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DIABETES MELITUS – FAKTORI KOJI DOPRINOSE NASTANKU, DIJAGNOZI I TERAPIJI BOLESTI

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DIABETES MELLITUS - FACTORS THAT CONTRIBUTE TO THE OCCURRENCE, DIAGNOSIS AND MANAGEMENT OF DISEASE

Diabetes melitus – faktori koji doprinose nastanku, dijagnozi i terapiji bolesti

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Key words: diabetes mellitus, vitamin D, insulin antibodies, insulin receptor antibodies, cardio-ankle vascular index

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Introduction

Type 2 diabetes is one of the most common endocrine disorders. Across the planet 415 million people have diabetes (1 in 11 adults), estimates are that by 2040 year it will be sick 642 million people, every 6 seconds one person dies from the consequences of diabetes (5 million lethal outcome). The International Federation of Diabetes (IDF) indicated the factors that play a role in development of disease including genetics, lifestyle, environment and diet. The underlying mechanism in the development of type 2 diabetes is insulin resistance and insulin secretion reduced as a result of exhaustion of the beta-cells. Diabetes mellitus represents a state of chronic hyperglycemia, characterized by disturbed metabolism of carbohydrates, proteins and fats. Occurs due to absolute or relative insulin deficiency, insulin resistance, increased glucose production, and excessive action of the hormones with the opposite effect of insulin. What are the additional contributing factors affecting the occurrence and treatment of this disease, science has so far not clearly defined. What is the basis of the generation of diabetes is not well understood. Therefore, any contribution that leads in this direction is valuable.

The role of insulin antibodies, antibodies to receptors for insulin and vitamin D in the development of diabetes mellitus

Insulin antibodies and insulin receptor antibodies in the onset of diabetes mellitus

In 1950, first described the association between insulin resistance (IR) and insulin antibodies (IA). The presence of IA are then attributed to the use of non-human insulin. Hypoglycemia simultaneously with the existence of a high titre of insulin antibodies, in patients with diabetes, describe as autoimmune insulin syndrome or Harate disease\(^1\). The presence of postprandial hyperglycemia and hypoglycemia fasting, are two of the same process in this disease and are due to binding of insulin antibodies. This insulin antibodies have a low binding affinity for insulin and never lead to IR.
Recent findings suggest that there is a need for monitoring the presence of IA in patients with insulin resistance (IR). Anti-insulin receptor antibodies (AIRA-s) are determined by method of radioreceptor essay. These antibodies are IgG and IgM. IgG antibodies were more frequent in patients with autoimmune diseases such as acanthosis nigricans. The antibodies of the IgM class are present in type 2 diabetes. 

AIRA are shown in circulation in patients with diabetes. All previous studies indicate that there is no link between insulin and receptor antibodies in type 1 diabetes. However, among patients with type 1 diabetes receiving insulin, there is a correlation between the dose of insulin and the levels of insulin receptor antibodies, but not with anti-insulin antibodies. In any case, AIRAs are proven in patients with diabetes but their role in the further development of diabetes is not fully understood.

In a study of 80 patients with type 1 and type 2 diabetes, along with a study of 20 patients with mixed autoimmune diseases and 20 healthy patients, AIRA are demonstrated in 13 of 33 patients with type 1 diabetes and in 6 of 47 with type 2 diabetes. The antibodies were mainly IgM groups. In both groups of diabetes, there is a good correlation between the % of binding to insulin receptors and % of antibody class IgM (p <0.001), but not with class IgG (p> 0.1). There is a correlation between the % inhibition of insulin binding to its receptor, and daily insulin doses (p <0.001). Based on the above it can be concluded that, there is the present of insulin receptor antibodies in patients with type 1 and type 2 diabetes.

The role of vitamin D in the development of diabetes

According to many authors, vitamin D plays an important role in controlling blood glucose levels, but also in alleviating chronic diabetic complications. The rationale for this is grounded on the following facts: the presence of the vitamin D receptor (VDR) in pancreatic beta-cells, vitamin D activating 1 alpha-hydroxylase present in that cells, the presence of the VDR gene for insulin, which results in the increased synthesis of insulin under the effect of vitamin D. Furthermore, VDRs are present in skeletal muscle cells, fact that 1,25 (OH) 2D is rounding gene transcription for the insulin receptor, which stimulates
this expression, and suppresses the renin gene, thus reducing hyperglycemia-induced increase in the level of renin and blocks renin-angiotensin activity.

