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Neopterin in chronic kidney disease; an updated mini-review

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Abstract
Neopterin is secreted by macrophages and monocytes during the activation of the immune system. There is an association between neopterin and kidney diseases, and there are two different procedures for measuring this substance. Based on recent studies, measuring the level of neopterin is important in some conditions such as diabetes, kidney transplantation, preeclampsia, and systemic inflammatory response syndrome (SIRS). Furthermore, this substance has an important role in the immediate diagnosis and prevention of complications in these conditions.

Keywords: Neopterin, Chronic kidney disease, Immune system
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Introduction

After an immune response, interferon-gamma (INFɤ) is secreted by T-cells and natural killer cells (NKs). It stimulates the production of neopterin by monocytes and macrophages through guanosine triphosphate (GTP) degradation. Macrophages and monocytes are crucial components of the immune system. Their involvement in neopterin production should also be considered due to their potential role in monitoring and screening some diseases (1, 2).

Neopterin, a marker of the cellular-mediated immune response, is increased in various disorders, including autoimmune diseases (such as lupus erythematosus and rheumatoid arthritis), infections (such as hepatitis, cytomegalovirus, and HIV), cancers (such as hepatocellular carcinoma, gastric cancer, and urinary tract carcinomas), heart diseases (such as congestive heart failure, coronary artery disease, and myocardial ischemia), and transplantation processes (2, 3).

Materials and Methods

We searched related articles in Scopus, Web of Science, PubMed, Google Scholar, and Directory of Open Access Journals (DOAJ) using the following keywords: Neopterin, glomerular filtration rate and chronic kidney disease.

Cellular mechanism of macrophages

Neopterin is produced by monocytes and macrophages in response to the factors that are secreted from activated T-cells, in particular the INFɤ cytokine. Monocytes and macrophages produce neopterin from GTP by GTP-cyclohydrolase (1-4). On the other hand, 5,6,7,8-tetrahydrobiopterin (BH4) is also produced by GTP-cyclohydrolase. BH4 is a cofactor for nitric oxide synthase (NOS) enzymes and is involved in the production of nitric oxide (NO) and superoxide by NOS enzymes. Decreased levels of BH4 cause NOS enzymes to produce more superoxide. Consequently, BH4 may have a role in inflammation and immune responses (1). Therefore, the level of neopterin level may also be an indirect indicator of the amount of oxidative activity mediated by the activated immune system.

Neopterin measurement methods

Neopterin can be measured in two ways

1) The radioimmune assay (RIA) method uses radioactive neopterin and a monoclonal antibody against neopterin.
2) The quantitative measurement compares samples containing specified amounts of neopterin using the high-performance liquid chromatography (HPLC) method.

Although neopterin is a relatively stable substance, errors of quantitative measurement may happen with the light, high temperature, and frequent freezing methods (4). In addition, the best way to quantify neopterin in a urine sample is the first self-spontaneous urine in correlation to the concurrent urine creatinine concentration.

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Implication for health policy/practice/research/ medical education

Neopterin is a substance that is involved in the activation of the immune system. Measuring the level of neopterin is important in the immediate diagnosis and prevention of complications in some conditions such as diabetes, kidney transplantation, and preeclampsia.

Neopterin in chronic kidney disease

According to the new guidelines, chronic kidney disease (CKD) is defined as the presence of a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2 or the presence of kidney damage signs, or both, for at least three months. Many patients with CKD are asymptomatic or have nonspecific symptoms such as lethargy, itching, and anorexia. These patients are usually diagnosed with random screening tests and, eventually, may require dialysis and transplantation (5).

Pentosidine is a marker of advanced glycation end-products (AGEs) and is involved in forming cross-links between proteins. It has been detected in the plasma and tissues of patients with uremia and hemodialysis (HD). The exact origin of pentosidine is still unknown, but it has been reported that it may have a role in the cardiovascular complications of end-stage renal disease (ESRD) (6). On the other hand, immune abnormalities in patients with chronic renal failure and those receiving dialysis influence their mortality. Therefore, an association between a blood marker, which is associated with immune dysfunction, and the plasma level of pentosidine may assist in immediately diagnosing the complications. One study examined non-diabetic patients with mild to advanced renal insufficiency and ESRD patients undergoing HD and peritoneal dialysis. In this study, pentosidine and neopterin were measured with HPLC and RIA, respectively. It was demonstrated that the plasma levels of pentosidine and neopterin increased with the progression and deterioration of renal failure. This association was also observed in patients with ESRD. These results suggest that pentosidine is associated with monocyte activation in patients with renal failure and may increase the morbidity and mortality of these patients through unknown mechanisms (7).

