Chapter 6

Periodontitis and Diabetes Mellitus

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1. Introduction

Diabetes mellitus is a serious metabolic disease and an important medical, social and economic problem globally. Long-term untreated hyperglycaemia – the main cause of a carbohydrate, lipid and osmotic imbalance – affects all tissues and organs in the body and leads to development of typical disease manifestations such as polydipsia, polyuria and polyphagia. This metabolic imbalance initiates other tissue and organ complications, some of which are extremely serious vasculopathies, cardiovascular diseases, neuropathies, myopathies, eye complications, renal complications and deteriorated regeneration and healing of wounds (Ceriello, 2005).

The basic etiopathogenetic mechanism in diabetes mellitus is either a real lack of insulin (type 1) or a biological lack of insulin (type 2) arising from its peripherally changed utilization and subsequent insufficiency. Insulin is a polypeptide produced by beta-cells of the pancreas and is necessary for glucose metabolism, keeping the glucose level in the blood within values of 4 – 6 mmol/1 ml. Glucose is metabolized in all tissues and is the main energy source in the organism. Lack of insulin causes hyperglycaemia and unmetabolised glucose is excreted mostly by the kidneys. This state leads to the development of polyuria, requiring increased intake of liquids and food and causing tissues to metabolise other sources of energy (fats, proteins) much more. Insufficient effectiveness of insulin means the energy requirements of the organism are not fulfilled; the organism searches for additional energy sources, mainly for proteins and fats. Increased metabolism of fats leads to excretion of so-called keto-compounds by the kidneys accompanied by a typical smell which can be detected in the patient's breath and sweat.

Nowadays we divide diabetes mellitus into the insulin-dependent type 1 DM, also called children's or adolescent DM, which presents an absolute lack of insulin caused by the autoimmune destruction of pancreatic beta-cells; and type 2 DM, which is known as adult diabetes, is a more frequent form of this illness and runs without clinical symptoms for a

longer time. The initial stages of the disease are characterized by insulin-tissue resistance connected with inadequate glucose tolerance. Increased insulin resistance of receptors and tissue produces an increased insulin requirement and forces its production in the pancreas. If insulin production in the pancreas drops below 50 per cent, a so-called pre-diabetic condition develops. This is characterized by after-strain hyperglycaemia, also called postprandial hyperglycaemia, which often runs sub-clinically. If it remains undiagnosed, it can develop into a more advanced form with various tissue and organ complications, oral manifestations and complications (Straka, 2011). The most frequent oral complications of diabetes are diabetes gingivitis and periodontitis, which are together considered to be the seventh most common complication of DM. In type 2 diabetes, the incidence of periodontitis is 2.9 – 3.0 times higher than in non-diabetic patients (Nelson et al., 1990; Tsai et al., 2002).

2. Classification of diabetes mellitus

The present classification of diabetes mellitus uses the AAD (American Association of Diabetes) division and distinguishes four types of DM.

1. Type 1 DM – autoimmune type (older synonym is IDDM – insulin-dependent diabetes mellitus), diabetes of young people;
2. Type 2 DM – non-autoimmune (an older synonym is NIDDM – non-insulin-dependent diabetes mellitus), diabetes of adults, insulin non-resistant type;
3. Specific types of DM
4. Gestational DM (Straka, 2001; Farkaš et al., 2011).

3. Etiopathogenesis of DM and diabetic periodontitis

3.1. Type 1 diabetes mellitus (T1DM)

T1DM starts as an autoimmune and destructive reaction against the patient's own pancreatic beta-cells. The main risk factor is a genetic predisposition to such an autoimmune reaction. Some authors distinguish six stages of T1DM development described as follows: the 1st stage, known as genetic predisposition, passes into the 2nd so-called activating stage, which is characterized by immediate activation of autoimmune reactions. The 3rd stage, for which immune abnormalities are typical, passes into the 4th stage characterized by loss of glucose-stimulating insulin production. Clinically present diabetes in the 5th stage is a reflection of the large destruction of B-cells and leads to their total destruction in the 6th and final stage (Rybka, 1990). In young patients with T1DM, an increased susceptibility to gingivitis and periodontitis has been detected. This state is often accompanied by more extensive damage to periodontal tissue and an early onset of gingivitis after the patients reach the age of 11. Periodontal pockets were detected in 9.8% of a group of young patients aged 13 – 18 years, compared with a 1.7% occurrence in a healthy control group (Straka, 2001; Rybka, 1990).

