

Chronic Pancreatitis and Diabetes of Exocrine Pancreas / Type 3c Diabetes Mellitus / Post-pancreatitis Diabetes Mellitus

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In 2011 and subsequently in 2012, the American Diabetes Association (ADA), together with the WHO, defined a new type of diabetes in connection with the disease of the exocrine pancreas. For this type of diabetes, the term pancreatogenic diabetes was used, or type 3c diabetes mellitus (DM3c, T3cDM) [1]. So far, the terms secondary pancreatic diabetes [2] and diabetes of the exocrine pancreas (DEP) [3] – as a synonym for the two above-mentioned terms – have still been used. In 2022, at the congress of the European Pancreatic Club another term appeared, namely post-pancreatitis DM (PPDM).

Diabetes of the exocrine pancreas is characterized by exocrine and endocrine dysfunction of the pancreas, involving not only insulin secretion but also pancreatic polypeptide producing cells. The authors present the DEP classification according to Hart et al. [4] from 2016, where changes are classified as a consequence of:

- a) a complete loss of functional islets of Langerhans (chronic pancreatitis, gland agenesis);
- b) an initial phase of loss of functional islets of Langerhans (severe acute pancreatitis, cystic fibrosis, etc.);
- c) paraneoplastic effect (adenocarcinoma of the gland, acute pancreatitis with transient hyperglycemia).

Type 3 DM is divided into 8 subtypes marked with capital letters:

- type 3A DM – a genetic defect in the beta-cells of the pancreas
- type 3B DM – genetic insulin defect – the so-called insulin resistance syndrome
- type 3C DM – in primary pancreatic disease
- type 3D DM – diabetes accompanying endocrinopathies (Cushing syndrome, glucagonoma, acromegaly etc.)
- type 3E DM – drug-induced diabetes (glucocorticoids, thiazides, beta-blockers, diazoxide)
- type 3F DM – infectious etiology (cytomegalovirus)
- type 3G DM – rarer forms – immune-mediated diabetes (insulin resistance, stiff person syndrome)
- type 3H DM – rare genetic syndromes (Down syndrome, Turner syndrome, Klinefelter syndrome etc.)

In 2022, the American Diabetes Association (ADA) published a classification of diabetes that includes 4 categories [5]:

- type 1 DM (autoimmune destruction of pancreatic beta cells with subsequent absolute insulin deficiency, including latent autoimmune diabetes in childhood)
- type 2 DM (progressive loss of adequate secretory ability of beta cells to produce insulin, insulin resistance)
- specific types of diabetes, for example the so-called monogenic diabetes syndrome, such as neonatal diabetes, or the so-called maturity-onset diabetes of young individuals; this group also includes cystic fibrosis-related diabetes and pancreatitis-related diabetes as well as drug-induced or chemically induced DM (glucocorticoids, HIV/AIDS drugs, conditions after organ transplantation)
- gestational diabetes (diabetes newly diagnosed in the second or third trimester of pregnancy).

Type 3c DM is a disease having an etiological relationship with a number of pancreatic diseases. In addition to chronic pancreatitis, this also includes acute pancreatitis, cystic fibrosis, pancreatic cancer, pancreatic hemochromatosis or rare pancreatic agenesis [3]. The prevalence of pancreatogenic diabetes in the so-called Western population is currently reported to be in the range of 5–10% of all diabetes types. Pancreatogenic diabetes occurs most often in people with chronic pancreatitis [4, 6]. In the study performed by English

authors, the median age at T3cDM diagnosis was 59 years, and men predominated in 58.9%. The median BMI was 29.2. Surprisingly, the prevalence of T3cDM is higher than that of type 1 DM (2.59 versus 1.64 per 100,000 inhabitants per calendar year) [7]. Several studies demonstrate a high risk of developing T3cDM in people with acute pancreatitis. A 2.5 times higher risk of developing DM was found in almost 3,000 people with acute pancreatitis [8].

