Serum neopterin as an immunological marker of disease activity in inflammatory diseases

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NEOPTERIN: A REVIEW.

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ABSTRACT

Neopterin was discovered in bee larvae, in worker bees and in royal jelly. The compound was termed 'neopterin' to denote that it might start a new (Greek, neo) epoch in pteridine research. Increased concentrations of neopterin were reported in patients with viral infections, suggesting that increased neopterin may originate from the immune response of patients to the infections. In vitro studies revealed that human monocytes/macrophages produce neopterin when stimulated by interferon-γ. Neopterin can easily been detected in serum and urine. The most important clinical applications for the determination of neopterin are prognostic indicator of malignant diseases, follow-up control of chronic infections, monitoring of immune-stimulatory therapy, differential diagnosis of acute viral and bacterial infections, prognostic indicator in HIV infections and early indications of complications in allograft recipients. In recent years new physiological functions of neopterin have been discovered such as inducing or enhancing cytotoxicity, inducing apoptosis and the role of a chain breaking antioxidant. This review will focus on the immunological and physiological properties of neopterin.

Keywords:

neopterin - biosynthesis - cell mediated immunity - immunological marker
INTRODUCTION

In 1889 Hopkins isolated a pigment from the wings of lepidoptera (1). This work was continued by Wieland and Schopf (2), who in 1936 named these pigments pteridines (3), a term which has its origin in the Greek word for wing, pteron. However, attempts to elucidate the structures of these compounds were unsuccessful until Purrmann (4,5,6) showed that three insect pigments, xanthopterin, isoxanthopterin and leucopterin, contain the bicyclic nitrogenous ring pyrazino-(2,3-d)-pyrimidine. The bicyclic nitrogenous ring system pyrazino-(2,3-d)-pyrimidine is now termed pteridine according to the international Union of Pure and Applied Chemistry. Neopterin was isolated from larvae of bee (7), from worker bees, and from royal jelly (8) in 1963. Originally, H. Rembold intended to term the new compound, 2-amino-4-hydroxy-(erythro-1',2',3'-trihydroxypropyl)—pteridine, “novapterin,” to indicate that it was a new (from Latin, novum) molecule isolated from honey bees (Latin, Apis) and with a pterin structure. The compound finally was termed “neopterin” to denote that it might start a new (Greek, neo) epoch in pteridine research. In 1967, Sakurai and Goto isolated 25 mg of neopterin from 500 liters of human urine (9). Following the identification of a pteridine as the fluorescent component that was elevated in the urine of mice with Ehrlich ascites tumor, compared to healthy mice, the corresponding substance from human urine was isolated and characterized. It was found that the fluorescent component previously observed in urine of patients with malignant diseases was neopterin. Wachter and co-workers found elevated rates of neopterin excretion in a group of patients with various malignant disorders, as well as in patients with viral diseases (10). In 1981, it was suggested that neopterin originated from the immune response of the host directed against tumor cells or virally transformed cells (11). Further in vitro studies (12,13,14) revealed that human monocytes/macrophages produce neopterin when stimulated by interferon-γ. This lymphokine is released from activated T cells. Other cell types do not produce measurable amounts of neopterin following various stimuli. Therefore, neopterin production appears to be closely associated with activation of the cellular immune system. These in vitro experiments are consistent with the results of numerous clinical studies.
CHEMISTRY

Chemical reactivities indicate that both neopterin and its acid-oxidizable reduced forms (total neopterin) can be measured with sufficient accuracy. Urine and serum specimens, however, sometimes have to be shipped from the clinician or physician to the laboratory, and sometimes have to be stored for a longer time. In this case, the acid-oxidizable reduced forms of neopterin are converted to a variable extent into dihydroxanthopterin, xanthopterin, and pterin. Storage for a longer period at -20°C does not influence the neopterin concentration. Furthermore, a study using freshly collected and uniformly handled samples (15) demonstrates that the ratio of neat neopterin to total neopterin (neopterin + 7,8 dihydroxynopterin) has a fairly constant value for both urine and serum.

