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VAP-1 and renalase in solid organ transplant recipients

VAP-1 i renalaza u pacjentów po transplantacji narządów unaczynionych

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Słowa kluczowe
VAP-1, renalaza, transplantacja nerki, transplantacja serca, śródbłonek

Summary

Transplantation of an organ harvested from another person is one of the methods of treatment of end-stage organ failure. Endothelial dysfunction is a frequent finding in transplant recipients. It is also very common in cardiovascular disorders and chronic kidney disease. Vascular adhesion protein-1 (VAP-1) is a dual-function glycoprotein. As an adhesion molecule, it is involved in rolling, adhesion and migration of leukocytes to the inflammatory site, and is a semicarbazide-sensitive amine oxidase. VAP-1 is secreted by a number of cells, including endothelial cells, vascular smooth muscle cells or adipocytes. Increased VAP-1 levels were shown in cardiac and renal transplant recipients. In cardiac transplant recipients its levels are mainly determined by left ventricular geometry. In both recipient groups VAP-1 was higher in patients with diabetes in comparison with their non-diabetic counterparts. Renalase belongs to a class of amine oxidases – secreted, for example, by the kidneys, adipocytes and endothelium. It causes degradation of bloodstream catecholamines, through which it may be involved in blood pressure regulation. Renalase concentration, markedly increased in renal and cardiac transplant recipients, was predicted by renal function which deteriorates with age and time from transplantation.

Further studies are necessary on the potential role of VAP-1 and renalase in the pathogenesis of cardiovascular disorders, including arterial hypertension, also in the population of organ transplant recipients.

Streszczenie

Jedną z metod leczenia schyłkowej niewydolności narządów jest przeszczep narządu pobranego od innej osoby. Wśród pacjentów po przeszczepieniu często obserwuje się dysfunkcję śródbłonka. Jest ona także bardzo powszechna w chorobach układu krążenia i przewlekłej chorobie nerek. VAP-1 (ang. *vascular adhesion protein-1* – naczyniowa cząsteczka adhezyjna-1) to glikoproteina o podwójnej roli. Jako cząsteczka adhezyjna bierze udział w rolowaniu, adhezji i migracji leukocytów do miejsca występowania procesu zapalnego oraz pełni funkcję aminooksydazy wrażliwej na semikarbazyd. Jest wydzielany przez szereg komórek: np. śródbłonka, mięśniówki gładkiej naczyń krwionośnych czy adipocytów. Wykazano, podwyższony poziom VAP-1 u pacjentów po przeszczepieniu serca (OHT) i nerek (Ktx). U pacjentów z OHT zależy przede wszystkim od geometrii lewej komory. W obu grupach przeszczepionych VAP-1 był wyższy u chorych na cukrzycę w porównaniu do osób bez cukrzycy. Renalaza należy do klasy oksydaz aminowych. Jest enzymem wydzielanym m.in. przez nerki, adipocyty, śródbłonek. Powoduje degradację krążących we krwi katecholamin, przez co może mieć wpływ na regulację ciśnienia tętniczego. Stężenie renalazy, znacznie zwiększone u chorych po przeszczepieniu nerki i przeszczepieniu serca, w głównym stopniu zależy od funkcji nerek, która pogarsza się z wiekiem i w miarę upływu czasu od przeszczepienia.

Konieczne są więc dalsze badania nad potencjalną rolą VAP-1 i renalazy w patogenezie chorób sercowo-naczyniowych, a także w populacji biorców przeszczepów narządów unaczynionych.

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INTRODUCTION

Transplantation of an organ harvested from another person is one of the methods of treatment of end-stage failure of vascularised organs (kidneys, heart, liver). Good results obtained with this method derive from advances in the graft rejection prevention treatment. The use of immunosuppressants is associated with numerous complications, such as increased frequency of infections, increased incidence of cancer, bone marrow damage or cardiovascular complications. Normal haemostasis is a result of equilibrium between coagulation factors and their inhibitors. Imbalance in this equilibrium leads to life-threatening bleeding or thrombosis, which is why its maintenance is very important. Studies suggest the presence of hypercoagulability in renal transplant recipients (1, 2). Haemostasis disturbances are inherently correlated with endothelial dysfunction. Early descriptions of endothelial dysfunction focused on structural changes or on the loss of anatomical integrity of this organ. It is currently known that endothelial cells are characterised by highly variable biological activity performing an extremely important role in functioning of the whole body. Małyszko et al. demonstrated impaired haemostasis and endothelial function in dialysed patients and in patients with chronic kidney disease (3, 4). Epithelial damage may contribute to accelerated atherosclerosis development in the group of transplant recipients.