3.1.1. Etiopathogenic and risk factors

An increased prevalence of gingivitis and periodontitis in adolescents with T1DM is mostly attributed to various etiopathogenetic and risk factors of the primary illness:

Altered immunity. The most frequent immunological disorder is an excessive production of the pro-inflammatory cytokines TNF-alpha, IL-1, PGE2 and others. They induce hyper-inflammatory systemic or local status and contribute to chronicity due to prolonged inflammation. The immune system is unable to eliminate significantly gram-negative bacteria from the subgingival area. The causes can be genetically determined in a form of dangerous phenotype of monocytes/macrophages and their increased inflammatory reaction to the LPS toxin as well as various polymorphisms of inflammatory mediators (Straka, 2001; Salvi et al. 1997).

Tissue glycation. Long-lasting hyperglycaemia initiates the rise of so-called non-enzymatic tissue glycosylation, which causes formation of AGEs (Advanced Glycosylation End-products). Increased amounts of AGEs condition a growth of receptors and cause all attendant changes in vascular structures and increased formation of inflammatory cytokines, adhesive molecules and other immunocompetent substances with possible subsequent multiplication of bacterial pathogens (Gislen et al., 1980; Mealey & Oates, 2006; Mandell et al, 1992).

Disorders of tissue regeneration and wound healing. Tissue glycation and expansion of inflammation in T1DM patients seem to be a cause of deterioration in the regenerative abilities of periodontal tissue, including osseous structures, which are measured by means of bone-building biomarkers such as osteocalcin, the values of which were reduced in comparison with the control group of non-diabetic patients (Lappin et al., 2009).

3.1.2. Influence of T1DM treatment on the state and course of periodontitis

Several studies report that balanced levels of glycaemia in T1DM patients have a beneficial influence on the degree of periodontal tissue damage during periodontitis as well as on its clinical course. These results associate total systemic changes with destructive changes to the periodontium depending on the therapeutic result of the glycaemia level. The given relationship acts reciprocally. (Straka, 2001; Farkaš et al., 2011; Cianciola et al. 1982, Lyons, 1992) However the results of other present-day clinical studies negate the positive correlation between periodontal therapy and its beneficial influence on the course of the primary illness. Periodontal therapy in T1DM subjects prevented periodontal infection, but did not significantly influence the level of glycated haemoglobin (Tervonen et al., 2009). Statistically insignificant results of periodontological therapy on glycated haemoglobin concentrations have also been confirmed by another independent study (Lambés et al., 2008).

3.2. Type 2 diabetes mellitus (T2DM)

The etiopathogenesis of T2DM and its most frequent oral complication are closely interconnected. Their mutual associations can be observed in various stages of the primary disease. One of the early pathological symptoms of broken homeostasis of glucose is its increased postprandial (after-strain) level in the blood. This type of hyperglycaemia is bound to food and develops several years before it is clinically manifested by T2DM. The pre-diabetic stage of the disease is characterized by the presence of several markers, of which the most important is glycated haemoglobin A1c, which represents the amount of glycated haemoglobin in erythrocytes (given in percentages). The pre-diabetic stage of the disease, measured by means of HB1c, FPG, and 2-hOGTT can be relevant in the development of some angiopathies, mainly retinopathy (Ceriello, 2005; Straka, 2011; Rybka, 1990). In T2DM aetiology as well as in the development of diabetic periodontitis, the following groups of factors and mechanisms play crucial roles:

Genetic associations. For some multifactoral diseases several genes were selected using relevant literature gene databases and listed by statistic methods into individual groups according to their severity. The most important group is formed by so-called leader genes, characteristic for both diseases (Covani et al. 2008). After their application into the databases of two leader genes selected from 986 genes for T2DM, four leader genes actively acting in both diseases were identified. The most significant of them was NFKB1, whose increased activity was detected in periodontal lesions and which seems to have a relationship with microvascular defects induced by a systemic inflammatory process. Another leader gene is RELA, which together with NFKB1 codes two subunits of the complex NFKB triggering an intracellular inflammatory reaction (Covani, Marconcini, Derchi; 2009). STRING software enabled us to determine a close association between periodontitis and T2DM by means of IL-6 and TNF-alpha (Covani et al., (2009); Nishimuraet al., 2003). It is also true that there are certain limitations in the given theoretical knowledge and that by removing these limitations, scientific research could more strongly validate the presented knowledge (Covani et al., 2009). Nowadays our ability to determine dangerous genetic predispositions to T2DM by means of certain genetic profiles, in wide populations, remains considerably limited. Genetic risk factors certainly play an important role in the etiopathogenesis of T2DM, genome-wide association studies having stated that genetic RF can be useful in establishing certain profiles of disease susceptibility and can be used in T2DM disease and therapy management (Khoury et al., 2008).