Neopterin in diabetes

Diabetes mellitus is the most prevalent non-communicable disease globally and is the fourth to fifth most common cause of death in developed countries. In addition, it is estimated that by 2025, 300 million individuals will be affected by diabetes globally (8).

Diabetes mellitus causes various complications that mostly affect the eyes, kidneys, nerves, and cardiovascular system due to chronic hyperglycemia. It has also been reported that about 45% of diabetic patients develop diabetic nephropathy which is a progressive condition (9-11). Controlling the blood pressure and glucose of diabetic patients and administration of angiotensin-converting enzyme (ACE) inhibitors may decrease the progression of diabetic nephropathy.

On the other hand, it has been reported that in diabetic patients, the increase in AGEs in the tissues and plasma proteins is associated with diabetic complications. Therefore, pentosidine is one of the first AGEs that may be detected in the tissue and plasma proteins of diabetic patients. Furthermore, the skin level of pentosidine in diabetic patients has been reported to be associated with diabetic complications. In addition, decreased renal function increases the free and protein-bound plasma levels, and both of these parameters can also be detected in the urine (12-17).

Pentosidine and neopterin have been reported to be associated with the activation of macrophages and monocytes in non-diabetic renal failure and diabetic nephropathy. Therefore, they may be indicators of the progression of diabetic nephropathy (7,18,19). Furthermore, neopterin can be used for prompt detection of diabetic peripheral neuropathy which is an important complication in type 1 diabetic pediatric patients (20,21).

Neopterin in kidney transplantation

Kidney transplantation is the treatment of choice for patients with ESRD. One of the major problems in kidney transplantation is the rejection of the transplanted kidney, which affects the survival of the transplant acutely or chronically. With the advent of immunosuppressive medications, fewer cases of transplant rejections are observed. However, these medications have many adverse side effects, and the ability to predict the transplant rejection through a test may help in the dosage adjustment of immunosuppressive drugs (22,23). Although kidney biopsy is appropriate for detecting the rejection of kidney transplantation, it is an invasive procedure; therefore, a non-invasive and replicable laboratory marker that has the ability to predict kidney rejection seems more convenient. An in vitro study reported an association between the neopterin level and prediction of transplant rejection. They showed that neopterin level increases with increased immune response and decreases with safe dosages of suppressors; therefore, neopterin may be an appropriate test marker in these patients (24-28).

Furthermore, neopterin can detect those transplant recipients who are immunologically less responsive to the transplant. This will help these transplant recipients be administered with lower doses of immunosuppressive drugs and prevent drug side effects. Therefore, decreased neopterin levels in transplant recipients may indicate a sufficient response to immunosuppressive medications (29,30).

Neopterin in preeclampsia

Preeclampsia is a type of hypertension that occurs after the twentieth week of pregnancy and is mostly associated

with proteinuria. In the United States, preeclampsia is the main cause of death of pregnant women and fetuses and affects about 8% of pregnant women. CKD is not only considered as a risk factor for preeclampsia but, interestingly, preeclampsia may also reveal the underlying kidney disease. A systematic review study reported an association between the serum neopterin levels in pregnant women and preeclampsia. Serum neopterin levels increase with the progression of pregnancy, and those pregnant patients with preeclampsia have increased serum levels of neopterin compared to pregnant women without preeclampsia. Although studies have shown the ability of neopterin in diagnosing preeclampsia, further investigations are required to determine its appropriate level and time of measurement in pregnancy (31-33).

Neopterin in systemic inflammatory response syndrome

Systemic inflammatory response syndrome (SIRS) develops following conditions such as infections, burns, injuries, and pancreatitis and is considered an inflammatory process. Furthermore, secretion of endotoxins from mononuclear phagocytes, including cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), occur in septic shock which is involved in its pathogenesis. Consequently, multiple organ dysfunction syndromes (MODS), such as kidney failure, may occur, increasing the risk of mortality in patients with delayed or no treatment (34, 35).

In addition, studies have reported that neopterin level increases during or after various situations such as non-emergency surgery, sepsis, and severe injuries (36). Furthermore, neopterin levels have been reported to be higher in patients with septic shock compared to patients with non-infectious-mediated SIRS (35). Consequently, the measurement of neopterin levels may help in the diagnosis and prognosis of septic conditions (37).

Conclusion

Neopterin is a substance that is involved in the activation of the immune system. It has been reported that there is an association between neopterin and renal disorders. In addition, measuring the level of neopterin has a role in the immediate diagnosis and prevention of complications in some conditions such as diabetes, kidney transplantation, preeclampsia, and SIRS.

Authors' contribution

AP and FK wrote the draft. SH conducted the English and scientific edit. All authors read and signed the final draft.

Conflicts of interests

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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