VAP-1

Vascular Adhesion Protein-1 (VAP-1) is a multifunction protein, which mediates lymphocyte adhesion to the vascular endothelium (5-9). Biochemically, VAP-1 is a homodimeric transmembrane glycoprotein with a molecular mass of 170-180 kDa, made of 764 amino acids, with a short N-terminal cytoplasmic part, a single transmembrane domain and a large extracellular C-terminal domain (5-9). Each subunit has six N-glycosylation sites (10). N-glycoside chains of VAP-1, ended with sialic acid, differ depending on the tissue in which they occur. This differentiation suggests their functional differences (11). The structure of DNA coding the VAP-1 molecule displays high homology with enzymes of the semicarbazide-sensitive amine oxidase (SSAO) class (12). VAP-1 also displays enzymatic activity of a semicarbazide-sensitive amine oxidase. Its active centre contains a copper atom (9, 13). SSAO/VAP-1 catalyses a reaction of two-stage deamination of primary amine groups (methylamine, aminoacetone, benzylamine) leading to the formation of aldehydes and additionally hydrogen peroxide and ammonia (14). On one hand, the activity of VAP-1 provides protection from amines of endo- and exogenous origins, and on the other hand, high concentration of the products formed increases the quantity of other adhesion molecules, leading to escalation of the inflammatory process. Increased concentration of toxic aldehydes and oxygen radicals, which are the source of oxidative stress, in the endothelial environment may result in endothelial damage and may contribute to the development of atherosclerosis and vascular damage in diabetic patients (15-17). Elevated activity of SSAO is observed in atherosclerosis, diabetes and obesity (18-20). VAP-1 concentration, SSAO activity and SSAO activity products are elevated in congestive heart failure and hepatitis (21). Elevated VAP-1 levels were found in persons with chronic kidney disease, which suggests that it may be excreted via the kidneys (22). Moreover, recently Li et al. have demonstrated that VAP-1 may be a good predictor of cardiovascular death in persons with type 2 diabetes (21). Constant expression of VAP-1 is observed in high endothelial venules (HEV), which physiologically are present in lymphoid organs, in the liver and in dendritic cells of lymph node proliferation centres (6). VAP-1 is also present in vascular smooth muscle cells and in adipocytes. Physiologically, soluble VAP-1 (sVAP-1) is present in the serum of healthy persons. It is probably released as a result of enzymatic proteolysis or is formed directly on messenger RNA devoid of the membrane region-coding fragment (12). Metalloproteinases may release VAP-1 from adipocytes and this process is intensified in hyperglycaemia (23). sVAP possesses immunomodulatory function causing much stronger binding of T-cells to endothelial cells, which may play an important role in the graft rejection process (24). In the case of kidney transplant, in which rejection signs were found, high expression of VAP-1 was detected in the endothelium of peritubular vessels that became morphologically similar to HEV (25). SSAO oxidates dopamine and, to a lower extent, norepinephrine, and does not oxidate epinephrine. SSAO/VAP-1 is insensitive to MAO inhibitors (26). In view of its monoamine oxidase activity, like renalase, VAP-1 may be a factor regulating blood pressure.

