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Review Article

Secondary Diabetes

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Abstract

Secondary diabetes may occur in association with endocrine or nonendocrine disorders. The most common endocrine diseases associated with glucose intolerance are those involving the overproduction of counter regulatory hormones. Nonendocrine conditions associated with glucose intolerance or diabetes fall into three general categories: pancreatic diseases, drug-induced diabetes, and genetic syndromes. The therapy for secondary diabetes centers on the correction of an underlying disturbance. Patients with fasting hyperglycemia should be treated with an understanding of the pathophysiologic basis of their diabetes.

Keywords: Secondary Diabetes; Deficient Insulin Secretion; Insulin Resistance; Decreased Peripheral Glucose Utilization; Impaired Glucose Tolerance; Endocrine Disorders; Overproduction Of Counter Regulatory Hormones; Genetic Syndromes; Pancreatic Diseases; Drug-Induced Diabetes

What is Secondary Diabetes?

Since 1999 we have been distinguishing four groups of diabetes:

- Type 1 diabetes,
- Type 2 diabetes mellitus,
- Other specific types of diabetes,
- Gestational diabetes mellitus.

The most common forms are Type 1 diabetes and Type 2 diabetes; together they account for almost 90% of all cases of diabetes. The group of disorders called "other specific types of diabetes" is very extensive [1]. This group includes many forms of diabetes with a very diverse background. Moreover, there are more uncommon cases such as genetically determined diabetes. These include monogenic diabetes represented by genetic disorders in the structure of the β-cell (MODY diabetes) [2]. Secondary diabetes is a separate group, which includes glucose metabolism disorders associated with various diseases or medications [3-5]. Among the reasons that may be accompanied by disorders of glucose homeostasis of varying severity are:

- Endocrinopathies;
- Diseases of the exocrine pancreas;
- Drug-induced secondary diabetes;
- Genetic disorders associated with diabetes.

Secondary diabetes is more common than it is diagnosed. The underlying condition that leads to glucose homeostasis disorders is often unrecognized. While in autoimmune diabetes (Type 1 diabetes and LADA Type diabetes), its etiopathogenesis is established and the primary disorder is pancreatic β-cell damage, and in Type 2 diabetes the primary cause is insulin resistance, in secondary diabetes, the etiopathogenesis of glucose homeostasis disorders is diverse and most often multifactorial.

Endocrine Disorders Involving the Overproduction of Hormones, Which may be Accompanied by Secondary Diabetes

Various endocrine diseases may be associated with glucose homeostasis disorders. In some endocrine diseases, there is an increased secretion of hormones, which are of the opposite effect to insulin, and as a result may cause hyperglycemia [6-8]. The cause of hyperglycemia may lie in an increase in hepatic glucose production and its reduction in peripheral tissue utilization [9]. In some cases, insulin secretion decreases. Endocrine disorders involving overproduction of hormones, which may be accompanied by secondary diabetes, include:

Acromegaly

Excessive secretion of Growth Hormone (GH) before puberty leads to gigantism, whereas acromegaly manifests in adults. Exaggerated GH secretion causes many disorders of carbohydrate metabolism [10]. In the first phase, growth hormone stimulates insulin secretion, which increases the production of IGF-I in the liver, and is involved in the activation of the insulin receptor. The late effect of GH is insulin antagonism. As a result, glucose utilization in adipocytes is disturbed and insulin resistance increases [11-13]. Approximately 60% of patients with acromegaly have glucose tolerance disorders after the Oral Glucose Tolerance Test. Most of these patients have normal fasting glucose. About 20% of patients with acromegaly and normal glucose tolerance have increased endogenous insulin levels. Glucose intolerance and insulin resistance in most patients with acromegaly disappears or at least significantly decreases after successful surgical treatment or radiotherapy. Almost a third of patients with acromegaly manifest abnormally high insulin secretion during the Oral Glucose Tolerance Test for up to two years after surgical treatment, regardless of normal blood glucose, GH and IGF-I levels. It may be related to the development of Type 2 diabetes. A small group of patients with acromegaly have low basal insulin secretion and display an abnormal response to stimulation, which results in very significant hyperglycemia and exogenous insulin requirements.

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It may be a group in which Type 1 diabetes develops. The occurrence of diabetes in patients with acromegaly is a serious complication because it increases the risk of cardiovascular complications and the development of cardiomyopathy [14]. The first-line treatment of acromegaly is surgery. A number of medications supporting therapy and enabling the correction of glucose metabolism disorders are used [15,16].

