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MALNUTRITION, INFLAMMATION, ATHEROSCLEROSIS IN HEMODIALYSIS PATIENTS

ZESPÓŁ MIA U PACJENTÓW HEMODIALIZOWANYCH

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Zespół MIA obejmuje współwystępowanie niedożywienia, zapalenia i miażdżycy u pacjentów ze schyłkową niewydolnością nerek leczonych powtarzanymi hemodializami. Występowanie zespołu MIA znacznie pogarsza przebieg kliniczny leczenia, zwiększa ilość powikłań oraz umieralność w tej grupie chorych.

Key words: malnutrition, inflammation, chronic renal diseases, nutrition
Słowa kluczowe: niedożywienie, zapalenie, przewlekłe choroby nerek, żywienie

INTRODUCTION

Numerous studies have shown increased comorbidity and mortality in dialysis patients with malnutrition. Most malnourished patients suffer from mixed marasmus - kwashiorkor type of malnutrition with both somatic and visceral protein mass loss. Up to 50% of patients on dialysis have protein energy malnutrition.

There is evidence that a chronic inflammation with activation of C-reactive protein, interleukin-6, interleukin-1, tumor necrosis factor alpha and other cytokines is associated with increased oxidative stress and endothelial dysfunction [2, 12]. Relations between malnutrition, inflammation and atherosclerosis in dialysis patients suggest the presence of a MIA (malnutrition, inflammation and atherosclerosis) syndrome. The MIA syndrome is associated with high mortality rate. It could be speculated that suppression of the vicious cycle of malnutrition, inflammation and atherosclerosis would improve survival in dialysis patients.

Malnutrition is common in dialysis patients and closely related to morbidity and mortality. Therefore, assessment of nutritional status and nutritional management of dialysis patients play a central role in everyday nephrological practice.

MALNUTRITION

Depending on the parameter measured, the prevalence of malnutrition in the chronic dialysis population ranges from 10 to 54% [1, 2 4]. There are two different mechanisms of malnutrition. The first type is associated with a low protein and energy intake due to uremic toxicity, to physical changes and to psychosocial and psycho economic factors. The second type of malnutrition is associated with increased protein catabolism from inflammatory/infections origin. Obviously, these two types of malnutrition are often combined in the clinical setting [10].

MARKERS OF MALNUTRITION AND INFLAMMATION

In patients undergoing hemodialysis chronic inflammation and malnutrition are crucial factors for disturbed immune competence. Inflammatory indices have been emphasized in hemodialysis patients, but their relationship to nutritional status is still debated. In hemodialysis patients C-reactive protein (CRP) is moderately elevated (in 40% of patients) and was positively associated with SGA (subjective global assessment of nutritional status) and negatively with plasma proteins [1, 5]. CRP is a highly sensitive but unspecific marker of inflammation. High CRP levels are an independent risk factor for hypoalbuminemia and a better predictor of mortality [2, 6]. CRP in infected hemodialysis patients was positively correlated to triceps skinfold and negatively to lean body mass and comorbidities directly followed the extracellular fluid pattern. CRP seems to be a reflection of the level of IL-6, a cytokine released by monocytes whose effects include degradation of muscle protein, induction of the synthesis of acute-phase reactants and a role in the regulation of immune response [2, 6, 7, 11]. Serum Il-1, Il-6 and TNFα levels are increased in patients already before the start of dialysis, suggesting that renal failure per se is a contributing factor [10]. Present evidence suggests that cytokines, as intercellular mediators, play a key role in the nutrition-infection complex. Protein-calorie malnutrition, deficiency of fatty acids, vitamins, trace elements, impair cytokine production. By the other hand, infections increase pro-inflammatory cytokine production interfering with nutritional status by impairing metabolic activity and by inducing diminished appetite (anorexia) [5]. Protein malnutrition alters T cell immune responses and decreases resistance to infection. In peripheral blood leukocytes basal TGF-β mRNA expression is about 2-fold decreased in end-stage renal failure patients, while expression of TNF-α becomes 2-fold increased, further doubling during hemodialysis. Survival analysis indicated that increased TNF mRNA levels and TNF/TGF mRNA ratios predict mortality. Although serum granulocyte colony stimulating factor (G-CSF) level is not affected by chronic renal failure long-term haemodialysis may induce an increase of G-CSF. In the case of macrophage colony stimulating factor (M-CSF), however, impaired renal metabolism and/or excretion may increase the serum concentration, but it is not modulated by haemodialysis [13, 14].