Beneficial effects of vitamin D, when it comes to diabetes may be due to its anti-inflammatory effects, and the effect on the metabolism of calcium and phosphate, and gene regulation of the insulin receptor. Vitamin D increases the amount of calcium in cells, leading to increased glucose transport in muscle. Vitamin D also regulates the nuclear PPAR (peroxisome proliferative activated receptor), which plays an important role in insulin sensitivity. Vitamin D deficiency is associated with the increase in inflammation. Vitamin D decreases the expression of proinflammatory cytokines involved in the development of insulin resistance, such as IL-1, IL-6, TNF-alpha. By such effect on this cytokine, vitamin D exerts antiapoptotic effect upon the pancreatic beta cells, the preservation of the insulin secretion from the same and increases insulin sensitivity.

In comparison to healthy population, in type 2 diabetes are present substantially lower concentrations of circulating 25(OH)D$^4$. Common risk factors for type 2 diabetes and hypovitaminosis D as obesity, age, association with black race and reduced physical activity. The probable mechanism by which vitamin D participates in the glucose homeostasis is the effect on the beta cell dysfunction and insulin resistance, in cases of vitamin D deficiency. Negative correlation between blood glucose and insulin levels to the level of 25(OH)D and the positive correlations 25(OH)D levels with insulin sensitivity was tested in several animal and human studies. In some of these studies it was observed that vitamin D supplementation may improve insulin secretion and reduce insulin resistance in type 2 diabetes. Possible role of vitamin D in type 2 diabetes and influence on HbA1C values is registered also. It should be noted that there are studies that not proven above report. It seems that there is still no general consensus on this issue.

Vitamin D deficiency has a role in type 1 and type 2 diabetes. The evidence indicates that treatment of vitamin D reduces insulin resistance and improves glucose tolerance. Vitamin D deficiency leads to reduced insulin secretion, and showed that vitamin D supplementation restores insulin secretion in animals. It is found indirect effect on insulin secretion through the calcium effect. In fact, vitamin D contributes to the normalization of extracellular calcium, ensuring the normal flow of calcium through the cell membrane, so that hypovitaminosis D may be harmful effects on calcium insulin secretion. Other potential mechanisms include stimulation of insulin receptor expression, improving insulin
response to glucose transport and a decrease in systemic inflammation by direct effects on cytokine\textsuperscript{5,6}.

In a prospective study Jannersjo P et al.\textsuperscript{7} investigated the relationship of serum 25(OH)D and PTH with all-cause mortality in patients with type 2 diabetes and found that in men with type 2 diabetes vitamin D levels inversely correlated with all-cause mortality independently of years, PTH, HbA1c, waist circumference, 24h-monitoring of blood pressure and serum apoB. In women with type 2 diabetes, serum PTH is directly proportional with all causes of death. In this study it was not proven that substitution of vitamin D reduces the risk of mortality, but in spite of this, it was suggested that the serum level of 25(OH)D in men and PTH in women, suffering from type 2 diabetes, can be used as surrogate markers for prognostic information related for mortality. This is an independent risk factor in terms of blood pressure, carotid intima-medial complex (as measured in the carotid artery) and flow rate (measured in the carotid arteries and femoral). De Boer\textsuperscript{8} in his study with hemodialysis patients showed that vitamin D treatment improves insulin secretion and sensitivity.

There are studies which have the opposite results in comparison to above conclusion. Thus in Sheth et al.\textsuperscript{9} study, 912 patients (429 patients of group type 2 diabetes and non-diabetic control group 483) from the West Indies were studied biochemical parameters (fasting glucose, postprandial glucose, HbA1c, basal insulinenia, insulin resistance in the form HOMA-IR) and compared to the level of 25(OH)D. It was concluded that, although there is a high prevalence of vitamin D deficiency in both groups, the effect of vitamin D on these parameters can not be confirmed. The explanation for this is the increased skin pigmentation of the population in India, but also reduced exposure to sunlight because of how they dress and the way of life\textsuperscript{9}. It takes twice as long exposure to the sun for the people of India in relation to the white race, for the same effect on the synthesis of vitamin D.