Cushing's syndrome

Cushing's syndrome is the result of a chronic increase in blood glucocorticoid levels of either exogenous or endogenous origin. Basically, glucocorticoids are glucose-sparing, triggering substrates for gluconeogenesis – amino acids from muscle tissue and free fatty acids from adipose tissue. The production and utilization of metabolic substrates is directly regulated by glucocorticoids. However, mainly insulin regulates these processes. Physiologically, insulin promotes glucose consumption and inhibits hepatic gluconeogenesis, blocks lipolysis and the release of amino acids from muscle tissue. Therefore, the presence of insulin prevents the glucocorticoid from increasing gluconeogenesis. With insulin deficiency or impairment, the stimulating effect of glucocorticoids on glucose production remains. Since insulin resistance in patients with Cushing's syndrome is almost unchanged, carbohydrate intolerance is mainly the result of a lack of an insulin-inhibitory effect. Probably the diabetogenic effect of glucocorticoids is caused by their influence on glucose production, insulin secretion, and peripheral sensitivity to its effects. Thus, the reduction of glucose utilization in Cushing's syndrome may be the result of the simultaneous occurrence of both insulin secretion disorders and its function disorders [17-19]. It is possible that patients with Type 2 diabetes include a group of patients with secondary diabetes caused the by excessive secretion of glucocorticoids. The mortality of patients with Cushing's syndrome who have impaired glucose metabolism is higher than those whose glucose metabolism is normal.

Glucagonoma

Cases of glucagonoma have been reported since 1966. The main target organ of glucagon is the liver, where it is with the participation of cyclic AMP that mechanisms increasing glycogenolysis and gluconeogenesis are activated. Glucagon also acts on muscle and fat tissue, and facilitates the release of amino acids and free fatty acids, which are substrates for gluconeogenesis. Consequently, glucagon is involved in maintaining blood glucose levels in hunger and after high-protein meals. The presence of insulin limits the catabolic effect of glucagon on muscle and adipose tissue. Blood glucagon levels are markedly increased in patients with this tumor. Compared to the state of excess growth hormone or cortisol, insulin resistance is not a major feature of carbohydrate intolerance associated with excess glucagon. Rather, hyperglucagonemia is associated with increased glucose production induced by an increase in hepatic glycogenolysis and gluconeogenesis. In addition, glucagon is a potent stimulator of epinephrine secretion from the adrenal medulla; therefore, glucose production may also be increased by the adrenergic mechanism. As mentioned above, the increase in glucose production alone is not sufficient to induce intolerance thereto. Reduced insulin secretion and/or insulin resistance gives reduced glucose utilization as a result. Nearly 100% of patients with glucagonoma have glucose intolerance. The intensity of the disorder can vary from very mild to very severe; however, these conditions are generally not associated with the development of ketoacidosis. Effective treatment through surgical resection is associated with the cure of insulin-dependent diabetes.

Pheochromocytoma

Pheochromocytoma is associated with constant or intermittent overproduction of epinephrine and norepinephrine. 95% of tumors are located in the adrenal medulla, the rest can be located along the abdominal aorta, bladder or mediastinum. In 95% of cases they are benign tumors, and more than 10% may occur in the adrenal medulla on both sides. Catecholamines have many opposing metabolic effects relative to insulin. At the physiological level, epinephrine stimulates muscle glycogenolysis, lipolysis in adipocytes, as well as hepatic glycogenolysis and gluconeogenesis. All of these increase glucose production. Essentially, catecholamines influence glucose utilization by affecting the level of insulin secretion and reducing the level of its peripheral consumption. Although patients with pheochromocytoma and impaired glucose tolerance usually have reduced insulin secretion, hyperinsulinemia has also been reported in the literature. Catecholamines reduce insulin sensitivity, especially in skeletal muscle. Glucose intolerance incidents occur in 25-75% of patients with pheochromocytoma. Usually, fasting blood glucose is normal. Glucose tolerance disorder is associated with decreased delayed insulin secretion. The absence of ketoacidosis is probably due to increased fatty acid re-esterification. Successful tumor removal restores glucose homeostasis. Response to treatment may not be immediate; it may occur only after more than four weeks after the surgery. During this period, insulin secretion is restored, but abnormal glucose tolerance remains. This suggests that decrease in insulin sensitivity persists to some degree, even if circulating catecholamines return to normal.

Hyperthyroidism

Thyroid hormones, apart from their direct effect on glucose production, change the activity of many enzymes, and also interfere with the suppressive effect of insulin on hepatic glycogenolysis and gluconeogenesis. Excessive thyroid hormones further disrupt glucose-induced GH suppression, which is an additional factor in the development of glucose intolerance. Thyrotoxicosis impairs glucose availability, especially in adipocytes, while it minimally increases insulin-stimulated glucose transport. This effect is associated with an increase in the number of glucose transporters (GLUT4) in the membrane of adipocytes [20-27].

Hyperprolactinemia

Moderate chronic hyperprolactinemia is associated with a reduction in the basal insulin secretion stimulation threshold. This process is controlled by glucose and β-cell proliferation, probably mediated by the altered expression of glucokinase, hexokinase and Glucose Transporter in Islet Cells (GLUT2). Prolactin also affects tissue insulin resistance and glucose tolerance.