Insulin resistance. In type 2 diabetes mellitus, there is sufficient insulin at an early stage of the disease, a fact confirmed by an abundance of B-cells in pancreatic tissues. But their effectiveness in producing insulin varies and is influenced by the progress of the disease, level of abdominal obesity and other factors. At the beginning of the disease there is enough insulin, but relevant structures are metabolically so altered that biological utilization of insulin is insufficient. Insulin in tissues and cells acts by means of its receptors, which are of glycoprotein character. A starting signal of cellular activity of insulin is activation by receptor tyrosine kinases, which phosphorylate substrates of insulin receptors in tyrosine

residues. Glucose transport is ensured by a lipid kinase and is stimulated by P13K into its fully active form determined for glucose transport by means of insulin. However these mechanisms are extremely complicated and there are several possible ways this complicated mechanism of glucose may function. The relationship between insulin and lipogenesis as well as the effects of various transcription factors in adipocyte are also very complicated (Nishimura et. al., 2003; Kahn & Flier, 2000). Both the prevalence and etiopathogenesis of T2DM are nowadays most often associated with obesity, mainly of the abdominal type. "Insulin resistance" is not an insulin-induced disorder of glucose metabolism, but an expression of decreased insulin-induced transport of glucose and its metabolism in striated muscles and adipocytes (Nishimura et al., 2003; Kahn & Flier, 2000; Watanabe et al., 2008; Al-Zahrani et al., 2003). Insulin controls glucose homeostasis in the blood, decreasing its level by reduced production in liver and increased absorption in muscles and adipose tissues. The most frequent disorders of insulin activity are defects of its signal systems, mainly in the adipocytes. These require higher effort to get insulin and to produce it in larger amounts, which leads to hyperinsulinemia. Excess levels of insulin in the blood can result in a receptors imbalance and loss of post-receptor sensitivity; all this can be accompanied by glucose intolerance and age-related insufficiency of insulin receptors (Kahn & Flier, 2000). Increased serum concentrations of fatty acids (usually connected with diabetes and T2DM) contribute to further development of insulin resistance. Excessive levels of fatty acids in blood and muscles brake phosphorylation and transport of glucose as well as the synthesis of muscular glycogen and subsequent glucose oxidation (Kahn & Flier, 2000; Ferenčík & Hulín, 2008; Shulman, 2000).

Metabolic syndrome. Obesity, hyperlipidaemia and insulin resistance are the principal symptoms of metabolic syndrome. Obesity also leads to other factors that contribute to metabolic syndrome. One of the dominant factors is dyslipidaemia characterized by increased triglyceride concentration, non-esterified fatty acids as well as a higher concentration of specific LDLs, also called low-density lipoprotein particles. Dyslipidaemia is accompanied by low HDL cholesterol levels. Nowadays it is obvious that individual components of metabolic syndrome represent independent risk factors in the etiopathogenesis of insulin resistance. Their mutual communicative effect also exists (Ferenčík & Hulín, 2008; Shulman, 2000; Coenen et al., 2007). Adipose tissue in obese people has various forms. As for formation of pro-inflammatory cytokines, the most harmful is white adipose tissue in the abdominal region, which contains residual macrophages (Straka, 2011; Coenen et al., 2007). Formation of inflammatory cytokines in these macrophages significantly increases the pro-inflammatory status of the organism with all its consequences. Adipocytes are the principal cells of adipose tissues and are excreted with the endocrine function. One of the most important products is leptin characterized by its pleiotropic effect, which plays an important role in energy-balance regulation. Adipocytes produce substances which have either a direct or indirect relation to insulin resistance. Production of pro-inflammatory cytokines and TNF-alpha, IL-6, CRP markers, angiotensinogen, but also of steroid hormones of oestrogen and cortisol, contribute to local biology of adipose tissue. Increased production of TNF-alpha increases lipolysis and inhibits

lipogenesis, which together with other co-factors, leads to insulin resistance (Ferenčík & Hulín, 2008; Shulman, 2000; Coenen et al., 2007).