Patients in end-stage renal disease undergoing dialysis have a high incidence of bacterial and viral infections [2, 9]. PHA and CD3-driven T cell proliferation were significantly decreased in ESRD patients. $CD3^+$, $CD19^+$ B cells, and percentage of $CD4^+$ T cells were significantly reduced [8]. Percent memory T cells ($CD45RO^+$), cells undergoing apoptosis ($CD95^+$/Annexin V+), sTNFRI and IL-10 were significantly increased strongly suggest that in ESRD patients Th1 T cells are selectively susceptible to undergo apoptosis [8].

There is evidence that a chronic inflammation with activation of C-reactive protein, interleukin-6, interleukin-1, tumor necrosis factor alpha and other cytokines is associated with increased oxidative stress and endothelial dysfunction [1, 2, 6]. There is an observation that serum albumin is a negative acute phase protein, which can be used as a actually marker of inflammation [1, 2]. Strong relations between malnutrition, inflammation and atherosclerosis in dialysis patients suggest the presence of a MIA (malnutrition, inflammation and atherosclerosis) syndrome, which is associated with high mortality rate. Thus, it could be speculated that suppression of the vicious cycle of malnutrition, inflammation and atherosclerosis would improve survival in dialysis patients.

Several reports have suggested that inflammation, alone or in combination with low protein intake, plays a significant role in etiology of malnutrition in uremic patients [6, 10]. Proinflammatory cytokines may represent the link between these two entities since these interleukins may promote loss of appetite, muscle protein breakdown and reduce hepatic synthesis of albumin, prealbumin and transferrin [11].

The diagnosis of malnutrition focused mainly on serum albumin reduction must be also based on the other parameters (clinical history of body mass wasting, dietary and anthropometric assessment, subjective global assessment, bioimpedance analysis etc) and pro-inflammatory cytokine.

There is increased clinical evidence for profound defects in the specific immune defense in uremia, such as the high susceptibility to viral and bacterial infection in uremic patients, the deficient responses of their T lymphocytes, and the significantly depressed specific antibody responses. The hemodialysis population is at increased risk of infection as a consequence of impaired humoral and cellular immunity. Malnutrition is one of the reasons of immune suppressed.

NUTRITION

It is now recognized that oxidative stress and inflammatory cytokine aggravates the nutritional status of these patients. However, dietary behavior itself may also independently affect inflammation. The treatments should aim at improving nutritional intake by increasing dialysis doses, dietary counseling and protein/calories supplementation. Enteral and intradialytic parenteral nutrition (IDPN) seems promising to improve nutritional status and reduce inflammatory cytokines, however it still needs further exploration [3, 4]. Enteral and intradialytic parenteral nutrition has been shown to be a safe and convenient approach. Most of the information on the nutritional effects of such treatment is based on estimates of the biochemical markers of malnutrition. Further studies are required to confirm beneficial effects of intradialytic parenteral nutrition on pro/anty-inflammatory cytokines.

The available studies suggest that the benefits of nutritional supplementation are most significant in patients with the highest degree of malnutrition [3, 4]. There were significant improvements in serum albumin, prealbumin concentration and also increase in body weight, fat mass and triceps skin fold. It is still unclear how we can modulate the inflammatory response in hemodialysis patients. Nutrients have a profound effect upon the production and actions of cytokines. Protein energy malnutrition, dietary n-3 polyunsaturated fatty acids and vitamin E suppress cytokine production and actions [1]. Future clinical trials are needed to define the diet composition that will have an anti-inflammatory effect maintaining a normal immune response. More particular attention should be devoted to the deregulation of the anti/pro-inflammatory balance in hemodialysis patients.

CONCLUSIONS

Depending on the parameter measured, the prevalence of malnutrition in the chronic dialysis population is up to 54%. Most of malnourished patients suffer from mixed marasmus-kwashiorkor type of malnutrition with both somatic and visceral protein mass loss. In patients undergoing hemodialysis chronic inflammation and malnutrition are crucial factors for disturbed immune competence.

Strong relations between malnutrition, inflammation and atherosclerosis in dialysis patients suggest the presence of a MIA (malnutrition, inflammation and atherosclerosis) syndrome, which is associated with high mortality rate.

Hypoalbuminemia is still the best clinical marker of malnutrition but the presence of inflammation may be a more powerful predictor.

The study to analyze the nutritional status and immune dysfunction in malnourished patients with end-stage renal failure should particularly focus on balance between pro-inflammatory and anti-inflammatory cytokines and on its change as a result of nutrition (enteral and intradialytic parenteral nutrition). It should be expected that evaluation of nutritional treatment based on cytokine measurement will improve diagnosis of immunity disorders and outcome in patients with end-stage renal failure.

