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Diabetes mellitus – factors that contribute to the occurrence, diagnosis and management of the disease

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

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Introduction

Type 2 diabetes mellitus is one of the most common endocrine disorders. Across the planet, 415 million people have diabetes (1 in 11 adults); estimates are that by the year 2040 there would be 642 million sick 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 the development of the disease: 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. It occurs due to the absolute or relative insulin deficiency, insulin resistance, increased glucose production and excessive action of the hormones with the opposite effect of insulin. Science has not clearly defined so far the additional contributing factors affecting the occurrence and treatment of this disease. What is the basis of the generation of diabetes is not well understood. Therefore, any contribution that leads in this direction is valuable.

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

In 1950, for the first time the association between insulin resistance (IR) and insulin antibodies (IA) was described The presence of IA were then attributed to the use of non-human insulin. Hypoglycemia simultaneously with the existence of a high titre of insulin antibodies, in the patients with diabetes, was decribed 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 the patients with insulin resistance (IR). Anti-insulin receptor antibodies (AIRAs) are determined by a metod of radioreceptor essay. These antibodies are IgG and IgM. IgG antibodies were more frequent in the patients with autoimmune diseases such as *acanthosis nigricans*. The antibodies of the IgM class are present in type 2 diabetes [2].

AIRAs are shown in circulation in the patients with diabetes. All previous studies indicate that there is no link between insulin and receptor antibodies in type 1 diabetes. However, among the 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 the 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, AIRAs were demon-

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strated 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. There is a correlation between the % of 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 presence of insulin receptor antibodies in patients with type 1 and type 2 diabetes [3].

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, the 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.

The 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. The Vitamin D also regulates the nuclear PPAR (*peroxisome proliferative activated receptor*), which plays an important role in insulin sensitivity. The vitamin D deficiency is associated with the increase in inflammation. The vitamin D decreases the expression of proinflammatory cytokines involved in the development of insulin resistance, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (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 the healthy population, in type 2 diabetes, substantially lower concentrations of circulating 25(OH)D are present [4]. Common risk factors for type 2 diabetes and hypovitaminosis D are 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 the vitamin D deficiency**.** Negative correlation between the 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. The possible role of vitamin D in type 2 diabetes and influence on the HbA1C values is also registered. It should be noted that there are studies that do not prove the 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 the treatment with vitamin D reduces the 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. Indirect effect on insulin secretion is found 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 have the harmful effects on calcium insulin secretion. Other potential mechanisms include stimulation of insulin receptor expression, improving the insulin response to glucose transport and a decrease in systemic inflammation by direct effects on cytokine [5, 6].

In a prospective study, Jannersjö et al.[7] investigated the relationship of serum 25(OH)D and parathyroid hormone (PTH) with all-cause mortality in the patients with type 2 diabetes and found that in the men with type 2 diabetes, vitamin D levels inversely correlated with all-cause mortality independently of years, levels of PTH, HbA1c, waist circumference, 24h-monitoring of blood pressure and serum apoB. In the women with type 2 diabetes, the serum PTH was directly proportional with all causes of death. In this study, it was not proven that the 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 the men and PTH in women, suffering from type 2 diabetes, could be used as the surrogate markers for prognostic information related to 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 and femoral arteries). De Boer [8] in his study with the hemodialysis patients showed that vitamin D treatment improved insulin secretion and sensitivity.

There are studies which have the opposite results in comparison to the conclusions given above. Thus in Shet et al. [9] study, 912 patients (429 patients of the group with type 2 diabetes and 483 patients of non-diabetic control group) from the West Indies studied the biochemical parameters [fasting glucose, postprandial glucose, HbA1c, basal insulinemia, insulin resistance in the form of homeostatic model assessment (HOMA- IR)] and compared to the level of 25(OH)D. It was concluded that, although there was a high prevalence of vitamin D deficiency in both groups, the effect of vitamin D on these parameters could not be confirmed. The explanation for this was the increased skin pigmentation of the population in this region, but also reduced exposure to sunlight because of how they dress and the way of life [9]. Exposure to the sun takes twice as long for the people of West Indies 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 oc-

currence of complications are modest. Ahmedieh et al. [10] in their study examined the relationship between levels of 25(OH)D and microvascular complications in the patients with type 2 diabetes. The conclusion was, that the low serum levels of 25(OH)D was independent predictor of HbA1c, diabetic neuropathy, and retinopathy. In the similar study by Zoppini et al. [11], it was found the inverse relationship between the levels of 25(OH)D and the prevalence of microvascular complications in the patients with type 2 diabetes. Whether the supplementation of vitamin D in these patients may have a benefit on the risk of microvascular complications remains to be explored. In another study, it was concluded that the vitamin D deficiency was more common in the diabetic patients with nephropathy, but not in those with retinopathy and neuropathy. Also, it was found that the level of vitamin D was lower in the patients with severe microvascular complications, and it was concluded that the vitamin D deficiency was associated with the microvascular complications in the patients with tip 2 diabetes.