BIOSYNTHESIS

Neopterin and its derivatives are synthesized in vivo from guanosine triphosphate (GTP) via GTP cyclohydrolase I (GTP-CH). The activity of GTP-CH can be greatly enhanced by interferon-γ (16,17). 7,8-dihydroxynopterintriphosphate (NH2TP) is on the biosynthetic pathway of 5,6,7,8-tetrahydrobiopterin (BH4). BH4 represents the electron donor in the hydroxylation of phenylalanine to tyrosine in the liver and of tyrosine to L-dopa and tryptophan into 5-hydroxy-tryptophan in neuroendocrine tissue synthesizing catecholamines or serotonin (18). In the above mentioned tissues and in lymphocytes the majority of NH2TP is

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Fig. 1. Human monocytes/macrophages lack the enzyme 6-pyruvoyl-tetrahydropterin synthetase which converts NH2TP to 6-pyruvoyl-tetrahydropterin (17). As a consequence, monocytes and macrophages instead of synthesising BH4 accumulate NH2TP which, after hydrolysis by phosphatases, is excreted as dihydroxynopterin (NH2) or neopterin (19,20).
metabolised to BH4 (8,9). Human monocytes/macrophages lack the enzyme 6-pyruvoyl-tetrahydropterin synthetase which converts NH2TP to 6-pyruvoyl-tetrahydropterin (17). As a consequence, monocytes and macrophages instead of synthesizing BH4 accumulate NH2TP which, after hydrolysis by phosphatases, is excreted as dihydronopterin (NH2) or neopterin (19,20). Fig. 1 On the basis of this biochemical in vitro evidence it has been concluded that increased neopterin biosynthesis during inflammatory disease is primarily derived from interferon-γ activated monocytes/macrophages. However, production of neopterin, a presumed primate homologue of nitric oxide in lower animals, was increased in THP-1 cells stimulated with interferon-γ and TNF-α. α-MSH significantly inhibited this production. The evidence indicates that an autocrine regulatory circuit based on α-MSH occurs in human monocyte/macrophages (21).

PHYSIOLOGICAL ROLE OF NEOPTERIN

Since the main physiological role of interferon-γ may be the induction of antibacterial, antiprotozoal, and antifungal activities of parasitized macrophages, it has been suggested that neopterin might act as an endogenous inhibitor of folate synthesis by intracellular pathogenic microorganisms (14). At slightly alkaline pH (pH 7.5) neopterin enhances hydrogen peroxide and chloramine-T activity. This is demonstrated by increase of signal intensity in aluminol assay and also by enhancement of toxicity towards bacteria. Thus, the macrophage derived substance neopterin is able both to enhance and to reduce cytotoxicity dependent of the pH value and the oxidation state of neopterin, and it may have a pivotal role in modulation of macrophage mediated effector mechanism (22). Recent data implied a potential role of neopterin derivatives in oxygen free-radical-mediated processes, e.g. high concentrations of 7,8-dihydronopterin were found to interfere with the oxidant-antioxidant balance, and may lead to apoptosis of human cells (23,24). In addition, 7,8-dihydronopterin was found to be effective in the activation of redox-sensitive transcription factors and in the induction of HIV-1 gene expression. Neopterin and 7,8-dihydronopterin are inducers of apoptosis which is not mediated by nitric oxide (25). In vitro 7,8-dihydronopterin increases in a dose dependent manner, the lag time of low density lipoprotein oxidation mediated by Cu++ ions or peroxyl radical generator 2,2'-azobis (2-amino propane) dihydrochloride (AAPH).
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dihydroneopterin also inhibits AAPH mediated oxidation of linoleate. The kinetic of
the inhibition suggest that 7,8-dihydroneopterin is a potent chain breaking
antioxidant which functions by scavenging lipid peroxyl radicals (26). Neopterin
stimulates inducible nitric oxide synthetase (iNOS) gene expression in vascular
smooth muscle cells in vitro. One possible explanation for the impact of neopterin
on iNOS gene expression is that neopterin activates the translocation of NF-
kappa B sub-units to the nucleus by modulating the intracellular redox state
(27). The enhancing potency of the oxidized form of neopterin towards long-
wave ultraviolet light (UV-A) induced cytotoxicity was examined in vitro using
mouse melanoma (B-16) cells. The results suggest that elevation of the hydrogen
peroxide-mediated cytotoxicity by neopterin may be involved in its enhancing
potency toward UVA-induced B-16 cell damage, and may also indicate the
possible utility of the oxidized form of neopterin as an enhancer for UV-A
irradiation treatment of tumors (28). Furthermore several pteridines - i.e.
neopterin - influenced the intracellular calcium level in human monocytes.
Whether this elevation of intracellular calcium level is caused by direct influence
of neopterin on the calcium channels or by synergistically effects has to be
investigated in the future (27). A summary of the main physiological properties
of neopterin is demonstrated in Table 1.

