nmol/l, regardless of gender (16, 17). In our studies we have found higher levels of neopterin in the serum of men exposed to dust than in women. Similar results reported Shu-Chun Chuang et al., 2016, who observed neopterin levels of 20,39 nmol/l for men and 19,81 nmol/l for women (18).

In the exposed workers increased neopterin was found in smokers (1,34 ± 0,87 ng/ml) compared to non-smokers (1,29 ± 0,55 ng/ml). This fact implies a higher level of activation of the macrophage system in smokers exposed to dust than in non-smokers, thus confirming the synergic effect of smoking and dust exposure demonstrated by the increased activity of macrophages synthesizing neopterin. A. A. Halim et al., 2016, established higher levels of serum neopterin in smokers (22,40 ± 3,04 nmol/l), compared to former smokers (20,33 ± 4,67 nmol/l) and nonsmokers (16,00 ± 5,3 nmol/l) (19). Djordjevic V.B. et al., 2008, also found a significant correlation between neopterin and smoking ($p<0,01$) in patients with angina pectoris, and a significant difference in the concentrations of neopterin between smokers and non-smokers ($p<0,05$) (20).



Correlation between age and neopterin in the control group



Correlation between age and neopterin in workers exposed to dust

Fig. 3. Correlations between neopterin and age in the control group and workers exposed to dust.

In the current study an increase in serum neopterin was found with increase of age (Fig. 3). A clearer correlation exists in the control group (r = 0,796) than in the workers exposed to dust (r = 0,013). In a study of 693 males and 463 females Schennach, N. et al., 2002, established a substantial increase in serum neopterin with age, which concurred with results by other authors (21-26).

Comparing mean neopterin levels of workers depending on the amount of dust in the working environment revealed no significant difference. Mean level of neopterin in the group exposed to dust up to 5 mg/m^3 was 1,35 ± 0,72 ng/ml, and in the group exposed to more than 5 mg/m^3 - 1,28 ± 0,66 ng/ml. These results are probably related to the absence of free crystalline silica in dust from synthetic abrasives.

Conclusions: Exposure to dust from synthetic abrasives containing corundum and carborundum tends to activate the MMC resulting in elevated levels of serum neopterin. Smoking potentiates the effect of dust and stimulates production of neopterin in exposed workers. Further

studies are needed to clarify the impact of synthetic abrasives dust on the biological response.

Acknowledgements: This study was funded through Project No 16/2014 by the Medical Faculty, Trakia University, Stara Zagora.

References:

1. Шевченко О.П., Олефиренко Г.А., Орлова О.В. Использование неоптерина для оценки активации клеточного иммунитета. Лаборатория, 2004, №48, 6.
2. Шевченко О.П.,ОлефиренкоГ.А., Орлова О.В. Неоптерин. Лабораторная медицина, 2001, №4, 55-61.
3. Werner-Fermayer G., Werner E.R., Fuchs D. et al. Tumor necrosis factor-alpha and lipopolysaccaride enhance interferon-induced tryptophan degradation and pteridine synthesis in human cells.// Biol.Chem.Hoppe-Seyler, 1989, Vol. 370. 1 063-1069.
4. Fuchs D. Neopterin. A massage from the immune system.-1998. BRAHMS Diagnostic GmbH
5. Fuchs D., Baier-Bitterlich G., Hausen A. et al. Neopterin as an immunodiagnostic parameter. Dtsch.Med.Wochenschr.1995.Vol. 120(16).567-570
6. Fuchs D., Weiss G., Wachter H. Neopterin biochemistry and clinical use as a marker for cellular immune reactions. Int.Arch.Allergy Immunol.1993.Vol.101.l-6
7. Ибадова, Т.И. Клиническое значение содержания неоптерина в крови новорожденных детей с гипоксическими поражениями ЦНС, Педиатрия/2012/Том 91/№ 4, 160-162.
8. Werner, E.R.; Werner-Felmayer, G.; Fuchs, D.; Hausen, A.Reibnegger, G.; Yim, J.J.; Pfleiderer, W. and Wachter, H. Tethrahydrobiopterin biosynthetic activites in human macrophages, fibroblasts, THP-1 and T 24 cells. GTP cyclohydrolase I is stimulated interferon -gamma and 6 pyrovoyl tetrahydropterin syntase and sepiapterin reductase are constitutively present, *J. Biol. Chem*., 1990 **265**, 3189-3192.
9. Hausen A., Fuchs D., Reibnegger G. et al. Neopterin in clinical use.Pteridines., 1989, Vol. L, 3-10.
10. Murr C., Bergant A., Widschwendter M. Neopterin is an independent prognostic variable in females with breast cancer. Clin.Chem., 2002, Vol.75. l 999-2001
11. Fuchs D., Weiss G., Reibnegger G. et al. The role of neopterin as a monitor of cellular immune activation in transplantation, inflammatory, infection and malignant disease. Crit.Rev.Clin.Lab.Sci., 1992, Vol.29, 307-341.
12. Oldhafer K.J., Schafer O., Wonigeit K. et al. Monitoring of serum neopterin levels after liver transplantation. Transplantation Proc., 1988, Vol.20.1.671-673.
13. Wachter H., Fuchs D., Hausen A. et al. Neopterin as a marker for activation of cellular immunity: immunologic basis and clinical application. Adv.Clin.Chem., 1989, Vol.27, 81-141.
14. Werner-Fermayer G., Werner E.R., Fuchs D. et al. Tumor necrosis factor-alpha and lipopolysaccaride enhance interferon-induced tryptophan degradation and pteridine synthesis in human cells. Biol.Chem.Hoppe-Seyler., 1989, Vol.370. 1 063-1069.
15. Prakova G., P. Gidikova, E.Slavov, G. Sandeva, R. Deliradeva**.** Serum neopterin in silicosis patients and workers exposed to inorganic dust. Scripta Scientifica Medica, Varna, vol.41 (1), 91-96.
16. Wachter, H.; Fuchs, D.; Hausen, A.; Reibnegger, G. Werner, E.R. Neopterin as marker for activation of cellular immunity: immunologic basis and clinical application. *Adv. Clin. Chem*., 1989, 27, 81-141.
17. Fuchs, D.; Milstien, S., Krämer, G.; Reibnegger, G., Werner, E.R.; Dierich, M.P. and Wachter, H. Urinary neopterin concentrations vs total neopterins for clinical utility. *Clin.Chem*., 1989, 35, 2305-2307.
18. Chuang Shu-Chun, Heiner Boeing, Stein Emil Vollset et al. Cellular immune activity biomarker

neopterin is associated hyperlipidemia: results from a large population-based study, Immunity & Ageing (2016) 13:5 DOI 10.1186/s12979-016-0059-y
19. Ashraf Abdel Halim, Zeinab Adawy, Manal Sayed. Role of neopterin among COPD patients, Egyptian Journal of Chest Diseases and Tuberculosis, 2016, 65, 23–27.
20. Djordjevic VB, Stojanovic I, Cosic V, Zvezdanovic L, Deljanin-Ilic M, Dimic S, Kundalic B, Cvetkovic T, Jevtovic-Stoimenov T. Serum neopterin, nitric oxide, inducible nitric oxide synthase and tumor necrosis factor-alpha levels in patients with ischemic heart disease, Clin Chem Lab Med. 2008;46(8):1149-55. doi: 10.1515/CCLM.2008.213.
21. Harald Schennach,Christian Murr2, Elmar Gächter, Peter Mayersbach, Diether Schönitzer, Dietmar Fuchs˙. Factors Influencing Serum Neopterin Concentrations in a Population of Blood Donors, Clinical Chemistry 48, No. 4, 2002, 643 – 645.
22. Reibnegger G, Huber LA, Ju¨rgens G, Scho¨nitzer D, Werner ER, Wachter H, et al. Approach to define "normal aging" in man. Immune function, serum lipids, lipoproteins and neopterin levels. Mech Ageing Dev 1988;46:67–82.
23. Diamondstone LS, Tollerud DJ, Fuchs D, Wachter H, Brown LM, Maloney E, et al. Factors influencing serum neopterin and 2-microglobulin levels in healthy diverse population. J Clin Immunol 1994;14:368–74.
24. Ledochowski M, Murr C, Widner B, Fuchs D. Association between insulin resistance, body mass and neopterin concentrations. Clin Chim Acta 1999;282:115–23.
25. Solichova D, Melichar B, Svobodova I, Blaha V, Zadak Z. Fluorescence analysis of antioxidant vitamins and neopterin in nonagenarians. Biomed Chromatogr 1999;13:117–8.
26. Ledochowski M, Murr C, Jager M, Fuchs D. Dehydroepiandrosterone, ageing and immune activation. Exp Gerontol 2001;36:1739–47.