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Less common forms of diabetes in young population

Mniej powszechne formy cukrzycy w młodej populacji

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Abstract

Types diabetes other than type 1 are generally considered rare in children and adolescents. The incidence of type 2 diabetes has increased dramatically over the past decade in some ethnic groups. The increased incidence of this type of diabetes mellitus has corresponded temporally to unprecedented increases in body weight and obesity prevalence in adolescents in various ethnic populations. Early treatment of insulin resistance is important to prevent the development of diabetes. In therapy, lifestyle modification is essential for weight loss, and if this is not enough, pharmacotherapy is required. Maturity-onset diabetes of the young (MODY), another type of insulin-dependent diabetes, is characterised by early onset and autosomal dominant inheritance. MODY is mainly caused by β-cell defects, resulting in insufficient insulin secretion for a given blood glucose level. Unlike non-insulin-dependent diabetes in youth (NIDDM-Y), there is no significant increase in insulin resistance. The purpose of this article is to characterise and present types of diabetes other than type 1 found in the young population.
Key words: insulin resistance, type 2 diabetes, youth-onset non-insulin-dependent diabetes mellitus (NIDDM-Y), maturity-onset diabetes of the young (MODY), oral antidiabetic agents.

Streszczenie

Inne typy cukrzycy niż cukrzyca typu 1 są ogólnie uważane za rzadkie u dzieci i młodzieży. Częstość występowania cukrzycy typu 2 dramatycznie wzrosła w ciągu ostatniej dekady w niektórych grupach etnicznych. Zwiększona częstość występowania tego typu cukrzycy odpowiadała czasowo bezprecedensowemu wzrostowi masy ciała i częstości występowania otyłości u nastolatków w różnych populacjach etnicznych. Wczesne leczenie insulinooporności jest ważne dla zapobiegania rozwojowi cukrzycy. W terapii modyfikacja stylu życia jest niezbędna do utraty masy ciała, a jeśli to nie wystarczy, konieczna jest farmakoterapia. Cukrzyca monogenowa MODY, inny typ cukrzycy insulinozależnej, charakteryzuje się wczesnym początkiem i dziedziczeniem autosomalnym dominującym. Cukrzyca MODY jest spowodowana głównie defektami komórek β, co skutkuje niewystarczającym wydzielaniem insuliny dla danego stężenia glukozy we krwi. W przeciwieństwie do cukrzycy insulinoniezależnej u młodzieży (NIDDM-Y) nie występuje znaczący wzrost insulinooporności. Celem artykułu jest scharakteryzowanie i przedstawienie innych typów cukrzycy niż cukrzyca typu 1 występujących w młodej populacji.
Słowa kluczowe: insulinooporność, cukrzyca typu 2, NIDDM-Y, cukrzyca monogenowa MODY, doustne leki przeciwcukrzycowe.

Introduction

Differentiating the types of diabetes mellitus (DM) has a long and unfinished history. Currently, in everyday practice, there is also a division in force since 1999, in which there are 4 types of diabetes: type 1 diabetes mellitus (associated with autoimmune destruction of pancreatic β-cells, usually leading to complete insulin deficiency; T1DM), type 2 diabetes mellitus (associated with progressive loss of adequate insulin secretion by pancreatic β-cells; T2DM), gestational diabetes (diagnosed in the second or third trimester of pregnancy, not being overt diabetes before pregnancy), and certain types of diabetes resulting from other causes, such as monogenic diabetes syndromes (neonatal diabetes and juvenile diabetes with onset in adulthood), exocrine pancreatic diseases (cystic fibrosis and pancreatitis), and diabetes caused by drugs or chemicals [1]. The results of immunological and genetic studies have broadened our knowledge on the aetiopathogenesis of glucose me-

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Table I. Clinical characteristics of T1DM, T2DM, and MODY in a population of children and adolescents based on a review article by Delvecchio *et al.* [37]