RENALASE

Renalase belongs to a class of amine oxidases containing flavin adenine dinucleotide (FAD). It is coded by a gene of approximately 311 kb, comprising 10 exons located on chromosome X (27). It consists of 342 amino acids forming a peptide containing the FAD domain (amino acids 4-35) and an amine oxidase domain (amino acids 75-339). Renalase is synthesised in the kidneys, secreted to the bloodstream, and subsequently excreted in the urine where it exerts ca. 100 times its activity in the blood in standard conditions (28). It is secreted into the bloodstream in the form of biologically inactive prorenalase. Renalase undergoes preferential expression in proximal tubules but is also observed in distal glomeruli and tubules and in cardiomyocytes, hepatocytes, skeletal muscle cells and the epithelium, and also in adrenals, peripheral nerves, the central nervous system and human adipose tissue (29). In 2005, Xu et al. described the probable role of renalase in hypertension. They evidenced significant decrease in plasma renalase activity in patients with chronic kidney disease (which may contribute to the development of arterial hypertension) (30). By metabolising

catecholamines (dopamine, norepinephrine, epinephrine), renalase probably participates in blood pressure regulation. It is insensitive to MAO inhibitors (30). Renalase deficiency in patients with chronic kidney disease causes an increase in blood pressure at least in patients with GG (rs 2576 178) and CC (rs 229 8545) polymorphisms. Recombinant renalase is hypotensive and cardioprotective in patients with coronary insufficiency (28). Blockade of this enzyme with the use of antisense RNA causes blood pressure elevation in animals (31). Chinese studies demonstrated a correlation between rs 2576178 GG and rs 2296545 CC mutations of the renalase gene and the occurrence of arterial hypertension (32). Similarly, Stec et al. found a relationship between renalase gene polymorphism and the presence of arterial hypertension in dialysed patients (33).

VAP-1 AND RENALASE IN RENAL OR CARDIAC TRANSPLANT RECIPIENTS

Epithelial dysfunction is very common both in cardiovascular disorders and chronic kidney disease. It is also a common finding in transplant recipients. Because VAP-1 and renalase are expressed in vascular endothelium and in adipocytes, the results of studies in renal or cardiac transplant recipients have been discussed. In renal or cardiac transplant recipients, the mean VAP-1 level was significantly higher in comparison with the control group of healthy volunteers. In these patients, higher values were also obtained for creatinine, NT-proBNP and hsCRP. In cardiac transplant recipients, VAP-1 was demonstrated to correlate with age, presence of diabetes, insulin therapy, ejection fraction, renal function, tacrolimus use, end-diastolic left ventricular diameter, heart failure NYHA (New York Heart Association) class or the NTproBNP level. In renal transplant recipients, correlations were observed between VAP-1 and time from transplantation as well as glucose blood levels. Furthermore, in both study groups VAP-1 was higher in patients with eGFR below 60 ml/min in comparison with those with eGFR $\geq$ 60 ml/min.

Even successful renal transplantation does not restore the normal function of the kidney. A vast majority of renal transplant recipients have chronic kidney disease (CKD) stage 2 or 3 according to KDIGO (Kidney Diseases Improving Global Outcomes). The studies of Przybyłowski et al. confirm increased CKD prevalence also in cardiac transplant recipients (34), ranging from one-third to two-thirds of this population (35). As demonstrated by studies, the development of chronic kidney disease (eGFR below 60 ml/min) is a predictor of early cardiovascular complications and deaths (36). Although clinical trials did not demonstrate a negative correlation between the ciclosporin level and renal function in non-renal transplant recipients, it is generally agreed that careful use of immunosuppression may reduce the risk of chronic renal failure (37, 38). On the basis of both retrospective and prospective single- and multicentre studies, and on the basis of register analyses, the use of tacrolimus is considered to be associated with lower nephrotoxicity in cardiac, pulmonary and hepatic transplant recipients (39, 40). Przybyłowski et al. evidenced better renal function in cardiac transplant recipients treated with tacrolimus (41). Their studies also demonstrated that tacrolimus-treated patients had higher eGFR (MDRD) in comparison with patients treated with ciclosporin. Therefore, the difference in VAP-1 between these groups could be attributed to renal function differences.

As evidenced in our preliminary studies in 50 renal transplant recipients, increased VAP-1 levels in those patients correlated with renalase levels, and predictors of this increase were impaired renal function and epithelial damage (42). In a much larger population of renal transplant recipients, we did not find any relationship between renal function and VAP-1, despite much higher levels of VAP-1 in patients with eGFR below 60 ml/min in comparison with patients with eGFR above 60 ml/min. As previously suggested by Lin et al., VAP-1 may be excreted by the kidneys (22).