Table 1. Main physiological properties of neopterin

- endogenous inhibitor of folate synthesis by intracellular pathogenic microorganisms
- enhance hydrogen peroxide and chloramine T activity at pH 7.5
- enhance and reduce cytotoxicity dependent of the pH value and the oxidation state
- modulation of macrophage mediated effector mechanism
- a role in oxygen free-radical -mediated processes e.g. apoptosis of human cells
- activation of redox-sensitive transcription factors
- induction of HIV-1 gene expression
- inducer of apoptosis which is not mediated by nitric oxide
- increasing the lag time of low density lipoprotein oxidation
- inhibits AAPH mediated oxidation of linoleate
- a potent chain breaking antioxidant
- stimulates inducible nitric oxide synthetase (iNOS) gene expression
- enhancing potency towards long-wave ultraviolet light (UV-A) induced cytotoxicity
- influences the intracellular calcium level in human monocytes
Macrophages and lymphocytes modify the behavior of each other in part, through the release of bioactive molecules such as interferon-γ and interleukin-1. Interleukin-1 acts on T cells in two ways: it induces receptors for interleukin-2, which would then allow the T cell to respond to this T cell growth factor; it also stimulates interleukin-2 production. Interleukin-2 triggers T cells to secrete interferon-γ.

**CELLULAR SOURCE AND INDUCTION SIGNAL**

T Lymphocytes play a role in nearly all skin diseases in which defense mechanisms are involved, or where primary intrinsic aberrations in the immune system are operative. The lesional infiltrate usually consists of different subsets of T cells, but the dominant T cell subset in the dermis is almost always the CD4+ T cell along with an admixture of CD8+ cells. Macrophages and lymphocytes modify the behavior of each other in part, through the release of bioactive molecules such as interferon-γ and interleukin-1. Interleukin-1 acts on T cells in two ways: it induces receptors for interleukin-2, which would then allow the T cell to respond to this T cell growth factor; it also stimulates interleukin-2 production. Interleukin-2 triggers T cells to secrete interferon-γ.

Fig. 2 Various in vitro and in vivo studies demonstrated that in inflammatory diseases stimulation of macrophages with T cell derived interferon-γ led to significant increase of GTP cyclohydrolase I activity and of neopterin concentration. Macrophages, when exposed to interferon-γ release large amounts of neopterin. Two different mechanisms underlay this phenomenon; first, directly interferon-γ stimulates the activity of the key enzyme cyclohydrolase I; second, human macrophages lack the activity of the 6-pyruvyltetrahydropterin synthetase, the first enzyme after dihydroneopterin triphosphate. As a consequence, monocytes and macrophages instead of synthesizing BH4 accumulate NH2TP which, after hydrolysis by phosphatases, is excreted as dihydroneopterin NH2 or neopterin (29). The human myelomonocytic cell line
THP-1 forms neopterin and degrades tryptophan upon treatment with interferon-γ. Thus the THP-1 cell line provides a permanent, easily accessible in vitro system for studying the induction and mechanism of neopterin. Neopterin production was not induced when the THP-1 cell line was stimulated with streptococcal-derived erythrogenic toxins. Treatment of THP-1 cells with 90K (a tumor-associated antigen) induced significant neopterin formation. In parallel a significant degradation of tryptophan was observed in culture supernatants leading to the formation of kynurenine.

METHODS OF DETECTION

Fully oxidized neopterin can be measured by high-performance liquid chromatography (HPLC) and radioimmunoassay (RIA). Both methods show comparable results. An ELISA test is also commercially available. Samples may be stored refrigerated at 2-8 °C for up to 24 hours, or for up to 6 months frozen at -20 °C, protected from light. The upper limit of the normal range is approximately 10 nmol/L serum (= 2.5 ng/ml). Measurement by HPLC. A method was developed for rapid separation and sensitive quantitation of urinary neat oxidized neopterin by reversed-phase HPLC on a 10-micrometer octadecylsilica column. The analyses are eluted with 15 mmol/liter potassium phosphate buffer at pH 6.4 and at a flow rate of 0.8 ml/min. Urinary neopterin can be measured by fluorescence and related to creatinine determined by ultraviolet absorption in order to account for fluctuating concentrations of urine. The method has good performance characteristics and is easy to handle. The procedure was modified for routine laboratory automated analysis without any pretreatment except dilution of samples with aqueous potassium phosphate buffer using guard columns. Determination of neopterin in serum by HPLC is more difficult to perform than in urine due to the presence of protein and due to the about 200-fold lower concentration of neopterin. Also in cerebrospinal fluid, neopterin can be measured by reversed-phase high-performance liquid chromatography. Measurement by RIA. The particular advantage of RIA compared to HPLC is its suitability for large scale applications. A RIA kit is commercially available. The RIA is based on the competition of unlabelled neopterin of the serum samples or standards and radiolabelled neopterin for the binding sites of the neopterin-specific antibody. Measurement by ELISA. The ELISA test is a competitive enzyme immunoassay for the quantitative determination of
Neopterin in serum using coated microtiter plates. The test is based on the competition of unlabelled neopterin of the serum samples or standards and horseradish peroxidase labelled neopterin for the binding sites of the neopterin specific antibody.