Inflammation and insulin resistance. Type 2 diabetes, insulin resistance and obesity with dyslepidaemia are pro-inflammatory states which are closely interconnected. While leptin and adiponektin are exclusively products of adipocytes, TNF-alpha, IL-6, MCP-1, resistin, visfatin and PAI-1 are produced by activated macrophages and other cells, and contribute to the maintenance and stimulation of low-grade inflammation in obesity (Straka, 2011; Shoelson, Jongsoon, Goldifine, 2006). The inflammatory kinases JNK, IKKbeta, PKC, STAT cause insulin resistance by decreasing insulin signalization on receptors (Kim et al., 2004; Mehta et al., 2010). Nowadays inflammatory cytokines, mainly TNF-alpha, represent important etiopathogenic factors of insulin resistance stimulation. Together with the LPS-toxin of periodontal bacterial pathogens, they activate NF-kapaB, which after displacement into the cell nuclei can induce insulin resistance (Ceriello, 2005; Salvi et al. 1997). Patients with the abdominal type of obesity show increased TNF-alpha serum levels, which drop with decrease of body mass (Gislen et al., 1980). Increased TNF-alpha levels and other pro-inflammatory mediators circulating in patients with metabolic syndrome can stimulate inflammation of the periodontium, where also in clinically healthy individuals, gram-negative anaerobic bacteria are present, and induce increased proteolytic and osteolytic destruction of tissues (Salvi et al., 1997; Mealey & Oates, 2006). Increased prevalence of periodontal illnesses in the obese, mainly in younger individuals, has also been confirmed by a NHANES III study involving 13,655 patients, who were tested according to periodontal indices (PD, AL) and BMI and WC indices. A correlation between these two diseases was established by using two different multivariable logistic regressive models containing other risk factors in periodontal disorders (sex, race, education, diabetes, smoking habits, date of last visit to the dentist) (Mandell et al., 1992). Nowadays the secreting activity of the adipocytes of adipose tissues is considered a source of chronic low-grade inflammation as well as an important pro-inflammatory etiopathogenetic factor in many serious diseases, including type 2 diabetes and inflammatory-destructive illnesses of the periodontium (Ceriello, 2005; Lappin, et al., 2009; Lyons, 1992).

Non-enzymatic glycation. Non-enzymatic glycation presents a basic chemical reaction by which glucose is bound to lysine residues and, by means of unstable or stable intermediate products, forms so-called advanced glycosylation end products. Production and accumulation of AGEs runs also in periodontal tissues and has an influence on their composition and immunological qualities in several possible ways. In a normal glycaemic regime AGE-receptors are present in small amounts in monocytes, smooth muscle cells, neurons, fibroblasts and endothelial cells. Increased levels of AGE-receptors can lead to overproduction of adhesive molecules and oxidative elements, the consequence of which is an increased uncontrolled anti-inflammatory immune response to the presence of microbial pathogens in the periodontium (Tervonen et al., 2009). Another serious factor in a severe anti-inflammatory reaction is excessive activity of proteolytic enzymes, which destroy periodontal soft tissues. Several studies have confirmed an increased concentration of metalloproteinases in the periodontium of a diabetic patient. These are caused by increased

transcription of local resident cells stimulated by overproduction of pro-inflammatory cytokines (Lambés et al. (2008). Collagen glycation results in strengthening of cross-links among its molecules, impairing solubility, natural homeostasis and biological regenerative qualities. Regeneration of ageing collagen and basal membrane is reduced and accumulation of AGEs products in these structures starts (Covani et al., (2008). Destruction of the periodontium correlates with imbalanced glycaemic curve as well as with a level of glycated haemoglobin. In diabetic patients with an HbA1c level higher than 8 %, their IL-1beta concentration was found to be two times higher than in patients with an HbA1c level lower than 8 % (Covani et al., 2009). The level of glycaemic control and length of diabetic disease have an impact on the stage of glycation and collagen regeneration in soft and osseous tissues. Defects in osteoblast differentiation and altered production of extracellular matrix contribute to this state (Cianciola et al., 1982; Nishimura et al., 2003). On the basis of given studies we can conclude that the glycation of various components of periodontal tissues significantly changes its immunity to various exogene elements (bacteria, viruses) and considerably decreases regeneration and healing of these tissues.

