Review article:

Missing the correct classification of diabetes mellitus: Reasons and implications on the patient's care

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Diabetes mellitus classification:

The most common types of diabetes mellitus are type 2 and type 1 diabetes mellitus, ,gestational diabetes, specific types of diabetes, and pancreatogenous diabetes mellitus (type 3c diabetes mellitus). Type 1 and type 3c may constitutes 10-20% of diabetes and are usually misdiagnosed as type 2 diabetes with deleterious consequences (1,2).

The classification of diabetes mellitus may not be easy, a recent study proposed a classification in to five clusters: severe autoimmune diabetes, severe insulin-deficient diabetes, severe-insulin resistant diabetes, mild obesity-related diabetes, and Mild age-related diabetes (3). The authors reported that this classification may direct the management more efficiently.

Obesity, although commoner in type 2 diabetes but is present in other types of diabetes:

Adiposity is considered as an important cardio-renal risk factor both in the general population and patients with type I diabetes, a plausible mechanism is the alteration of renal hemodynamic (4). Nineteen percent of patients with type 1 diabetes mellitus may be overweight, and 5.2% may be obese. Furthermore, obese and overweight patient were more likely suffering from the metabolic syndrome (5). A study published in Poland reported a prevalence of 35.5% and 13.2% of overweight and obesity respectively vs. 26.1% and 7.3% in control group (6).

Type 2 diabetes among children and adolescent is a real nightmare:

Type 2 diabetes mellitus may constitutes up to 45% of diabetes in young people due to the rising rates of obesity and it is shown to be more aggressive that type 2 diabetes in the adult population (β-cells are more hyper responsive and deteriorate more rapidly in children than adults). Most children with type 2 diabetes mellitus present with microvascular complications Importantly, Maturity-onset diabetes of the young (type 3 being the most prevalent) usually presents in the young (usually before 25 years). The diagnosis is usually clinical characterized by non-autoimmune, not insulin dependent, and a family history of diabetes suggesting a dominant inheritance. The differentiation between MODY and early onset type 2 diabetes is difficult and genetic testing may be needed (7). A recent study published in the United Kingdom found 4.5% of cases in overweight and obese youth diagnosed with type 2 diabetes are due to monogenic diabetes (8).

Type 1 in the adult and pancreatogenous diabetes mellitus (type 3 diabetes mellitus:

On the other hand type 1 diabetes mellitus is as likely to occur in over 30-year of age as it is in young population (42% vs. 58%), it could be hard for the physician to pick up cases of type 1 diabetes when it occurs in the adult age group. Thus type 1 diabetes mellitus should not be thought of it as a disease of children and young adults. In this regards type 1 diabetes should be considered in particular if the patients require insulin within one year or the oral antidiabetic medications failed rapidly. Autoantibody (at least two of them targeting insulin) presence and C-peptide<600pmol/l (more sensitive after three years of the diagnosis) favor type 1 diabetes mellitus which is less common, but these tests may be present in both type 1 and type 2 diabetes and will not make 100% distinction (9). It is clear that type 1 diabetes mellitus may be shadowed with the most prevalent type 2 diabetes. To complicate the matter more, type 3c diabetes mellitus (pancreatogenous diabetes mellitus) peaks in 50s) and is usually labeled as type 2 diabetes. Chronic pancteatitis is the cause in 80% of patients and may be subclinical,   Clinically overt steatorrhea is usually not observed until over 90% of exocrine pancreatic function.   Type 3c diabetes constitutes 5-10% of diabetes (more common than type 1 diabetes). Patients with pancreatogenous diabetes are also deficient in glucagon, and pancreatic polypeptide and are more prone to hypoglycemia and diabetes complications, they may require insulin early in their course of the disease (1).

Proposed diagnostic criteria for type 3c diabetes diagnosis (10):

Major criteria (all should be present):

- The presence of pancreatic exocrine insufficiency
- The presence of pathological imaging (CT, endoscopic ultrasound, and MRI)
- And absence of type 1 diabetes associated autoimmunity

Minor criteria:

- Impaired β-cell function (as measured by homoeostatic model assessment for β-cell function, or C-peptide or glucose concentrations)
- Absence of insulin resistance (as defined by homoeostatic model assessment for insulin resistance), impaired incretin secretion (glucagon-like peptide-1 [GLP-1] or pancreatic polypeptide, or both), and low serum concentrations of lipid soluble vitamins (A, D, E, and K). Lack of standardization of the above tests methods, and the features overlap in long standing type1 and type2 diabetes mellitus are major limitations of the minor criteria.