Vitamin D, according to some studies, has a role in alleviating chronic diabetic complications. Data on the effect of vitamin D deficiency in the control of diabetes and the occurrence of complications have been modest. Ahmedieh et al.\textsuperscript{10} in their study examined the relationship between levels of 25(OH)D and microvascular complications in patients with type 2 diabetes. The conclusion was, that the low serum levels of 25(OH)D is independent predictor of HbA1c, diabetic neuropathy, and retinopathy. The same study was
aimed Zoppini\textsuperscript{11}, where found the inverse relationship between the levels of 25(OH)D and the prevalence of microvascular complications in patients with type 2 diabetes. Does supplementation of vitamin D in these patients may have a benefit on the risk for microvascular complications remains to be explored. In another study, it was concluded that vitamin D deficiency is more common in diabetic patients with nephropathy, which is not verified for retinopathy and neuropathy. Also, it was found that the level of vitamin D is lower in patients with severe microvascular complications, and it was concluded that vitamin D deficiency is associated with the microvascular complications in patients with type 2 diabetes.

Diabetic nephropathy (DN) decreases progressively vitamin D body level: due to loss of vitamin D-binding protein in proteinuria, compromised the synthesis of vitamin D in the skin and due to lower activation of vitamin D in the damaged kidney. It was noted that the lack of vitamin D is higher in diabetic chronic renal failure than in nondiabetic patient. There are indications that the VDRs are modulator of glomerular damage. Calcitriol, endogenous VDR activator reduces glomerulosclerosis index. In clinical terms, patients with chronic renal failure (CRF) treated with paricalcitol (selective VDR activator), exhibited significant reduction of proteinuria after 23 weeks of treatment, regardless of GFR, blood pressure or ACE inhibition. However, in clinical studies proteinuria response in patients treated by VDR activators was not unique. The question is whether these patients may benefit from therapy with activators of VDR. The above mentioned benefit of therapy with VDR activators refers precisely to the anti-inflammatory effect. In animal models of primary glomerulopathy, VDR activators have reduced glomerular infiltration of inflammatory cells. In addition, high serum vitamin D in CKD patients is associated with reduced systemic inflammation\textsuperscript{12}. Subanti-proteinuric dose of calcitriol and paricalcitol reduces glomerular inflammation in experimental DN\textsuperscript{13}. Clinical studies in human population with paricalcitol in DN revealed that it has a modest and variable effect on proteinuria. Calcitriol and paricalcitol have reduced the expression of inflammatory cytokines in the kidney, reduced glomerular expression of IL-6 and MCP-1, decreased glomerular infiltration of CD43 + leukocytes, which synthesize chemotactic factors.

Vitamin D decreases expression of renin, suppressing the transcription of renin in mesangial cell that contribute to the reduction of inflammation. Hyperglycemia suppressed calcitriol and activate renin-angiotensin system. Thus, in the study of Li et al.\textsuperscript{14} vitamin D
is recognized as a negative endocrine regulator of the renin-angiotensin system by reducing the biosynthesis of renin. VDR deficiency resulted in the production of renin and angiotensin II, leading to arterial hypertension, and myocardial hypertrophy. In case of vitamin D deficiency, increased renin secretion occur, while injection of 1,25(OH)2D reduces its synthesis.

Combination therapy with losartan and paricalcitol in diabetic patients, prevent albuminuria, leading restoring glomerular filtration membranes structure and significantly reducing glomerulosclerosis\textsuperscript{15}. Does VDR activators should be used to reduce the progression of CKD still can not be answered with certainty. It takes a larger randomized controlled studies. The reduction of proteinuria in these studies takes place without changes in blood pressure, which indicates that the mechanism of action is nonhaemodinamic. Finally, some meta-analyzes suggest that VDR gene polymorphism may affect individual susceptibility to the development of DN in the white population.

Regarding diabetic retinopathy (DR), calcitriol inhibits angiogenesis in tumours\textsuperscript{16}. Diabetic retinopathy is characterized by neovascularisation and the angiogenesis, and high serum 1,25 (OH)2D reduces angiogenesis in ischemic retinopathy\textsuperscript{17}. The level of 25(OH)D is significantly lower in patients with two or three microvascular complications compared to those with no complications, and this is especially related to diabetic retinopathy. From the study of Inuki et al.\textsuperscript{18} it was found the low level of 25(OH)D and higher PTH in patients with diabetic retinopathy and/or proteinuria in comparison with those without the same. That vitamin D deficiency is an independent factor of risk for diabetic retinopathy was confirmed in studies in 1520 patients with type 2 diabetes. In the second study of Jee et al.\textsuperscript{19} in 204 patients, statistically significant influence of vitamin D deficiency on diabetic retinopathy was found in male sex, while for females it was not the case.