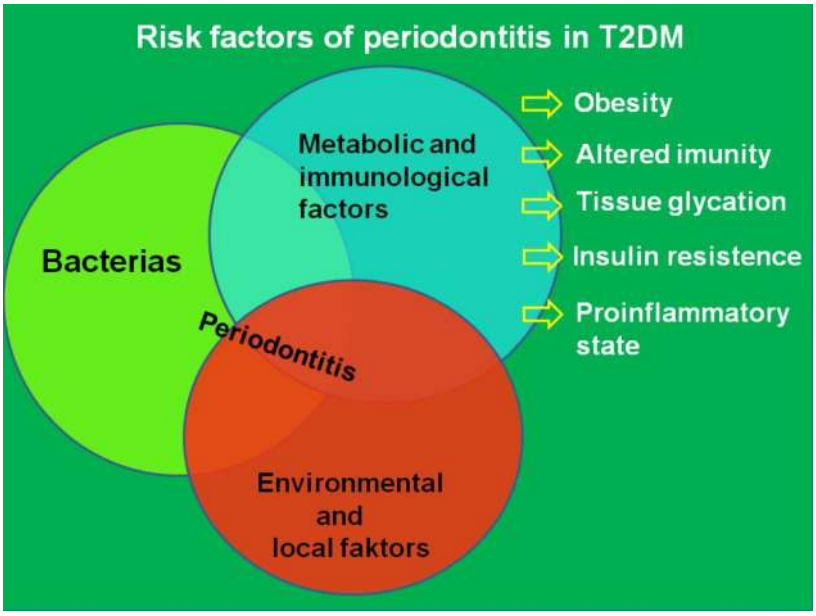
Defects in cell-mediated immunity. In subjects with DM, defects of polymorphonuclear leukocytes have been repeatedly confirmed. These are based in defects of chemotaxis and phagocytosis and result in insufficient antibacterial protection of periodontal structures (McMullen et al., 1981; King, 2008). In subjects with DM, the hypersecretive type of monocytes was detected, which on irritation with LPS-endotoxin gram-negative periodontopathic bacteria, reacted with increased IL-lbeta and TNF-alpha production, which stimulated inflammation of periodontal tissues with excessively destructive osteolysis and tissue destruction of periodontal ligaments (Collins et al., 1997; Galbraith et al., 1998).

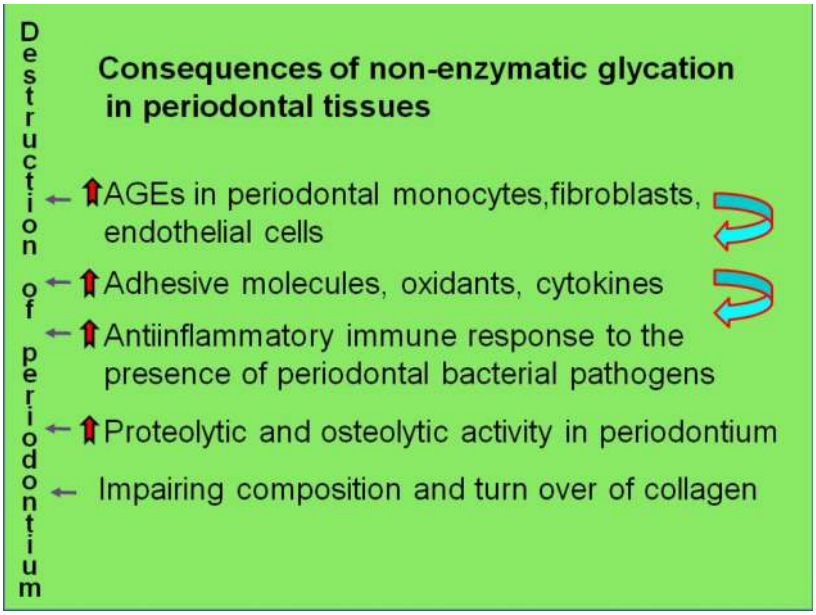
Influence of microbial factors. Altered immunity, vasculopathy of periodontal structures, decreased solubility of glycated tissues, defects of protein and osseous regeneration and repair all cause that immunity of the periodontium to typical periodontal pathogens is considerably reduced and is less effective against infections. Some studies report differences between groups of patients with long-lasting and correctly managed monitoring of glycaemia and those with an insufficiently monitored and managed course of glycaemia. Increased amounts of periodontal microbial pathogens were confirmed in diabetic patients but their microbial strains were no different from those of non-diabetic patients (Mandel et al. 1992; Zambon et al., 1988; Straka, 2011).