NEOPTERIN CONCENTRATIONS IN HEALTHY SUBJECTS
There is a temporal variability in the values of immunological parameters in a healthy population (38). Neopterin concentrations measured in serum by RIA and HPLC are consistent. Concentrations of neopterin in serum from 662 apparently healthy individuals (ages 1 to 97 years, median 22 years) were measured by RIA and the results statistically analyzed. Three age groups were identified as showing significantly different values for neopterin (Kruskal-Wallis test, p<0.0001) but there was no statistically significant sex dependence (Kruskal-Wallis, p>0.05). Subjects between ages 18 and 75 years showed no significant age dependence of the serum concentrations, but children (<18 years) and elderly subjects (>75 years) had significantly higher neopterin concentrations than did the middle group. The 95th percentiles was chosen as the upper normal limits (37). These results agreed well with data obtained for 1837 blood donors (ages 18-67 years), who had a mean neopterin concentration of 5.89 nmol/L, SD 1.78 nmol/L, and a upper 99% confidence limit of 10.5 nmol/L, estimated with an assumption of Gaussian distribution (39). In healthy pregnant woman there is a significant correlation between neopterin increase and tryptophan decrease as well as kynurenine increase and tryptophan decrease (40).

DISEASES ASSOCIATED WITH ELEVATED NEOPTERIN LEVELS
Increased concentrations of neopterin and dihydronopterin are found in serum, cerebrospinal fluid (CSF) and urine taken from patients with a wide variety of malignant and non-malignant conditions in which the cell mediated immune system is activated (41,42). Neopterin concentrations in serum or urine seem of equal value for diagnostic application as long as renal function is normal (43). Neopterin concentrations may be significantly increased in a particular disease state compared to controls, serial measurement of neopterin concentrations in a particular patient may be useful in monitoring the course of a condition. As
neopterin release depends on activation of macrophages, it is associated with a variety of conditions involving activity of cell mediated immunity (CMI) (44). Measurement of neopterin levels is a useful early indicator of complications in allograft recipients. In patients who received allografts of tissue such as kidney, liver, pancreas and heart, immunological rejections are indicated by increasing neopterin levels in urine (45) or serum (46,47,48), earlier (mean 2 days) than using conventional diagnostic procedures. Similar changes in neopterin levels occur in patients after bone marrow transplantation (49). Urinary nitric oxide (NO) and neopterin were significantly increased in children breast fed by mothers with silicone breast implants (BFSI) compared with controls. There was a significant inverse relationship between urinary neopterin excretion and the severity of esophageal dysfunction (50). In general, acute viral infections such as hepatitis, rubella, several herpes infections (e.g. herpes simplex, Epstein-Barr, cytomegalovirus) are accompanied by high neopterin levels (45,49,51). Elevated neopterin levels also occur during acute phase of Kawasaki disease (52). Urinary neopterin excretion is increased in patients with both progressive and relapsing multiple sclerosis and therefore has potential as a surrogate marker of the inflammatory component of multiple sclerosis disease activity (53). In infections, high neopterin levels usually decrease when antibodies against the pathogen become detectable, for example in children after vaccination with live vaccines (51). The extent and activity of infections with intracellular bacterial infections (e.g. Mycobacterium tuberculosis, M. leprae, or parasites e.g. malarial parasites Plasmodium falciparum or P. vivax) correlated significantly with elevated neopterin levels (54,55). Highest neopterin levels are associated with poorer prognosis in patients with septicemia and in allograft recipients, during cytomegalovirus infection. High neopterin levels have also been found in CSF of patients with cerebral infections and in some cases of multiple sclerosis. Measurement of CSF neopterin concentration may be useful for differentiating between hereditary progressive dystonia/dopa-responsive dystonia (HPD/DRD) and early-onset parkinsonism with dystonia (EOP-D) (56). In the auto-aggressive diseases as rheumatoid arthritis (57,58), Crohn’s disease (59), ulcerative colitis (60), autoimmune thyroiditis (61), systemic lupus erythematosus (62) and early onset of autoimmune diabetes mellitus (63), neopterin levels are highest in acute phase of the disease and correlate with the extent and activity of disease. In rheumatoid arthritis neopterin is also detectable in synovial fluid (64). A similar correlation exists in patients with sarcoidosis (65) and in children with coeliac