Diabetic polyneuropathy and the influence of vitamin D as a neurotropic substance on neuropathic pain is unclear. It is believed that vitamin D deficiency can potentially stimulate diabetic nerve damage. In the Basit and sar\textsuperscript{20} study, high dose vitamin D effect was investigated in patients with painful diabetic neuropathy and concluded that a single intramuscular dose of 600,000 IU of vitamin D leads to a significant reduction of the symptoms of diabetic neuropathy. Its deficiency is more common in patients with distal symmetrical polyneuropathy and pain reduction is achieved after vitamin D deficiency
correction. Three studies have shown that vitamin D deficiency is independently associated with increased risk for diabetic peripheral neuropathy in type 2 diabetes patients.

When it comes to published studies on diabetic macroangiopathy and affecting vitamin D (Somjen et al.\textsuperscript{21}), they first discovered enzymatic 1 alpha-hydroxylase activity in human vascular smooth muscle cells that may be stimulated with PTH and inhibited by exogenous vitamin D intake. It was proven the physiological effect of vitamin D on the vascular structure. Its serum level is directly proportional to endothelial function, and \textit{vice versa} to arterial calcification. Unfortunately, there are not enough valid studies regarding direct correlation of vitamin D and diabetic macroangiopathies.

Based on the above, there appears to be serious evidence of the role of vitamin D in metabolic syndrome and type 2 diabetes mellitus. Although, there are studies that have the opposite impetus. Further randomized control studies are needed to achieve a generally accepted attitude. The role of vitamin D in type 2 diabetes and metabolic syndrome is clear when it comes to the pathophysiological mechanism of the way it performs its activity on target tissues.

\textbf{Cardio-ankl Vascular Index (CAVI), parameter in the diagnosis of occlusive blood vessel disease}

This is a new parameter for determining the rigidity of the artery walls, starting from the aorta to the arteries at the lower extremity joints\textsuperscript{22}. The determination of this index is based on beta receptor domination, the effect of the beta 1 receptor on the rigidity of the blood vessels. There is a change in the blood artery caliber and consequently the changes in the internal pressure of the blood vessel\textsuperscript{23}. This index is independent of the height of the pressure at that point. Parameters of blood stiffness \textit{beta} are determined as the ratio of pulse wave velocity and diastolic blood pressure. CAVI is a constant value. Administration of alpha-blockers, which reduce contracture of smooth musculature of arterial wall decrease CAVI value or the blood pressure value. This means that CAVI is the indicator of arteries compliance or vascular function indicator of transport blood from the heart to the peripheral arteries.

Thiazide diuretics and ACE inhibitors, beta 1 blockers, do not reduce CAVI when they reduce the blood pressure.
Parameter of constriction artery $\beta$, is determined over the length of the main arteries. It is calculated by measuring the pulse wave velocity over the brachial artery and arteries of the lower leg at the level of the ankle joint. It is measured systolic and diastolic blood pressure over the brachial artery. The measured values of the application is given in equation. Then he gets a new parameter called Cardio-Ankle-Vascular-Index (CAVI).

There is a positive correlation between the value of CAVI and the degree of arteriosclerotic disease. CAVI decreases with improving cardiovascular risk. He is a predictive factor of cardiovascular events. CAVI, at the same time, indirectly represent contracture status of vascular smooth musculature of arterial blood vessels.$^{24, 25}$ When it comes to influence blood glucose level and the value of CAVI, high blood glucose causes contracture of smooth muscles of arteries and increases CAVI in a short period of time. Thereby, reducing HbA1C reduces CAVI, therefore CAVI may be a marker of glucose control. In patients with high LDL cholesterol, it have been shown low CAVI values. In the initial stages of hypercholesterolemia arteries are not rigid, but when in the process of arteriosclerosis include inflammation process then occurs rigidity of blood vessels. Of course, giving statins reduces CAVI. In the pathogenesis of apnea sleeping, the concentration of high and low oxygen, pass through the walls of blood vessel and contribute rigidity.$^{26}$

It has been shown that mortality decreased when the CAVI less than 9 in relation to the higher CAVI values. Cerebrovascular events are more common when the CAVI over these values. The results of preliminary studies indicate that it is preferable to CAVI is less or equal 9. It was proven that have been linked value CAVI and diastolic ventricular heart function, and therefore CAVI is indicator of afterload. Or CAVI was determined by compliance of the arterial blood vessel. So, CAVI value increased in: poorly regulated diabetes, obesity, hypertension, infection, cerebral hemorrhage, change in the structure of smooth muscles of the arteries. CAVI is an indicator of the degree artheriosclerosis and degree of contractility of blood vessels.$^{27}$
Role of concentration levels of PAI-1 in the process of angiogenesis and wound healing in diabetes type 2.