Chronic pancreatitis is, as previously stated, another etiological factor in the development of T3cDM [9], especially in the presence of pancreatic calcifications, in smokers and in the long-term duration of the disease [10]. Pancreatic cancer can also arise in chronic pancreatitis, or where fibrosis of the parenchyma is developing in the terrain of chronic inflammation [4]. There is a significant risk of developing pancreatic ductal carcinoma in persons with newly diagnosed diabetes [11]. The question is whether the presence of diabetes is the cause of the process of carcinogenesis, or whether diabetes is solely an accompanying symptom of cancer. This concept has currently been evaluated by several epidemiological and clinical studies. It has been confirmed that 80% of patients with pancreatic ductal carcinoma have abnormal fasting glucose levels or an abnormal glucose tolerance test, regardless of the stage of pancreatic carcinoma [12, 13]. The pathophysiological mechanism of T3cDM is primarily the process of pancreatic inflammation and the associated irreversible fibrotization, including pancreatic islet cells. The terminal stage is the loss of pancreatic islets. In the case of T3cDM, damage occurs not only to pancreatic beta-cells, but also to cells producing pancreatic polypeptide (PP cells), namely already in the early phase of the disease [14]. Damage to pancreatic alpha cells is the cause of decreased glucagon levels. The pathogenesis of T3cDM is significantly different from that of type 1 DM and type 2 DM. In these types of diabetes, only pancreatic beta-cells are damaged. Patients with diabetes thus experience a number of significant functional changes, such as insulin resistance, insufficient insulin production, pancreatic immunopathogenesis, insufficient incretin effect or the contribution of genetics [14-17].

Insufficient Secretion of Insulin

In the capillaries of the vascular system, which connects the endocrine part of the gland with the exocrine part, a high concentration of endocrine hormones such as insulin, glucagon and pancreatic polypeptide was demonstrated [13]. These hormones are apparently involved in the synthesis of pancreatic enzymes in the exocrine part of the gland [14]. Logically, the fibrotic process affecting the parenchyma of the gland will also significantly affect insulin synthesis in the pancreas [14]. Current findings show that chronic pancreatitis is associated with insulin insufficiency which may be present even before the development of diabetes itself [15]. At the same time, it is important to note that in the early phase of chronic pancreatitis, the first change is a significant increase in the level of cytokines and inflammatory markers, which leads to pancreatic beta-cell dysfunction [16]. Another important factor is the loss of vascularization of the pancreatic parenchyma, leading to the replacement of functional pancreatic tissue by connective tissue, or ligament [17, 18]. In the pathogenesis of T3cDM,

the cause of insulin deficiency is not only a reduced function of beta cells, but also an absolute lack of beta cells where the cause is the inflammatory process and the related fibrotization and sclerotization of the pancreatic parenchyma [18].

In very advanced pancreatic lesions, the destruction of pancreatic beta cells is associated with an imbalance between insulinemia and hyperglucagonemia and may be the cause of episodes of hypoglycemic states [19, 20].

Impaired insulin secretion and impaired pancreatic beta-cell function are common findings in people with pancreatic ductal adenocarcinoma. At the same time, insulin resistance in these persons is either not present at all, or increases only slightly [21].

Another important factor is the release of pro-inflammatory cytokines, such as interleukin 1 beta, tumor necrosis factor (TNF) or interleukin 1R. Expression of interleukin 1R and interleukin 1beta by islets of Langerhans induces pancreatic beta cell apoptosis. In people with chronic pancreatitis, the high expression of interferon gamma leads to a translocation disorder of pancreatic islet cells [4]. In clinical studies, plasma levels of adrenomedullin are higher in people with pancreatic cancer than in healthy people [22]. At the same time, adrenomedullin, like vanin-1, is a key factor that is secreted to an increased extent in people with pancreatic cancer and is of fundamental importance in terms of tumor aggressiveness [23]. Thanks to its effect on pancreatic cells, it is also involved in the development of type 3c diabetes.

Insulin Resistance

It was described as one of the symptoms of chronic pancreatitis where insulin sensitivity is significantly reduced compared to healthy people or people with type 1 DM. However, other studies show that people with T3cDM have a higher insulin sensitivity than those with type 1 DM [24]. A possible association between the severity of pancreatic involvement and insulin resistance is discussed [25]. A significant factor in insulin resistance is hepatic insulin resistance which is demonstrated in patients with T3cDM after pancreatic resection procedures, chronic pancreatitis, pancreatic ductal carcinoma and in patients with cystic fibrosis. The cause is multifactorial but particularly significant is the insufficient function of the pancreatic polypeptide, the deficiency of which is associated with a reduction of insulin receptors in the liver [26]. Pancreatic polypeptide is currently referred to as a glucoregulatory hormone that regulates hepatic insulin sensitivity [27]. Impairment of hepatic insulin function in subjects with chronic pancreatitis is accompanied by activation of hepatic I-kappaB kinase and NF-kappa B [28]. Blockade of NF kappaB leads to improvement of hepatic insulin sensitivity [29].