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disease (66). In several malignant diseases, haematological tumors, gynecological tumors (67), tumors of the genitourinary tract in males (68), in pediatric cancer (69) and in lung tumors (70), high neopterin levels are significantly associated with poor prognosis. In patients with malignant melanoma, there is a remarkable increase of the excretion of neopterin, which depends on the extent of the involvement and by contrast to this, in patients with Hodgkin’s disease there is a remarkable decrease of the excretion of biopterin also dependent on the extent of the involvement. In both types of tumor disease the ratio neopterin/biopterin is remarkably increased as compared to controls (71). Lymphocyte proliferative response to PHA is significantly diminished in cancer patients, and this depression appears to be partly linked to systemic inflammatory response. Plasma interferon-γ and urinary neopterin was significantly increased in cancer patients, whereas interleukin-4 was undetectable (72). Neopterin, interleukin-10 and interleukin-6 mean concentrations were significantly higher in cancer patients than in controls. Mean values of both neopterin and interleukin-6 were significantly higher in metastatic patients than in those with locally limited disease. This suggest that macrophage- and TH2-mediated immunosuppression may occur independently in solid tumors and that it becomes more evident with disease progression (73). Several clinical studies have noted elevated neopterin levels in HIV infection (74,75,76,77). Increased neopterin concentrations are prevalent in asymptomatic HIV antibody seropositive individuals. A predisposition to seroconversion and progressive disease is linked to certain behavioral and immunological conditions, in addition to a high risk of exposure to HIV (78,79,80). An individual with pre-activated T cells and macrophages, once infected with marginal amounts of HIV, will be more effectively infected since replication of HIV may start immediately (81). In a rural African population, high neopterin levels were found in apparently healthy subjects. Many of these showed subclinical parasitic infections (82). These elevated neopterin levels were found with a similar frequency in both sexes. Progressive HIV infection is associated with a further increase in neopterin levels (76). Asymptomatic seropositive individuals and those with persistent generalized lymphadenopathy have similar neopterin levels. The correlation with the Walter Reed Staging Classification is highly significant (83). A significant inverse correlation exists between neopterin levels and CD4+/CD8+ T cell ratios and absolute CD4+ T cell numbers (84) in ARC and AIDS patients, which is weak in asymptomatic individuals. Increase in CD8+ T cells do not seem to be directly correlated with increased neopterin levels. It is interesting to note that
in the final stage of AIDS, extremely low numbers of CD4+ cells and total lymphocytes can induce the release of extremely high neopterin concentrations. Particularly in HIV+ patients with current opportunistic infections β-2-microglobulin, neopterin and CD14+ monocytes expressing FcγRIII are increased, while CD4+ lymphocyte counts are reduced (85). Besides the role of neopterin as sensitive indicator of disease activity in HIV infection, neopterin derivatives are associated with the cascade of events that regulate the HIV production in infected individuals and augment progression to higher stages of HIV-associated disease(86). There are two further conditions known to lead to elevated neopterin levels. One condition is impaired renal function, which leads to elevated neopterin levels in serum but to normal neopterin/creatinine ratios in serum and urine. The other condition is atypical phenylketonuria (87). This rare metabolic defect is caused by dihydrobiopterin synthetase deficiency of 6-pyruvoyltetrahydropterin synthetase, an enzyme eliminating the triphosphate group from dihydronopterin triphosphate. Patients are commonly detected by postnatal screening for concentrations of serum phenylalanine.

COMPARISON OF NEOPTERIN CONCENTRATIONS AND OTHER LABORATORY PARAMETERS.