Type of diabetes	Clinical features
Type 1 diabetes mellitus	Average age of diagnosis 5–20 years Inheritance polygenic Rare incidence of insulin resistance Frequent occurrence of ketoacidosis Frequent presence of β-cell antibodies Frequent occurrence of polydipsia and polyuria Insulin therapy in treatment
Type 2 diabetes	Average age of diagnosis > 10 years Inheritance polygenic Common incidence of insulin resistance Rare occurrence of ketoacidosis Rare presence of β-cell antibodies Different incidence of polydipsia and polyuria Treatment in the form of diet/oral anti-diabetic drugs/insulin therapy
MODY	Average age of diagnosis < 25 years Inheritance autosomal dominant Rare incidence of insulin resistance Rare occurrence of ketoacidosis Rare presence of β-cell antibodies Different incidence of polydipsia and polyuria Treatment in the form of diet/oral anti-diabetic drugs/insulin therapy

tabolism disorders and require a revision of the currently valid classification of diabetes [2, 3]. There are 2 basic disorders underlying the development of diabetes mellitus: impaired insulin secretion and/or insulin resistance [4].

In diabetes classified as type 2, the predominant disorder is an insulin resistance. Type 2 diabetes is usually associated with excessive accumulation of adipose tissue, and it is a component of so-called "metabolic syndrome" [5]. This type of diabetes is generally considered rare in children and adolescents. The incidence of T2DM has increased dramatically over the past decade in certain ethnic groups [6, 7]. The increased incidence of this type of diabetes mellitus has corresponded to a temporally unprecedented increase in body weight and obesity prevalence in adolescents in various ethnic populations.

Maturity-onset diabetes of the young (MODY), a type other than type 1, is characterised by early onset and autosomal dominant inheritance. MODY is mainly caused by β-cell defects, resulting in insufficient insulin secretion for a given blood glucose level.

The purpose of this article is to characterise and present other types of diabetes found in the young population.

Table I shows the clinical characteristics of T1DM, T2DM, and MODY diabetes in the child and adolescent population.

Type 2 diabetes mellitus in children and youngsters

Type 2 diabetes mellitus is the most common type of diabetes in the general population. However, distinguishing it from other forms of diabetes, including T1DM, monogenic diabetes, or diabetes with onset in adulthood or latent autoimmune diabetes in adults (LADA), is sometimes a challenge in clinical practice. Insulin resistance and hyperinsulinaemia are involved in the pathogenesis of T2DM, with consequent dysfunction of pancreatic β-cells to produce insulin [8, 9]. If suspected, the diagnosis of T2DM can be made on the basis of plasma glucose or glycated haemoglobin (HbA1c) analysis. In clinical practice, the diagnosis of T2DM is made based on the analysis of certain characteristics, such as BMI, or the diagnosis is made after ruling out other types of diabetes [10]. The prevalence of T2DM in children and adolescents correlates strongly with the prevalence of obesity, and numerous studies show that more than 85% of children with T2DM are overweight or obese at the time of diagnosis [11–13]. Determinants of prenatal life [14–16], diet and obesity [17, 18], reduced physical activity [19, 20], as well as female gender [21] and the presence of polycystic ovarian syndrome [22] in women and the presence of nonalcoholic steatohepatitis [23, 24], are considered key factors in the development of T2DM in young people. Another important aspect is that the more cases of diabetes found in the family, the younger the age of onset of T2DM. This means that the genetic risk of T2DM is associated with younger age at diagnosis and younger age at onset of insulin treatment [25]. Poor glycaemic control ultimately leads to serious health complications such as retinopathy, neuropathy and nephropathy, and cardiovascular disease. Studies show early signs of micro- and macrovascular complications, hypertension, dyslipidaemia, and hepatic steatosis in young patients with T2DM. As for the treatment of T2DM, in addition to metformin and insulin [26], the GLP-1 agonist liraglutide, and a representative of SGLT-2 inhibitors, dapagliflozin, have recently been introduced into the treatment of type 2 diabetes in adolescents over 10 years of age [27, 28]. The long-term prognosis of adolescents with T2DM is an object of observation, but it is estimated that adolescents may lose up to 15 years of life expectancy and increase their risk of serious health complications by the time they reach age 40 years, depending on their level of glycaemic control [29].