Diabetic nephropathy (DN) reduces progressively the vitamin D body level due to: the loss of vitamin D-binding protein in proteinuria, compromised synthesis of vitamin D in the skin and lower activation of vitamin D in the damaged kidney. It was noted that the lack of vitamin D is higher in the diabetic chronic renal failure (CRF) than in the non diabetic patients. There are indications that the VDRs are modulators of glomerular damage. Calcitriol, endogenous VDR activator reduces the glomerulosclerosis index. In clinical terms, the patients with CRF treated with paricalcitol (selective VDR activator), exhibited a significant reduction of proteinuria after 23 weeks of the treatment, regardless of GFR, blood pressure or angiotensin converting enzyme (ACE) inhibition. However, in clinical studies, the proteinuria response in the patients treated by VDR activators was not unique. The question is whether these patients may benefit from the therapy with VDR activators. The above mentioned benefit of therapy with VDR activators refers precisely to the anti-inflammatory effect. In animal models of primary glomerulopathy, VDR activators reduced glomerular infiltration of inflammatory cells. In addition, a high serum vitamin D level in the CRF patients is associated with the reduced systemic inflammation [12]. Subantiproteinuric dose of calcitriol and paricalcitol reduces glomerular inflammation in experimental DN [13]. Clinical studies in the 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 monocyte chemoattractant protein-1 (MCP-1), decreased glomerular infiltration of CD43 + leukocytes, which synthesize the chemotactic factors.

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

Combination therapy with losartan and paricalcitol in the diabetic patients, prevents albuminuria, restores glomerular filtration membranes structure and significantly reduces glomerulosclerosis [15].

Whether VDR activators should be used to reduce the progression of CRF could still not be answered with certainty. It would take larger randomized controlled studies. The reduction of proteinuria in previous studies takes place without changes in blood pressure, which indicates that the mechanism of action is non- haemodynamic. 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 [16]. Diabetic retinopathy is characterized by neovascularisation and angiogenesis, and high serum 1,25 (OH)2D reduces angiogenesis in ischemic retinopathy [17]. The level of 25(OH)D is significantly lower in the patients with two or three microvascular complications compared to those with no complications, and this is especially related to DR. In the study of Inuki et al. [18] , it was found the low level of 25(OH)D and higher PTH in the patients with DR and/or proteinuria in comparison with those without. In studies including 1,520 patients with type 2 diabetes it was confirmed that the vitamin D deficiency is an independent factor of risk for DR. In the another study of Jee et al. [19] of 204 patients, a statistically significant influence of vitamin D deficiency on DR was found in the males, while it was not the case in the females.

Diabetic polyneuropathy and the influence of vitamin D as a neurotropic substance on neuropathic pain is unclear. It is believed that the vitamin D deficiency can potentially stimulate the diabetic nerve damage. In the Basit et al. [20] study, a high dose vitamin D effect was investigated in the patients with painful diabetic neuropathy and it was 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 the patients with distal symmetrical polyneuropathy, and pain reduction is achieved after vitamin D deficiency correction. Three studies showed that vitamin D deficiency is independently associated with increased risk for diabetic peripheral neuropathy in the type 2 diabetes patients.

When it comes to published studies on diabetic macroangiopathy and the affecting vitamin D, Somjen et al.[21], first discovered enzymatic 1 alpha-hydroxylase activity in human vascular smooth muscle cells that may be stimulated with PTH and inhibited by the 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 vice versa to arterial calcification. Unfortunately, there are not enough valid studies regarding direct correlation of the 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. However, 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.

Cardio-Ankle 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 [22]. The determination of this index is based on the 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 [23]. This index is independent of the height of the pressure at that point. The parameters of blood stiffness *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 the 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 and beta 1 blockers, do not reduce CAVI when they reduce the blood pressure.

The 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 measures systolic and diastolic blood pressure over the brachial artery. The measured values of the application are given in equation. Then it gets a new parameter called Cardio-Ankle-Vascular-Index (Figure 1).