Gastrointestinal Tract Microbiome and Diabetes Mellitus

The normal ecology of the gastrointestinal tract plays an important role in the activity and function of the alimentary canal, in the synthesis of vitamins, the metabolism of drugs and xenobiotics as well as in the control of sugar metabolism [30] which concerns people with type 1 DM, type 2 DM and T3cDM [31, 32]. In patients with chronic pancreatitis, microbial dysbiosis is altered in a similar way as it is in

persons with T3cDM. While in people with type 1 DM the condition is associated with insufficient insulin secretion, in patients with type 2 DM diabetes is initially associated with insulin resistance and subsequently with insulin deficiency, based on changes in immunity. Type 3c diabetes is, among other things, a consequence of insulin insufficiency in hepatic insulin resistance [30, 32]. The loss of pancreatic polypeptide effect, with which hepatic insulin resistance is associated, is a characteristic feature of T3cDM [4]. There is an interesting theory related to the effect of endotoxemia and a change in the spectrum of intestinal microbes associated with the influence of mucosal permeability, as an etiological factor inducing inflammatory involvement of the pancreatic islets [33].

Incretin Effect

Glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP) are hormones of the digestive tract. GLP-1 is secreted by L-cells, mainly in the ileum and colon. Its functions include, among others, regulation of insulin secretion and slowing of gastric motility. The suppression of glucagon secretion and the regulation of gastric evacuation depending on glycemia are also significant [34]. Secretion of GIP hormone is ensured by K cells of the small intestine. A very rapid inactivation of both hormones is caused by the presence of dipeptidyl peptidase 4 (DPP-4) and an increase in insulin secretion in glucose-dependent persons. Insufficient GLP-1 secretion also occurs in patients with type 2 DM, which is reflected in clinical practice by the introduction of drugs such as GLP-analogues or DPP4 inhibitors. In people with T3cDM, GLP-1 sensitivity is intact, but the late phase of insulin secretion, for which the GIP hormone is responsible, is reduced, similarly, to type 2 DM [35, 36]. Nevertheless, there are discrepancies in the results of individual studies in this area, partly due to the small number of people evaluated in individual studies, but also due to the methodological complexity of determining individual incretin substances and the resulting possible errors in the methods used. Therefore, the results on the relationship between the incretin effect and the existence of hyperglycemia are accepted with some caution [31].

Genetic Associations

Several studies have confirmed the existence of specific genes for chronic pancreatitis. Some of the genes are the cause of hereditary chronic pancreatitis, others are genes that induce, in the presence of other risk factors, changes in the sense of chronic pancreatitis. Mutations for the cationic trypsinogen PRSS1 belong to the mutations inducing chronic pancreatitis with a possible relationship to DM [37]. The median age of persons with positive PRSS1 mutations and DM is low: 36.6 years, and the risk of developing diabetes in this group is 60% [38] but the positivity of this mutation is also demonstrated in juveniles with pancreatopathy, including DM. Risk factors such as smoking, or alcohol have numerous interactions with the mentioned genetic factors.

Adipocytokine Chemerin

Chemerin belongs to the group of adipocytokines. Its functions include immune regulation, adipocytokine differentiation, and regulation of sugar metabolism, but its

role in T3cDM is still the focus of attention. The serum level of chemerin in subjects with T3cDM is significantly lower when compared to that in subjects with type 2 DM [39]. A positive significant association was found between chemerin and HOMA-IR and a negative association between chemerin and insulin resistance [40]. The effect and mechanism of action seem to be different between type 2 DM and pancreatogenic diabetes.

Diagnosis of Type 3c Diabetes Mellitus

Diagnostic criteria for this type of diabetes, in connection with chronic pancreatitis, are not standardized. In general, the diagnosis is based on the presence of exocrine pancreatic insufficiency, supported by the determination of the values of liposoluble vitamins, especially vitamin D, and evidence of persistent pancreatic abnormalities, using imaging methods. However, the condition is the absence of autoimmune markers that are associated with type 1 DM [41]. Currently, attention is paid to the determination of some metabolites that are different between type 2 DM and T3cDM. These metabolites include the product of partial hydrolysis of phosphatidylethanolamine, designated as Lyso PE.

Although our knowledge of this type of DM is quite broad, there is no doubt that further studies, focused primarily on diagnosis, including, for example, the identification of new biomarkers or new therapeutic approaches, are desirable.

Conflicts of interest: None to declare.

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