MODY diabetes

Maturity-onset diabetes of the young (MODY) is a rare, inherited form of diabetes that results from heterozygous mutations in various transcription factors involved in the maturation of pancreatic β-cells [30], as well as mutations in enzymes involved in the detection of glucose in β-cells [31]. The defining characteristics of MODY diabetes are autosomal dominant inheritance, early onset of the disease, usually before the age of 25 years, absence of symptoms related to the autoimmune process or insulin resistance, and preservation of endogenous insulin secretion [32, 33]. The incidence of MODY is 21–45/1,000,000 in

children and 100/1,000,000 in adults [34, 35]. Depending on the circular gene mutations, pathophysiology, and clinical characteristics, there are 14 subtypes of MODY diabetes [36, 37]. Table II shows the characteristics of each type of MODY diabetes. The diagnosis of MODY diabetes is based on the use of genetic testing. Direct sequencing is a technique that can diagnose MODY with up to 100% sensitivity [38]. However, performing genetic tests on individuals without specific criteria can lead to inappropriate results and is not cost-effective, which is a problem in diagnosing MODY. Various algorithms using different clinical and laboratory parameters have been developed to define MODY [36]. Correct diagnosis and differentiation of MODY from T1DM and T2DM are important in deciding patient treatment and determining prognosis, while treatment as well as

Table II. Characterisation of each type of MODY diabetes based on a review article by Ahmet Anık *et al.* [36] and Delvecchio *et al.* [37]

Type of MODY	Gene	Frequency	Clinical features	Options of treatment
1	*HNF4A*	5%	Decreased insulin secretion, low triglycerides, risk of microvascular complications	Diet, sulphonylureas, insulin
2	*GCK*	30–50%	Increased fasting glucose, mild diabetes	Diet, not require anti-diabetes medication
3	*HNF1A*	30–50%	Decreased insulin secretion, progressive β-cell damage, glycosuria, microvascular complications	Sulphonylureas, meglitinides, GLP-1 RA, SGLT-2 inhibitors, insulin
4	*PDX1/IPF1*	1%	Impaired development of the pancreas, In homozygotes pancreatic agenesis	Oral antidiabetic drugs, insulin
5	*HNF1B*	5%	Decreased insulin secretion, additional pancreatic manifestations (kidney cysts or dysplasia, genital abnormalities in women, azoospermia) accompanying diabetes mellitus, end-stage renal failure without diabetic nephropathy is observed at the age of 45 years in half of these individuals, renal signs may be encountered before diabetes, microvascular complications	Early insulin therapy
6	*NEUROD1*	< 1%	Adult-onset diabetes, abnormal β-cell function, majority obese	Oral antidiabetic drugs, insulin
7	*KLF11*	< 1%	Decreased glucose sensitivity of β-cells	Insulin
8	*CEL*	< 1%	Decreased endocrine and exocrine pancreas functions, autosomal dominant diabetes	Insulin
9	*PAX4*	< 1%	Disruption of the processes of β-cell proliferation and apoptosis, possible ketoacidosis	Oral antidiabetic drugs, insulin
10	*INS*	< 1%	Diabetes before age 20	Sulphonylureas or insulin
11	*BLK*	< 1%	Impaired insulin secretion, increased penetration at higher body mass indexes	Diet, oral antidiabetic drugs, insulin
12	*ABCC8*	< 1%	ATP-sensitive potassium channel dysfunction	Sulphonylureas
13	*KCNJ11*	< 1%	ATP-sensitive potassium channel dysfunction	Sulphonylureas
14	*APPL1*	< 1%	Hyperglycaemia; diabetes	Diet, oral antidiabetic drugs, insulin

the presence of long-term vascular complications depend on the MODY diabetes subtype [36]. In patients with mild hyperglycaemia at the time of diagnosis, diet is an effective treatment in most cases. In cases of progressive hyperglycaemia, drug therapy should be implemented. Molecular diagnostics are crucial for choosing the best treatment for most MODY patients. Particularly effective therapeutic options for most types of MODY diabetes are oral hypoglycaemic drugs, in particular, sulphonylureas, which bypass the molecular defect and activate the ATP-sensitive potassium channel [37].