The importance of differentiation between different types of diabetes mellitus:

Failure to introduce insulin in timely proper way may result in deleterious consequences in term of microvascular complications, type 1 diabetes genetic risk score may accurately classify patients with diabetes when the clinical picture and autoimmune markers are equivocal (11). It is important to differentiate between type 1 and type 2 diabetes mellitus even if insulin is introduce early because the regimen and health education are different. Furthermore some countries provide insulin pumps and continuous glucose monitoring systems for type 1 and not type 2 diabetes.

In conclusion: Type 2 diabetes is common among youth and adolescence, high body mass index is now common among patients with type 1 diabetes that affects children and adults in the same frequency. Type 3c diabetes is not uncommon and is usually misdiagnosed as type 2 diabetes. It is important to

327

correctly classify the different types of diabetes mellitus because the education, treatment and regimen are different.

References:

1. American Diabetes Association Standards of Medical Care in Diabetes. Lifestyle Management Diabetes Care 2017;40(Suppl. 1):S33–S43 | DOI: 10.2337/dc17-S007

2. Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spégel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark Å, Lahti K, Forsén T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-drivencluster analysis of six variables. Lancet Diabetes Endocrinol. 2018 May;6(5):361-369. doi: 10.1016/S2213-8587(18)30051-2. Epub 2018 Mar 5.

3. Bjornstad P, Lovshin JA, Lytvyn Y, Boulet G, Lovblom LE, Alhuzaim ON, Farooqi MA, Lai V, Tse J, Cham L, Orszag A, Scarr D, Weisman A, Keenan HA, Brent MH, Paul N, Bril V, Perkins BA, Cherney DZI. Adiposity Impacts Intrarenal Hemodynamic Function in Adults With Long-standing Type 1 Diabetes With and Without Diabetic Nephropathy: Results From the Canadian Study of Longevity in Type 1 Diabetes. Diabetes Care. 2018 Apr;41(4):831-839. doi: 10.2337/dc17-2475. Epub 2018 Feb 2.

4. Pinhas-Hamiel O, Levek-Motola N, Kaidar K, Boyko V, Tisch E, Mazor-Aronovitch K, Graf-Barel C, Landau Z, Lerner-Geva L, Frumkin Ben-David R. Prevalence of overweight, obesity and metabolic syndrome components in children, adolescents and young adults with type 1 diabetes mellitus. Diabetes Metab Res Rev. 2015 Jan;31(1):76-84. doi: 10.1002/dmrr.2565.

5. Szadkowska A, Madej A, Ziółkowska K, Szymańska M, Jeziorny K, Mianowska B[1], Pietrzak I. Gender and Age - Dependent effect of type 1 diabetes on obesity and altered body composition in young adults. Ann Agric Environ Med. 2015;22(1):124-8. doi: 10.5604/12321966.1141381.

6. Bellanné-Chantelot C, Lévy DJ, Carette C, Saint-Martin C, Riveline JP, Larger E, Valéro R, Gautier JF, Reznik Y, Sola A, Hartemann A, Laboureau-Soares S, Laloi-Michelin M, Lecomte P, Chaillous L, Dubois-Laforgue D, Timsit J; French Monogenic Diabetes Study Group. Clinical characteristics and diagnostic criteria of maturity-onset diabetes of the young (MODY) due to molecular anomalies of the HNF1A gene. J Clin Endocrinol Metab. 2011 Aug;96(8):E1346-51. doi: 10.1210/jc.2011-0268. Epub 2011 Jun 15.

7. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol. 2018 Feb;6(2):122-129. doi: 10.1016/S2213-8587(17)30362-5. Epub 2017 Nov 30.

8. Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefsen S, White NH, Pollin TI. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. Genet Med. 2018 Jun;20(6):583-590. doi: 10.1038/gim.2017.150. Epub 2017 Oct 12.

9. Oram RA, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A Type 1 Diabetes Genetic Risk Score Can Aid Discrimination Between Type 1 and Type 2 Diabetes in Young Adults. Diabetes Care. 2016 Mar;39(3):337-44. doi: 10.2337/dc15-1111. Epub 2015 Nov 17.

10. Roeyen G, De Block C.A plea for more practical and clinically applicable criteria defining type 3c diabetes. Pancreatology. 2017 Nov - Dec;17(6):875. doi: 10.1016/j.pan.2017.10.004. Epub 2017 Oct 14.

11. Duggan SN. Negotiating the complexities of exocrine and endocrine dysfunction in chronic pancreatitis. ProcNutr Soc. 2017 Nov;76(4):484-494. doi: 10.1017/S0029665117001045. Epub 2017 Jul 24.