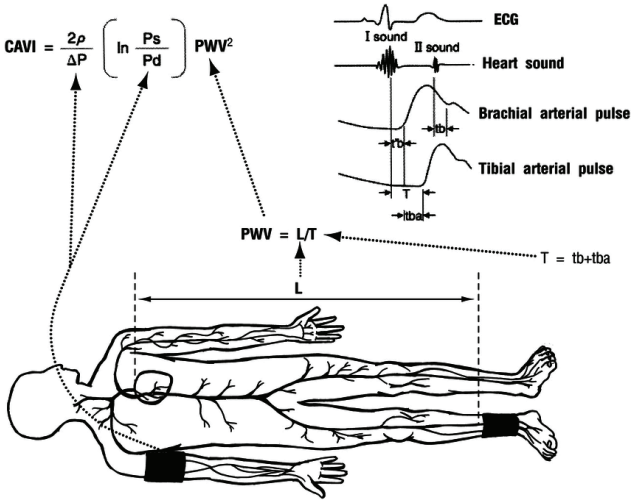

Fig. 1 – Cardio-ankle vascular index (CAVI).

PWV – pulse wave velocity; L – distance between aortic value and ankle; T – time taken for arterial pulse wave to travel from aortic value to ankle; tb – time between aortic value closing and notch of brachial pulse wave; tba – time between rise of brachial pulse wave to rise of ankle pulse wave; Ps – systolic pressure; Pd – diastolic pressure; ΔP – pulse pressure = Ps – Pd; ρ – blood density.

There is a positive correlation between the value of CAVI and the degree of arteriosclerotic disease. CAVI decreases with improving cardiovascular risk. It is a predictive factor of cardiovascular events. CAVI, at the same time, indirectly represent the 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, and therefore, CAVI may be a marker of glucose control. In the patients with high low density lipoprotein (LDL) cholesterol, the low CAVI values are shown. In the initial stages of hypercholesterolemia, the arteries are not rigid, but rigidity of blood vessels occurs when the process of arteriosclerosis inflammation is included. Of course, giving statins reduces CAVI. In the pathogenesis of apnea sleeping, the concentration of high and low oxygen passes through the walls of blood vessel and contrubute to rigidity [26].

It was showed that mortality decreased when the CAVI values were lower than 9 in relation to the higher CAVI. Cerebrovascular events are more common when CAVI was over these values. The results of preliminary studies indicate that preferable CAVI should be lower or equal to 9. It was proven that CAVI and diastolic ventricular heart function had linked value, and therefore CAVI is an indicator of the afterload (or CAVI was determined by compliance of the arterial blood vessel). So, the CAVI value is 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 artheriosclerosis degree 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

Plasminogen activator inhibitor-1 (PAI-1) has an important role in the local and systemic responses to a trauma as well as in wound healing. Therefore, this 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 affects 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 [28, 29].

As for the role of PAI-1 in the 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 decreases the concentration of proteins in the inflamed region with the delayed wound healing. This suggests that the increased concentration of PAI-1 in the acute phase protein response. It is known that PAI-1 is 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 eight hours after the tissue injury. The decrease of PAI-1 results in a decrease of IL-6, increasing the levels of protein and faster wound healing [30]. It was shown that PAI-1 at low concentration has antiapoptotic effect and increases the cell proliferation via its activity and encourages angiogenesis [31, 32].

Ischemia of lower leg represents a large problem in therapy, but these properties of the normal PAI-1 concentration can be used in the treatment of ischemia of diabetic 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 of the stimulation of secretion of neutrophilic granulocytes from bone marrow and from the tissue. The produced stimulation of secretion of vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2) and the free matrix metalloproteinase 9 (MMP-9) in tissues, increases secretion of angiogenic factors from bone marrow: VEGF, hematopoietic growth factors. Muscular infiltration with CD11h + Gr1 + neutrophils potentiates the inhibition of PAI-1 by increasing the level of FGF2 and VEGF and thus angiogenesis [33].

PAI-1 stimulate angiogenesis by increasing the FGF receptor at the endothelial level, which increases the binding of VEGF to the endothelial cells in the ischemic tissue [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 the bone marrow, accelerates healing and neovascularisation of ischemic tissue [36]. This process indicates that the normal concentrations of PAI-1 in circulation is another therapeutic approach in the treatment of ischemic tissue in the type 2 diabetic patients.

Conclusion

The determination of concentration of vitamin D levels in the 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 is always overlooked the presence of insulin antibodies and insulin receptor antibody, which substantially impairs the quality of glycemic control both in type 1 and type 2 diabetes. Normal concentrations of PAI-1 is another therapeutic approach in the treatment of the ischemic tissue in the type 2 diabetic patients.

By applying new parameter 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 acheieve the clear diagnosis and treatment of this disease.

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