Discussion

Correct diagnosis and distinguishing MODY from T1DM and T2DM are important in deciding patient treatment and determining prognosis, as well as detecting at-risk family members. Patients experience a delay in receiving a diagnosis of MODY from the onset of diabetes, and some patients with MODY diabetes are misdiagnosed with T1DM and T2DM at the time of diagnosis. This indicates that the diagnosis of MODY is rarely considered by many primary care physicians. In everyday practice, when the diagnosis of the type of diabetes is based on the clinical picture and basic laboratory tests, it is relatively common to encounter an incorrect diagnosis of the type of diabetes. According to many authors, in many cases, after some time, it is necessary to verify the initially established type of diabetes [39]. One of the elements constituting the basis for differentiation is the history and assessment of the dynamics of the development of symptoms of the disease. However, it is known that the dynamics of diabetes symptom development does not always allow differentiation of the type of diabetes. Another indicator taken into consideration in establishing the type of diabetes is the presence or absence of obesity. It is worth noting that overweight and obesity also occur in children with T1DM, and this differentiating sign is not as good as it used to be in diagnosing the type of diabetes. If hyperglycaemia is found in an obese or severely overweight patient, this is often, but not always, T2DM. In such cases, it should be checked if it is not diabetes of "other types", i.e. diabetes associated with genetic syndromes, endocrinopathies, or drug-induced diabetes. Often these forms of diabetes run together with obesity. Although T1DM is most common in children and adolescents, all other forms of diabetes, including the increasingly recognised group of monogenic diabetes, may also occur in these age groups. Initial diagnosis of hyperglycaemia or verification of the diagnosis, in addition to routine monitoring of blood glucose, urine sugar and acetone, and HbA1c, includes determination of antibodies to glutamic acid decarboxylase and 1–2 of the following: pancreatic islet cell antibodies – ICA, insulin autoantibodies – IAA, insulinoma associated autoantigen 2 – IA-2, and zinc transporter family member 8 – ZnT8. Determination of C-peptide levels is also very important. This allows assessment of endogenous insulin secretion and confirmation or exclusion of autoimmunity. Determination of C-peptide levels also allows assessment of insulin resistance characteristic of many disease syndromes [40]. It has been shown that C-peptide can help differentiate between T1DM, T2DM, and MODY. C-peptide levels correlate with disease type, duration of diabetes, and age of diagnosis. In insulin-treated patients, low values were found to correlate significantly with T1DM. However, it should be borne in mind that C-peptide, especially at the onset of T1DM, may be within the normal range. C-peptide concentrations have been shown to decrease over the decades with diabetes duration, and diabetes duration was associated with c-peptide values. More recently, it has also been confirmed that c-peptide concentration decreases over time and is significantly associated with age of onset, where younger age (less than 10 years old) results in a significantly faster decline in c-peptide concentration. In contrast, a higher percentage of detectable c-peptide was found in T1DM patients over 18 years of age compared to younger individuals. C-peptide has been proposed as a useful marker in detecting MODY diabetes before genetic testing. In MODY, while there is a reduction in β-cell function, some insulin secretion is preserved compared to T1DM. It should be remembered, however, that while c-peptide is useful in classifying diabetes, it should always be interpreted in the context of disease duration, the presence of comorbidities, and family history. In particular, there are many diagnostic errors in the young adult patient group. If diabetes is diagnosed in patients between 25–30 and 55 years of age, the type of diabetes should be considered very carefully. The correct diagnosis determines the correct treatment. If no autoantibodies are found in young patients with mild diabetes, monogenic diabetes is likely to be suspected. In that case, genetic tests are decisive. Unfortunately, access to these tests is limited for the time being. The possibility of monogenic diabetes should also be considered in patients with gestational diabetes mellitus (GDM). In young patients, T1DM is the most common form of diabetes. However during the last 2 decades an increasing incidence of T2DM in children and adolescents has been observed. This coincides with an increase in the prevalence of overweight and obesity [41]. This type of diabetes differs not only from T1DM but also from T2DM found in adult patients. It is characterised by rapidly progressive β-cell decline, high treatment failure rate, and accelerated development of complications [42]. A comprehensive discussion of issues related to the prevalence of T2DM in the developmental population was recently presented by Valaiyapathi *et al.* [43]. These authors confirmed that in over the past 20 years, the prevalence of T2DM among children and adolescents has increased. This increase in the paediatric age group is associated with an increase in childhood obesity. Genetic conditions are an important factor. The main factors are the occurrence of insulin resistance, as well as a deficit in insulin secretion. Impaired insulin secretion is a result of defective production in β-cells as well as decreased β-cell mass. The more aggressive course of T2DM in adolescent patients is confirmed by other authors [44].