As observed by Kurkijarvi et al., patients with end-stage renal disease had higher sVAP levels than patients in the control group. These levels significantly decreased on average 3 weeks after transplantation. In patients with a history of a rejection episode, sVAP-1 levels increased once again but did not attain the pre-transplantation values (25), which would suggest a correlation with the graft function. In both study groups (of cardiac and renal transplant recipients), VAP-1 was higher in patients with diabetes in comparison with their non-diabetic counterparts. Similar results were obtained in our own studies in haemodialysed patients and renal transplant recipients (43). As observed by Li et al. in their studies, VAP-1 was higher in persons with acute and chronic hyperglycaemia and with diabetes. Moreover, VAP-1 was evidenced by them to be a predictor of cardiovascular death in patients with type 2 diabetes in 10-year follow-up (23, 44).

RENALASE

The mean level of renalase in renal transplant recipients was much higher in comparison with the control group and correlated with age, time from transplantation, sCD44, VCAM, creatinine level, estimated glomerular filtration, levels of phosphate, urea, sCD146, vWF and trombomodulin and showed a trend towards correlation with tPA. In patients with eGFR > 60 ml/min, renalase levels were lower than in patients with a lower eGFR. In transplant recipients with arterial hypertension, renalase levels were higher than in patients without arterial hypertension. As demonstrated by multivariate regression analysis, a predictive factor of the renalase level was creatinine concentration in 58% of the cases (45). The mean level of renalase in cardiac transplant recipients

was also significantly higher in comparison with the control group. Renalase in cardiac transplant recipients was predominantly dependent on renal function which deteriorated with time from transplantation and with increasing age of the recipient. Renalase poorly correlated with time from transplantation and TRAIL, moderately correlated with age and ejection fraction, strongly correlated with red blood count, haemoglobin, serum creatinine, 24-hour creatinine clearance, eGFR, NT-proBNP, vWF, midkine and IL-6. As demonstrated by multivariate regression analysis, a predictive factor of the renalase level was creatinine concentration in 70% of the cases (45). In cardiac transplant recipients with eGFR above 60 ml/min, renalase levels were significantly lower than in patients with eGFR below 60 ml/min. Similar results were obtained in renal transplant recipients.

As demonstrated by the studies of Przybyłowski and by our own studies (46), in univariate analysis renalase is correlated with epithelial damage markers and with inflammation. In multivariate analysis, serum creatinine was a predictor of renalase levels. Epithelial cell damage is inherently associated with renal function impairment. This explains the monofactorial correlation between vWF, IL-6, and renalase in cardiac transplant recipients. As demonstrated by univariate analysis, in renal transplant recipients renalase was correlated with epithelial damage markers such as vWF, thrombomodulin and VAP-1 but not IL-6. However, multivariate analysis demonstrated that the only predictor of renalase levels was renal function (47).

Renalase levels were significantly higher in the group of renal transplant recipients with hypertension than in the group of their normotensive counterparts, while in cardiac transplant recipients, renalase levels did not differ significantly between normotensive and hypertensive patients (45). Therefore, after cardiac transplantation, where cardiomyocytes originate from the donor, renal renalase may not be sufficient for obtaining a difference between normotensive and hypertensive patients. Furthermore, in cardiac transplant recipients, arterial hypertension is less common and better controlled, with a lower systolic value in comparison with renal transplant recipients (48).

CONCLUSIONS

In summary, renal function impairment is significantly correlated with epithelial damage and inflammation, and thus may have an impact on both renalase and VAP-1 levels. Furthermore, elevated levels of renalase and VAP-1 in the population of cardiac or renal transplant recipients may be a consequence of renal function impairment common in this patient group. In view of extensive tissue distribution of renalase and VAP-1, their functions may be organ-specific, and thus their synthesis and secretion may be associated not only with renal function. Further studies are necessary on the potential role of VAP-1 and renalase in the pathogenesis of cardiovascular disorders, including arterial hypertension, also in the population of organ transplant recipients, especially in the aspect of potential therapeutic options.

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