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Summary

Protein-energy malnutrition with muscle wasting occurs in a large proportion of patients with chronic renal failure and is, in addition to atherosclerosis, a strong risk factor for cardiovascular mortality in dialysis patients. There is evidence that a chronic inflammation with activation of C-reactive protein and proinfalammatory cytokines is associated with increased oxidative stress and endothelial dysfunction. Strong relations between malnutrition, inflammation and atherosclerosis in dialysis patients suggest the presence of a MIA (malnutrition, inflammation and atherosclerosis) syndrome, which is associated with high mortality rate. Thus, it could be speculated that suppression of the vicious cycle of malnutrition, inflammation and atherosclerosis would improve survival in dialysis patients.

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Streszczenie

Zaburzenia odżywiania w chorobach nerek znacznie pogarszają rokowanie pacjentów. Wraz z rozwojem medycyny, a w tym nefrologii stale zwiększają się możliwości leczenia nerkozastępczego powodując z jednej strony wzrost liczby pacjentów a jednocześnie pojawianie się nowych problemów klinicznych takich jak np. zespół MIA (niedożywienie, zapalenia, miażdżyca). Od dłuższego czasu podkreślana jest rola czynników zapalnych w rozwoju miażdżycy. Istniejąca zależność pomiędzy podwyższonymi stężeniami białka C reaktywnego (CRP), pozapalnych cytokin, niedożywieniem a zwiększoną umieralnością wśród chorych z zaburzeniami funkcji nerek, wskazuje na niedożywienie nie tylko jako na objaw, ale także jako na element patofizjologicznych powikłań u pacjentów z niewydolnością nerek.

REFERENCES

1. *Don B., Kaysen G.*: Assessment of inflammation and nutrition in patients with end-stage renal disease, J. of Nephrology, 2000, 13, 249-259.
2. *Fernandez-Reyes M., Alvarez-Ude F., Sanchez R., Mon C., Iglesias P., Diez J., Vazquez A.*: Inflammation and malnutrition ass predictors of mortality in patients on hemodialysis, J. of Nephrology, 2002, 15, 136-143.
3. *How P., Lau A.*: Malnutrition in patients undergoing hemodialysis : is intradialytic parenteral nutrition the answer?, Pharmacotherapy, 2004, 24 (12), 1748-58.
4. *Ikizler T.*: Poor nutritional status and inflammation, Protein and energy: recommended intake and nutrient supplementation in chronic dialysis patients, Seminars in Dialysis, 2004, 17(6), 471.
5. *Kalantar – Zadeh K., Block G., McAllister C., Humphreys M., Kopple J.*: Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients, Am. J. Clinical Nutrition, 2004, 80(2), 299-307.
6. *Kaysen G.*: The microinflammatory state in uremia: causes and potential consequences, J. Am. Soc. Nephrol,, 2001, 12, 1549-1557.
7. *King A., Kehayias J., Roubenoff R., Schmid C., Pereira B.*: Cytokine production and nutritional status in hemodialysis patients, Int. J. Artif. Organs, 1998, 21(1), 4-11.
8. *Knerr K., Futh R., Hemsen P., Mohne W., Heinig A., Kleophas W., Scherbaum W., Martin S.*: Chronic inflammation and hemodialysis reduce immune competence of peripheral blood leukocytes in end-stage renal failure patients, Cytokine, 2005, 30, 132-138.
9. *Kuhlmann M., Levin N.*: Interaction between nutrition and inflammation in hemodialysis patients, Contrib. Nephrol., 2005, 149, 200-207.
10. *Locatelli F., Fouque D., Heimburger O., Drueke T., Cannata – Andia J., Horl W., Ritz E.*: Nutritional status in dialysis patients: a European consensus, Nephrology, Dialysis Transplantation, 2002, 17, 563-572.
11. *Memoli B., Guida B., Saravo M., Nastasi A., Trio R., Liberti R., D'Arcangelo R., Romano G., Esposito A., Cianciaruso B.*: Predictive and diagnostic factors of malnutrition in hemodialysis patients, G. Ital. Nefrol., 2002, 19(4), 456-66 (Abstract).
12. *Pawlaczyk K, Oko A., Lindholm B., Czekalski S.*: Malnutrion – inflammation – atherosclerosis in patients with renal failure, Pol. Merkuriusz Lekarski, 2003, 15(88), 334-41, in Polish.
13. *Pawlak K., Pawlak D., Myśliwiec M.*: Oxidative stress influences CC-chemokine levels in hemodialyzed patients, Nephron. Physiol., 2004, 96(4), 105-112.

14. *Yoshizumi M., Pereeila M.A., Burnett J.C., Lee M.E.:* Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-live, Circ.Res., 1993, 73, 205.