Measurement of neopterin and total neopterins (neopterin + dihydronopterin), are of almost equal potential for clinical diagnosis. However, when measuring total neopterins, which includes oxidation of 7,8-dihydronopterin to neopterin, more strict requirements of sample collection and handling are necessary to avoid degradation of the 7,8-dihydro derivative (88). In comparison with the direct measurement of interferon-γ the determination of neopterin levels represents various advantages. Interferon-γ is subject to fast degradation and is able to bound to soluble or cell bound receptors so that the actual biological effective concentration indicates deviations to the obtained free measurable concentration. In connection with neopterin all these problems do not appear. In renal allografts, rejection episodes were associated by increasing neopterin levels even when interferon-γ could not be detected. It has been assumed that interferon-γ is produced in peripheral tissues but rarely enters the bloodstream. In contrast, neopterin enters the circulation due to its small size and chemical stability (89). In addition, the clinical value of neopterin levels was compared to
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that of β-2 -microglobulin for monitoring the course of disease in 116 renal allograft recipients (90). The data of these studies indicated that elevations of neopterin levels clearly preceded those of serum creatinine, but β-2-microglobulin levels remained nearly constant 4 days prior to and 4 days after bolus steroid therapy. Neopterin levels provide an especially valuable picture concerning clinical activity in diseases which show rapid and acute changes in the severity of the disease. Therefore, neopterin estimations may under these circumstances be more useful than erythrocyte sedimentation rate (ESR) estimations, which has a long latency period (95). Simultaneous determination of serum neopterin and C-reactive protein (CRP) showed an increase for both markers in infections in bone marrow transplantation patients, whereas an increased neopterin in the absence of increasing CRP was characteristic for graft vs host disease (GVHD) (92).

NEOPTERIN LEVELS AFTER VACCINATION

Vaccination of children with a live measles-mumps vaccine showed increased neopterin levels in all post-vaccination-courses, also in asymptomatic ones. The typical pattern of sharply increased levels was observed, with a peak at the time when viremia is known to be highest in wild-type measles infection (12 to 15 days after vaccination). Subsequently, neopterin levels rapidly declined and normalized. This decline coincided with the period in which specific antibodies become detectable. It is important to note that in none of these children clinical symptoms were apparent.

INFLUENCE OF IMMUNOTHERAPY ON NEOPTERIN LEVELS

Patients undergoing immunostimulatory treatment with interferon-α, interleukin-2 or tumor necrosis factor (93), show increased levels of neopterin, probably due to the induction of immunoregulatory cascades which stimulate release of interferon-γ. The opposite has been observed during immunosuppressive therapy: for example, neopterin levels decrease when graft rejection is successfully treated by cyclosporin A or corticosteroids (37,38). Excretion of urinary neopterin decreases immediately at the start of therapy with the immunosuppressant cyclosporine in patients with mycosis fungoides (94). Increased neopterin levels
also followed withdrawal of cyclosporine A, since this drug inhibits secretion of interferon-g by T cells (27). A significant increase in plasma levels of neopterin was seen in patients with primary hypogammaglobulinaemia after one bolus injection (400 mg/kg) of intravenous immunoglobulin (IVIG) (95). A fast increase of neopterin values in sera of advanced cancer patients was seen during subcutaneous treatment with recombinant interleukin-2 (96). Mean serum neopterin levels were elevated during polyclonal antibody therapy (ATG) and monoclonal (OKT3) in patients following organ transplantation (97). Plasma concentrations of interferon-γ are increased in several inflammatory conditions. Administration of interferon-α (rhIFN-α2b; 5 x 10(6) U/m2) to eight healthy human subjects in a randomized controlled cross-over study showed significantly increase of neopterin 10 hours after administration. (98).

CONCLUSION

Human monocytes/macrophages produce neopterin when stimulated by interferon-γ released from activated T cells. Neopterin production appears to be closely associated with activation of the cellular immune system. High neopterin levels are found in different inflammatory diseases and certain malignancies and can easily be measured in serum and urine. Determination of the neopterin level in serum and urine from these patients have been demonstrated to be predictive for the course and progression of the disease and the response to therapy as its level rapidly declines and normalizes. Patients undergoing immunostimulatory treatment show increased levels of neopterin, probably due to the induction of immunoregulatory cascades which stimulate release of interferon-γ. The opposite has been observed during immunosuppressive therapy. In recent years new physiological functions of neopterin have been discovered such as inducing or enhancing cytotoxicity, inducing apoptosis and the role of a chain breaking antioxidant. Measurement of neopterin concentration in serum, plasma, urine or cerebrospinal fluid is easily to perform and can provide particular information.
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