Correct Diabetes Types Differentiation - An Ongoing Problem

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Abstract: *Until recently the diagnostic criteria and division into two main types of diabetes seemed clear enough. It was thought that just as islet autoantibodies and tendency to ketosis was a feature of type 1 diabetes, insulin resistance and slow progress of the disease was typical of type 2 diabetes. However, the latest study results and case reports supply evidence which questions this present order. Is there a 1.5 type diabetes? The growing diagnostic abilities in the field of genetics and immunology offer new measures to broaden studies of diabetes pathogenesis and pathophysiology. Formerly described characteristics of types of diabetes become blurred and tend to permeate one another. All those data contribute to a great need to verify the old and establish the new diagnostic criteria for type 1 and type 2 diabetes. There is an increasing view that one should assume that type 1 and type 2 diabetes and non-autoimmune syndromes occur in both adults and children.*

Keywords: type diabetes, diagnostic criteria, revision of present classification, autoimmune diabetes, type 1 diabetes, type 2 diabetes, monogenic diabetes.

1. Introduction

Discussion on the differentiation of the diabetes types has been continuing for several years now. The division of diabetes into four types, in force since 1999, has lost its legitimacy. Quite recently, differentiation criteria for diabetes seemed to be clear. However, there are more and more reports confirming the presence of forms of diabetes impossible to be unequivocally classified. This subject recurred during the last session of ADA (American Diabetes Association) [1]

Naturally, in all cases of diabetes, irrespective of the patient's age, during diagnostic deliberations it is necessary to exclude **secondary diabetes from the group of "other forms of diabetes".** It is crucial to determine whether the diagnosed diabetes is not associated with genetic or endocrine disorders or whether it is not a type of diabetes secondary towards the treatment applied. The introduction of immunological and genetic tests has broadened the knowledge on the etiopathogensis of glucose metabolism disorders, which imposes a need to revise the classification that is currently in force.

When diabetes manifests itself, attempts are made in order to determine the type of the diabetes. The prevalence of diabetes has alarmingly increased across the world in the recent years. [2]

The data relating to the increase of diabetes incidence in juvenile patients have been recently presented by French authors, basing on the data from the subject literature. [3,4]

Hence, large-scale studies have been conducted, aiming at the identification of causes of this incidence increase, as well as at launching the search of methods of prevention and treatment of this disorder. The underlying condition of the development of diabetes is a glucose metabolism disorder, manifesting itself in the form of hyperglycaemia. The fundamental mechanisms leading to these disorders are the dysfunction of meta cells producing insulin, as well as the resistance of tissues to insulin, predominantly in the liver and muscles.

So as to undertake measures leading to treating these disorders, it is necessary to determine the pathogenesis and mechanisms leading to their occurrence as precisely as possible. It becomes indispensable to differentiate individual types of diabetes. Attempts at such a classification were undertaken as early as early 20th century. Due to very limited possibilities of a precise assessment of the disorder, these divisions were very simplified. As diagnostic opportunities grew, attempts at modifying these divisions were made. [5,6,7,8,9]

The division in force today is the one coming from 1999, although it calls for verification. Earlier differentiation of diabetes types was based predominantly on data from the patient's medical history and on the clinical symptoms. One of elements constituting the foundation for the differentiation process was the **dynamics of symptoms accumulation**, and on this basis two types of diabetes were differentiated: acute diabetes, which according to the current classification is identified with type 1 diabetes, and chronic diabetes, which is usually identified with type 2 diabetes. Today we know that this criterion often fails, and applying it uncritically leads to diagnostic errors.

Another indicator considered when determining the type of diabetes was the **occurrence or non-occurrence of obesity.** Formerly, when diabetes was diagnosed usually when metabolic disorders were advanced, obesity was not encountered in patients with insulin dependent diabetes. Therefore, if diabetes was detected in overweight or obese patients, it was diagnosed as type 2 diabetes. Nowadays, more and more often we encounter overweight in patients suffering from type 1 diabetes. [10,11]

Therefore, overweight cannot be a decisive factor in diagnosing the type of diabetes. Overweight or obesity can

be an element of the course of diabetes that accompanies genetic syndromes, endocrinopathies, or drug induced diabetes.

Another factor that differentiates diabetes types is the **patient's age**. Admittedly, the most common type of diabetes occurring in children and adolescents is type 1 diabetes, but all other types of diabetes can appear in these age groups: type 2 diabetes, secondary diabetes, or the group of monogenic diabetes. The source of errors could also be classifying all cases of diabetes in mature patients as type 2 diabetes. It is known that monogenic diabetes, secondary diabetes, as well as more and more frequently diagnosed LADA (*Latent Autoimmune Diabetes in Adults*) can occur in these age groups. [12]