In treating T2DM, as in adults, diet and increased physical activity are the cornerstones [45]. If symptoms persist despite lifestyle changes, which is common in pubertal adolescents when disease-related insulin resistance adds up to physiologi-

cal insulin resistance, the inclusion of pharmacotherapy may be needed. The drug of choice was metformin, which is considered safe in children and adolescents [46]. Metformin plays an important role in the prevention of T2DM in people with abdominal obesity. It improves glucose tolerance and impedes the conversion of the pre-diabetic state to T2DM [47]. Many authors have noted its usefulness in the treatment of glucose tolerance disorders in adolescent patients [48]. This is supported by extensive randomised trials [49]. Attempts have also been made to use other drugs [50–53]. There are now reports of other drugs being used in young patients as well [54]. There are no clear recommendations for the treatment of pre-diabetic conditions in adolescent patients [55]. As mentioned earlier, liraglutide and dapagliflozin have recently been introduced for the treatment of T2DM in adolescents. The authors presented the results of a randomised trial of glucagon-like peptide-1 (GLP-1) agonists in T2DM, pre-diabetes, and obesity in children aged < 18 years. They found that GLP-1 agonists are efficacious in treating children with obesity and/or T2DM. Effect sizes are comparable with those reported in adults. The effectiveness of GLP-1 agonists therapy, especially in pre-diabetic state, is also pointed out by other authors [56]. These studies suggest that further observations are needed regarding the indications and safety of modern therapy for T2DM in adolescent patients [42]. The significant increase in the prevalence of obesity in children and adolescents over past decades caused a concomitant rise in the incidence of glucose intolerance and diabetes. Young patients develop clinical DM and complications more rapidly and aggressively. Therefore, early diagnosis, prevention, and treatment of disorders are important. Referring to the International Society for Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2022 [57], there are certain features that, taken together, may suggest monogenic diabetes in children initially suspected of having T1DM. The significant increase in obesity in children and adolescents has meant that children and adolescents with monogenic diabetes can also be obese and very difficult to distinguish from T2DM. For such cases there are also certain characteristics that can be taken into account in verifying the diagnosis.

Conclusions

Becoming more familiar with other types of diabetes in the young population is an extremely important element in daily medical practice because misdiagnosis of the type of diabetes and inadequate treatment can translate into a reduction in the patient's quality of life and health. Thus, it is worth paying attention to the increasing prevalence of T2DM in the young population, not forgetting the monogenic types of diabetes, the clinical picture of which may confusingly resemble the most common types of diabetes.

References

1. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020; 43 (Suppl 1): S14–S31. doi: 10.2337/dc20-S002.
2. Elsayed NA, Aleppo G, Aroda VR, et al. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. Diabetes Care 2023; 46: S19–S40. doi: 10.2337/dc23-S002.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37 (Suppl. 1): 81–90. doi: 10.2337/dc14-S081.
4. Park SY, Gautier JF, Chon S. Assessment of insulin secretion and insulin resistance in human. Diabetes Metab J 2021; 45: 641–654. doi: 10.4093/DMJ.2021.0220.
5. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am 2014; 43: 1–23. doi: 10.1016/j.ecl.2013.09.009.
6. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 2011; 8: 228–236. doi: 10.1038/nrendo.2011.183.
7. Cizza G, Brown RJ, Rother KI. Rising incidence and challenges of childhood diabetes. A mini review. J Endocrinol Invest 2012; 35: 541–546. doi:10.3275/8411.
8. Wysham C, Shubrook J. Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications. Postgrad Med 2020; 132: 676–686. doi:10.1080/00325481.2020.1771047.
9. Chen C, Cohrs CM, Stertmann J, et al. Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis. Mol Metab 2017; 6: 943–957. doi: 10.1016/j.molmet.2017.06.019.
10. Ahmad E, Lim S, Lamptey R, et al. Type 2 diabetes. Lancet 2022; 400: 1803–1820. doi:10.1016/S0140-6736(22)01655-5.
11. Arslanian SA. Type 2 diabetes mellitus in children: pathophysiology and risk factors. J Pediatr Endocr Met 2000; 13 Suppl 6: 1385–1394. doi: 10.1515/jpem-2000-s612.
12. Rosenbloom AL, Silverstein JH, Amemiya S, et al. ISPAD Clinical Practice Consensus Guidelines 2007-2007. Type 2 diabetes mellitus in the child and adolescent. Pediatr Diabetes 2009; 9: 512–526. doi: 10.1111/j.1399-5448.2008.00429.x.
13. Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr 2000; 136: 664–672. doi:10.1067/mpd.2000.105141.
14. Vrachnis N, Antonakopoulos N, Iliodromiti Z, et al. Impact of maternal diabetes on epigenetic modifications leading to diseases in the offspring. Exp Diabetes Res 2012; 2012: 538474. doi: 10.1155/2012/538474.
15. Pettitt DJ, Lawrence JM, Beyer J, et al. Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. Diabetes Care 2008; 31: 2126–2130. doi: 10.2337/dc08-0769.
16. Jiang X, Ma H, Wang Y, Liu Y. Early life factors and type 2 diabetes mellitus. J Diabetes Res 2013; 2013: 485082. doi: 10.1155/2013/485082.
17. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease

Study 2013. Lancet 2014; 384: 766–781. doi: 10.1016/S0140-6736(14)60460-8.
18. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002; 360: 473–482. doi: 10.1016/S0140-6736(02)09678-2.
19. Gustat J, Srinivasan SR, Elkasabany A, Berenson GS. Relation of self-rated measures of physical activity to multiple risk factors of insulin resistance syndrome in young adults: the Bogalusa Heart Study. J Clin Epidemiol 2002; 55: 997–1006. doi: 10.1016/s0895-4356(02)00427-4.
20. Carnethon MR, Gidding SS, Nehgme R, et al. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA 2003; 290: 3092–3100. doi: 10.1001/jama.290.23.3092.
21. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al, for the SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. N Engl J Med 2017; 376: 1419–1429.
22. Joham AE, Ranasinha S, Zoungas S, et al. Gestational diabetes and type 2 diabetes in reproductive-aged women with polycystic ovary syndrome. J Clin Endocrinol Metab 2014; 99: e447–e452. doi: 10.1210/jc.2013-2007.
23. Hecht L, Weiss R. Nonalcoholic fatty liver disease and type 2 diabetes in obese children. Curr Diab Rep 2014; 14: 448. doi: 10.1007/s11892-013-0448-y.
24. Bloomgarden ZT. Nonalcoholic fatty liver disease and insulin resistance in youth. Diabetes Care 2007; 30: 1663–1669. doi: 10.2337/dc07-zb06.
25. Molyneaux L, Constantino M, Yue D. Strong family history predicts a younger age of onset for subjects diagnosed with type 2 diabetes. Diabetes Obes Metab 2004; 6: 187–194. doi: 10.1111/j.1462-8902.2004.00330.x.
26. Pulgaron ER, Delamater AM. Obesity and type 2 diabetes in children: Epidemiology and treatment. Curr Diab Rep 2014; 14: 1–21. doi: 10.1007/s11892-014-0508-y.
27. Chadda KR, Cheng TS, Ong KK. GLP-1 agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis. Obes Rev 2021; 22: e13177. doi: 10.1111/obr.13177.
28. https://www.astrazeneca.pl/content/dam/az-pl/SPC/SPC_Forxiga_5mg.pdf.
29. Rhodes ET, Prosser LA, Hoerger TJ, et al. Estimated morbidity and mortality in adolescents and young adults diagnosed with type 2 diabetes mellitus. Diabet Med 2012; 29: 453–463. doi: 10.1111/j.1464-5491.2011.03542.x.
30. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care 2011; 34: 1878–1884. doi: 10.2337/dc11-0035.
31. Osbak KK, Colclough K, Saint-Martin C, et al. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. Hum Mutat 2009; 30: 15. doi: 10.1002/humu.21110.
32. McDonald TJ, Colclough K, Brown R, et al. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet Med 2011; 28: 1028–1033. doi: 10.1111/j.1464-5491.2011.03287.x.
33. Owen KR, Roland J, Smith K, Hattersley AT. Adolescent onset Type 2 diabetes in a non-obese Caucasian patient with an unbalanced translocation. Diabet Med 2003; 20: 483–485. doi: 10.1046/j.1464-5491.2003.00961.x.
34. Kropff J, Selwood MP, McCarthy MI, et al. Prevalence of monogenic diabetes in young adults: a community- based, cross-sectional study in Oxfordshire, UK. Diabetologia 2011; 54: 1261–1263. doi: 10.1007/s00125-011-2090-z.
35. Pihoker C, Gilliam LK, Ellard S, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013; 98: 4055–4062. doi: 10.1210/jc.2013-1279.
36. Anik A, Çatli G, Abaci A, Böber E. Maturity-onset diabetes of the young (MODY): An update. J Pediatr Endocrinol Metab 2015; 28: 251–263. doi: 10.1515/jpem-2014-0384.
37. Delvecchio M, Pastore C, Giordano P. Treatment Options for MODY Patients: A Systematic Review of Literature. Diabetes Ther 2020; 11: 1667–1685. doi: 10.1007/s13300-020-00864-4.
38. Kavvoura FK, Owen KR. Maturity onset diabetes of the young: clinical characteristics, diagnosis and management. Pediatr Endocrinol Rev 2012; 10: 234–242.
39. Chwalba A, Otto-Buczkowska E. Correct diabetes types differentiation – An ongoing problem. Int J Sci Res 2018; 7: 816–819.
40. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther 2017; 8: 475–487. doi: 10.1007/s13300-017-0265-4.
41. Chwalba A, Otto-Buczkowska E. Metabolic syndrome is the problem in young diabetics? Fam Med Sci 2014; 3: 2–7.
42. Serbis A, Giapros V, Kotanidou EP, et al. Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents. World J Diabetes 2021; 12: 344–365. doi: 10.4239/wjd.v12.i4.344.
43. Valaiyapathi B, Gower B, Ashraf AP. Pathophysiology of Type 2 Diabetes in Children and Adolescents. Diabetes Rev 2020; 16: 220–229. doi: 10.2174/1573399814666180608074510.
44. Arslanian S, Bacha F, Grey M, et al. Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association. Diabetes Care 2018; 41: 2648–2668. doi: 10.2337/dci18-0052.
45. Esquivel Zuniga R, DeBoer MD. Prediabetes in Adolescents: Prevalence, Management and Diabetes Prevention Strategies. Diabetes Metab Syndr Obes 2021; 14: 4609–4619. doi: 10.2147/DMSO.S284401.
46. Otto-Buczkowska E, Jarosz-Chobot P. Alterations of blood glucose homeostasis in children and adolescents – what news in diagnostics and therapy? Part I. Med Rodz 2008; 11: 11–18.
47. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care 2012; 35: 731–737. doi: 10.2337/dc11-1299.
48. Bassols J, Martínez-Calcerrada JM, Osiniri I, et al. Effects of metformin administration on endocrine-metabolic parameters, visceral adiposity and cardiovascular risk factors in children with obesity and risk. PLoS One 2019; 14: e0226303. doi: 10.1371/journal.pone.0226303.
49. TODAY Study Group; Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012; 366: 2247–2256. doi: 10.1056/NEJMoa1109333.