3.3. Gestational DM (GDM)

Gestational DM is characterized with high blood sugar levels inpregnant women, who were not diagnosed for DM previously. Its prevalencein pregnant women varies from 5 to 7 percent. Usually is concern atransient form, while placental and maternal adipose tissues producehormones which can change metabolism of glucose (Friedlander et al.,2007). Some authors state that in up to 50 per cent of women with GDM,T2DM can develop within 3.5 years. Although there is lack of relevantstudies to this topic and no anonymous conclusion was done, most authorsconfirm the hypothesis that pregnant women with GDM have a high

risk todevelop a severe form of an inflammatory diseases of the periodont (Novak et al.,2006; Friedlander et al., 2007; Xiong, et al., 2006). Thisrelationship runs in both directions and presence of inflammatorydiseases unfavorably influences the mother's organism and the healthstate of the foetus (Novak et al., 2006; Straka et al., 2011).





4. Conclusion

From the given knowledge we can summarise several theoretical and practical conclusions which are important for the diabetological and periodontological management of a patient as well as for management of mutual therapeutical associations and procedures:

Patients with diabetes mellitus have twice or three times a larger incidence of periodontitis. This is in relation to significant deterioration of several periodontal parameters such as gingivitis, higher prevalence of periodontal pockets, deeper periodontal pockets, higher BOP score and loss of attachment.

Our present state of knowledge defines DM periodontitis as one of the systemic complications of diabetes though its main etiopathogenic associations in cell-altered immunity, in glycation of periodontal tissues, vascular damage of the periodontium, increased proteolysis and osteolysis of periodontal structures, which result from increased concentrations of pro-inflammatory cytokines, deficient regeneration of collagen structures and quantitative multiplication of periodontal bacterial pathogens.

The level of inflammatory destruction of the periodontium is different in patients with a good level of control of the primary diabetic disease from patients with insufficient control. Changes in periodontal structures can also be detected during the latent stage of diabetes and are reflected in unspecified laboratory and clinical findings.

Nowadays the mutual relationship between these two diseases is considered to run in two directions. Local inflammation in the periodontium significantly influences the systemic disease due to increased susceptibility of the diabetic patient to infection and increased insulin resistance. Deterioration of periodontal parameters and clinical manifestations lead to worsening of the diabetic disease. Without reduction of inflammation in the periodontium we cannot expect any significant improvement of the primary disease.

In collaboration with a diabetologist, we are trying to diagnose gingivitis and periodontitis in the initial stages of diabetes and in detection of the patient's genetic predisposition to diabetic disease.

During treatment of resistant and refractory types of periodontitis, it is necessary to test for diabetic disease, to contact a diabetologist and to try to detect individual pre-diabetic states.

Microbial factors were considerably emphasized in the past. Some studies indicated specific subgingival microflora of some strains, namely P. intermedia and strain capnocytophaga (Khoury et al., 2008). Our current knowledge, described in several studies, indicates that there is no difference in the distribution of individual pathogens in non-diabetic and diabetic patients with periodontitis. However patients with DM are afflicted more often by repeated infectious diseases (Khoury, et al., 2008).

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In the chapter, Periodontitis and Diabetes mellitus,, authors deal with mutual relation between both diseases which we percept nowadays as a bidirectional, in the meaning of a mutual reciprocal etiopathogenetic association. They briefly present etiopathogenesis and classification of two main types of diabetes mellitus. The main objective of chapter is to outline and present the mutual etiopathogenetic association. In spite there is not known any distinct causal molecular relation between mentioned diseases in present, exists the certain multifactorial interpretation of mutual pathogenetic coherence in larger epidemiologic, genetic, metabolic, immunologic and therapeutic context. These more specifically defined etiological associations help us as well in diagnostic and therapeutic management in the practice of both diseases, what is emphasized in the conclusion section.

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