Secondary Diabetes Associated with Pancreatic Diseases

The pancreas is the organ that is responsible for the production and secretion of insulin into the blood, and therefore its damage through a disease process or injury can lead to diabetes. The most common causes of pancreatic damage that can cause diabetes are pancreatitis, mechanical trauma, pancreatic cancer, and the surgical

removal of some or all of this organ. Usually, for secondary diabetes to occur, pancreatic damage must be significant. The exception is pancreatic cancer, some forms of which cause diabetes when even a small part of the pancreas is involved.

Pancreatectomy

Partial or complete resection of the pancreas may be dictated by a tumor process, cystic disease, or it may be the result of a therapy of a recurrent inflammation process. The deficit of the exocrine and endocrine pancreatic function is rarely revealed if less than 75% of the organ has been removed or damaged. When endocrine secretion of all types of cells is reduced, we not only observe insulin secretion deficiency but also pancreatic glucagon, somatostatin, and Pancreatic Peptide (PP) secretion. In patients whose duodenum has not been removed, the intestinal glucagon fraction is secreted. Due to the reduced level of pancreatic glucagon, despite insulin deficiency, the risk of ketoacidosis in these patients is definitely lower. A clear decrease in insulin secretion is a major cause of postoperative diabetes. Patients after pancreatectomy also demonstrate a reduced adrenaline secretion response to insulin-induced hypoglycemia.

Inflammation of the pancreas

Glucose intolerance may be part of the clinical picture of both acute and chronic pancreatitis [28-31]. Hyperglycemia in acute inflammations is usually transient, but can be severe. Abnormalities may persist in 3-5% of patients. Chronic pancreatitis may be associated with diabetes in approximately 60% of patients. Secondary diabetes in the course of pancreatitis in relation to secondary diabetes after pancreatectomy differs in the lower incidence of hypoglycemia, more frequent incidence of ketosis, and a higher demand for exogenous insulin [32-35].

Drug-Induced Secondary Diabetes

Many drugs and hormones can interfere with insulin secretion and function. They cannot cause diabetes themselves, but they can cause diabetes in people with insulin resistance or lead to changes in blood glucose homeostasis [36,37]. These factors may reveal previous latent defects of insulin secretion or resistance and lead to the discovery of glucose intolerance in previously undiagnosed patients. They can also make diabetes worse if given to patients with pre-existing diabetes.

Diabetogenic effect of steroids therapy

Various pharmacological drugs may cause glucose intolerance. They can affect glucose homeostasis by affecting insulin secretion as well as its effect. They may act directly or indirectly through insulin-regulating hormones. Steroids are a group of commonly used diabetogenic drugs [38-41]. The diabetic effect of steroids has been known for a long time; however, the hyperglycemia they induce is usually not very high and ketosis is rare. Adrenal steroids affect glucose homeostasis through a variety of mechanisms. The inflow of substrates for the formation of glucose is associated with the catabolic action of adrenal steroids in muscle and adipose tissue. Peripheral glucose consumption also decreases during such therapy. The effect of adrenal steroids on β-cell function cannot be overlooked. Drugs from this group are usually given on an ad hoc basis or, if chronically, in the lowest possible doses. Then, usually, glucose homeostasis disorders are not large and can be self-regulating. However, in some conditions, adrenal steroid drugs are used at high doses and for long periods of time. In these cases, one should be aware of serious chronic carbohydrate metabolism disorders - if not clinically apparent diabetes – where manifested. In any case, glucose tolerance becomes significantly impaired. As mentioned earlier, due to the need for the prophylaxis of macro- and microangiopathy, these conditions absolutely require monitoring and therapy.

Genetic Disorders Associated with Diabetes

One of the factors responsible for diabetes may be genetic mutations within the genes responsible for the functioning of insulin-producing cells in the pancreas, i.e. pancreatic islet cells. Insulin is insufficient and, as a result, blood sugar levels that are too high persist. Genetic disorders leading to diabetes may also be associated with insulin action. One of them is a defect in the insulin formation pathway, resulting in the inability to convert insulin to its precursor, proinsulin. As a result, the right hormone, which is able to lower blood sugar levels, is not created. Another cause of secondary diabetes is the cellular production of defective insulin molecules that have more difficulties binding to their receptor, and that perform their regulatory function less well. In the cases above, the health consequences are usually moderate, and usually manifest themselves in varying degrees of insulin resistance.

Cystic Fibrosis-Related Diabetes-CFRD

Cystic fibrosis is a condition that is relatively often associated with diabetes. This combination has genetic conditions [42-44]. The nature of glucose homeostasis disorders may vary. It depends on both possible insulin secretion disorders and peripheral insulin resistance.

Insulin resistance syndromes associated with the insulin receptor gene mutation

Genetically determined disorders of glucose homeostasis also include insulin resistance syndromes such as the Rabson-Mendenhall syndrome, Type A insulin resistance syndrome, congenital lipodystrophic diabetes, and other syndromes [45-48].

Conclusion

Causal treatment is crucial in secondary diabetes. The treatment must be adapted to the pathogenesis of the disorder. It is important for patients with the first symptoms of glucose metabolism disorders to be carefully interviewed. Therefore, it is very important to diagnose them as early as possible, and implement appropriate treatment.

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