50. Gottschalk M, Danne T, Vlajnic A, et al. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. Diabetes Care 2007; 30: 790–794. doi: 10.2337/dc06-1554.
51. Otto-Buczkowska E, Nowowiejska B, Jarosz-Chobot P, Stańczyk J. [Could be useful oral antidiabetic agents in the management of children and adolescents with different types of diabetes and insulin resistance?] Przegl Lek 2009; 66: 388–393.
52. Otto-Buczkowska E, Machnica Ł. The perspectives of adjunctive drugs usage in treatment of glucose metabolism disturbances in adolescent patients. Pediatr Endocrinol Diabetes Metab 2009; 15: 260–265.
53. TODAY Study Group, Zeitler P, Epstein L, et al. Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. Pediatr Diabet 2007; 8: 74–87. doi: 10.1111/j.1399-5448.2007.00237.x.
54. Singhal S, Kumar S. Current Perspectives on Management of Type 2 Diabetes in Youth. Children (Basel) 2021; 8: 37. doi: 10.3390/children8010037.
55. Magge SN, Silverstein J, Elder D, et al. Evaluation and Treatment of Prediabetes in Youth. J Pediatr 2020; 219: 11–22. doi: 10.1016/j.jpeds.2019.12.061.
56. Zhou QX, Wang ZY, Zhao HF, Wang S. The effects of GLP-1 analogues on pre-diabetes of the children. Exp Ther Med 2017; 13: 1426–1430. doi: 10.3892/etm.2017.4129.
57. Greeley SAW, Polak M, Njølstad PR, et al. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2022; 23: 1188–1211. doi: 10.1111/pedi.13426.