PAI-1 has an important role in the local and systemic responses to a trauma, as well as in wound healing. Therefore, points out the importance of the normal levels of PAI-1 in the treatment of tissue ischemia and necrosis of any aetiology. This fact has a bigger role in the patient with diabetes, due to the already present endothelial dysfunction.

It is known that plasminogen affect the wound healing process, the process of the proteolysis of the extracellular matrix, activation of growth factors and activation of cell migration of smooth muscle blood vessel\textsuperscript{28,29}.

As for the role of PAI-1 in wound healing of inflamed tissue in the ischemic type 2 diabetes, it was significantly increased at the early stage of the reaction in the process of neutrophil inflammation. This directly increases the swelling and tissue necrosis. Therefore, at an early stage, PAI-1 inhibits the effects of IL-6, which decrease the concentration of proteins in the inflamed region, with delayed wound healing. This suggests that the increased concentration of PAI-1 in the acute phase protein response. It is known that PAI-1 increased locally in the damaged tissue, under the influence of macrophages and endothelial damage. The decrease of PAI-1 increases the impact wound in the region of neutrophil inflammation, leading to reduced tissue necrosis and edema, after eight hours of the tissue injury. The decrease of PAI-1 results in a decrease of IL-6, increasing the levels of protein and faster wound healing\textsuperscript{30}.

It has been shown that PAI-1 at low concentration has antiapoptotic effect and increases the cell proliferation via its activity and encourages angiogenesis\textsuperscript{31,32}.

Ischemia of lower leg represents a large problem in therapy, but these properties of normal PAI-1 concentration can be used in the treatment of ischemia of diabetics patients. Tissue ischemia itself constitutes a stimulus for the secretion of stem cell transplantation. The angiogenic effect of inhibition of PAI-1, in terms of tissue ischemia, consists in the stimulation of secretion of neutrophilic granulocytes from bone marrow and from tissue. Produced stimulation of secretion of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2) and the free matrix metalloproteinase (MMP-9) in tissues, increased secretion of angiogenic factors from bone marrow: VEGF, hematopoietic growth factors.
Muscular infiltration with CD11h + Gr1 + neutrophils potentiate the inhibition of PAI-1 by increasing the level of FGF2 and VEGF and thus angiogenesis\textsuperscript{33}. PAI-1 stimulate angiogenesis by increasing FGF receptor on endothelial level, which increases the binding of VEGF to the endothelial cells in ischemic tissue\textsuperscript{34, 35}. Thus, FGFs activate VEGF affecting other growth factors and cytokines, which stimulate the development of basic and collateral circulation. tPA mobilise CD11b cells and VEGFR-1 + cells from bone marrow, accelerates healing and neovascularisation of ischemic tissue\textsuperscript{36}. This process indicates that of normal level of concentrations PAI-1 in circulation is another therapeutic approach in the treatment of ischemic tissue in type 2 diabetic patients.

**Conclusion**

Determination of concentration of vitamin D levels in obese patients, patients with metabolic syndrome and type 2 diabetes is useful, because the concentration of vitamin D in these patients is reduced. An adequate substitution of vitamin D contributes to a better quality of glycemic control. In fasting hypoglycaemia and postprandial hyperglycaemia always overlooked the presence of insulin antibodies and insulin receptor antibody, which substantially impairs the quality of glycemic control in both type 1 and the type 2 diabetes. Normal concentrations of PAI-1, is another therapeutic approach in the treatment of ischemic tissue in type 2 diabetic patients.

By applying new parameter cardio-ankle vascular index (CAVI), data on early and evolutionary arteriosclerosis could be obtained. Every contribution to the science pointing to all processes in the development of diabetes is valuable in order to clear diagnosis and treatment of this disease.
References


Fig 1 Cardio-ankle vascular index

CAVI = \frac{2p}{\Delta P} \left( \ln \frac{P_s}{P_d} \right) PWV^2

PWV = \frac{L}{T}

T = tb+tba

ECG
Heart sound
Brachial arterial pulse
Tibial arterial pulse

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