Broadening the diagnostic base facilitated the differentiation of diabetes accompanying genetic syndromes and endocrinopathies. The problem of differentiating autoimmunological diabetes types – type 1 and type diabetes – was still to be solved. It seemed that this differentiation could be decided about by the **C-peptide level**, and most of all the occurrence or non-occurrence of anti-pancreatic autoantibodies. Determination of the level of C peptide allows to assess the secretion of endogenic insulin and to confirm or exclude the diagnosis of autoimmunological diabetes. If this level is clearly lowered, it is a signal of a considerable reduction of insulin secretion; if the level is high, it probably indicates increased insulin secretion in response to resistance to its activity. This marker is useful in the assessment of insulin resistance characteristic for many diseases, including type 2 diabetes. The presence of insulin dependence has been associated with type 2 diabetes. Today it is beyond any reasonable doubt that insulin resistance accompanies many conditions, including autoimmunological diabetes, today diagnosed as the "classical" type 1 diabetes and the LADA type diabetes. There are different markers for measuring insulin resistance, but the simplest one is increased secretion of endogenic insulin, manifested in a high level of C peptide. Nevertheless, as it turns out, when assessing this marker it is necessary to take into account in which phase of the diabetes development it was evaluated. In advanced stages of the diabetes development the difference in the level of C peptide in type 1 and type 2 diabetes is clear. However, if the C peptide level test is performed at an initial stage of autoimmunological diabetes, especially in LADA diabetes, this level may fall into the normal limits. Therefore, the assessment of this marker is useful in the differentiation of diabetes types; the interpretation of the results, however, needs to be cautious. Recently Guglielmi et al. proposed to measure the level of C peptide after stimulation by means of the glucagon stimulation test (GST) versus the mixed meal tolerance test (MMTT). [13]

The second marker adopted in the differentiation of the classical type 1 diabetes and LADA diabetes with type 2 diabetes is the **anti-pancreatic autoantibodies titre.** The most frequently detected autoantibodies are GAD autoantibodies, IA-2 autoantibodies, insulin autoantibodies, and ZnT8 autoantibodies. An elevated titre of autoantibodies testifies to the presence of the autoimmunisation process

towards pancreatic islet cells and is suggestive of the diagnosis of type 1 diabetes or LADA diabetes. [14, 15, 16]

It turns out, however, that there are more and more reports undermining this criterion. As early as in 2001, Hathout et al. , who analysed 48 children and adolescents with type 2 diabetes and compared them with 39 randomly selected children with type 1 diabetes, stated that the presence of diabetes autoimmune markers should not be used to exclude the diagnosis of type 2 diabetes in children and adolescents. [17]

Genetic determinants specific to either type of diabetes, e.g. human leukocyte antigen-DQ/DR subtypes, might be needed in the future for typing of diabetes. Dib drew attention to the complex pathogenesis of diabetes in juvenile patients with insulin resistance and obesity, along with the presence of pancreatic autoimmunity markers, namely autoantibodies to islet cell antigens, specified as double diabetes (type 1 plus type 2 diabetes). [18]

The complex mechanism of the development of diabetes in juvenile patients is also indicated by Italian authors. They draw attention to more and more frequent forms of diabetes characterised by the occurrence of hyperglycaemia in overweight/obese children and youth with the combination of markers typical of both type 2 and type 1 diabetes. [19, 20, 21]

American authors point out that the only diabetes in which it is possible to accurately diagnose by DNA sequencing, monogenic diabetes, remains undiagnosed in more than 90% of individuals who have diabetes caused by one of the known gene mutations. [22]

Many errors in the diagnosis of diabetes types relate to monogenic diabetes. Maturity-onset diabetes of the young (MODY) is a group of monogenic diseases that result in primary defects in insulin secretion and dominantly inherited forms of nonautoimmune diabetes. Diagnosis may be difficult, particularly with type 2 diabetes, but also type 1 diabetes. [23,24]
For the final diagnosis it is necessary to conduct genetic tests [25,26,27,28].

In the current situation unequivocal determination of the type of diabetes can be difficult, especially in juvenile patients. [29].

Assessment of such clinical factors as the dynamics of the development of symptoms of the disease, the occurrence of overweight or obesity, the patient's age, diabetes in the patient's family history, observation of the demand for insulin, as well as the assessment of the insulin secretion, the insulin resistance marker, pancreatic immunity markers, is necessary in order to select the treatment method. Genetic tests are often necessary to complete the picture. Chances are that the near future will have to bring attempts at a new classification of types of diabetes basing on new markers of the pathomechanism of the development of glucose metabolism disorders.

American authors have pointed to the diversity of pathomechanisms of the development of type 2 diabetes. They have demonstrated that systemic inflammation has to be involved in the development of type 2 diabetes. [30]

These studies underscore the heterogeneity of type 2 diabetes and demonstrate an overlap between the causes of β-cell dysfunction in type 1 and type 2 diabetes, because they reveal that a strikingly high percentage of patients classified as type 2 possess islet-specific autoreactive T cells. Research into the pathophysiology of T2D has identified the presence of islet-specific T cells and the islet autoimmune disease in type 2 diabetic patients.[31] According to the authors the cell-mediated islet autoimmunity has also been correlated with the progressive loss of β-cell function associated with the pathogenesis of type 2 diabetes. These studies demonstrate the involvement of the cell-mediated islet autoimmune disease in the progression of the T2D disease and similarities in the islet-specific T-cell reactivity between type 1 diabetes (T1D) and type 2 diabetes (T2D).

2. Conclusions

The question of differentiating between individual types of diabetes remains open. It is obvious that the currently used division into types of diabetes must be modified. It is more and more often raised that it should be assumed that type 1 and type 2 diabetes are not as distinct as once believed, and diabetes mellitus appears to consist of autoimmune and non-autoimmune syndromes in both adults and children. Such a division identifying diabetes patients as either autoimmune or non-autoimmune may come in handy when choosing the right therapy. This applies in particular to the application of immunomodulating agents targeted at arresting further β-cell autoimmune destruction, but also to making decisions on an early onset of insulin therapy in cases of autoimmunological diabetes.

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