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Youth-Onset Type 2 Diabetes Manifestations in other Specialties: Its Many Disguises

Daniel Weghuber[a] Margarita Barrientos-Pérez[b] Margarita Kovarenko[c]

[a]Department of Pediatrics, Paracelsus Medical School, Salzburg, Austria; [b]Servicio de Endocrinología Pediátrica, Angeles Hospital of Puebla, Puebla, Mexico; [c]Department of Pediatrics, Novosibirsk Medical University, Novosibirsk, Russia

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Abstract
Background: Youth-onset type 2 diabetes (T2D) is increasing in many countries, creating large personal and societal burdens. While many primary health-care professionals (HCPs) are aware of the classic symptoms of T2D, there are several other manifestations that could indicate its presence. ***Summary:*** This narrative review summarizes information on these symptoms and indicators, focusing on those less well known. The classic symptoms and comorbidities include frequent urination, excessive thirst, metabolic syndrome, and obesity. In addition to these, the presence of dermatological (e.g., acanthosis nigricans, granuloma annulare, necrobiosis lipoidica diabeticorum, and scleredema), gynecological (e.g., polycystic ovary syndrome, oligomenorrhea, and vulvovaginitis), hepatological (e.g., nonalcoholic fatty liver disease), and psychiatric diseases (e.g., psychosis, depression, and autism) could indicate that a patient has T2D or is at increased risk of T2D. Other less well-known indicators include abnormal blood tests (e.g., oxidized lipids, inflammation markers, hepatokines, and adipokines), prescriptions for antipsychotic medications or statins, and disrupted sleep patterns. ***Key Message:*** Due to the diversity of T2D manifestations in young people, primary HCPs need to remain alert to its possible presence.

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Daniel Weghuber
Department of Pediatrics
Paracelsus Medical School
Strubergasse 22, AT–5020 Salzburg (Austria)
E-Mail d.weghuber@salk.at

Introduction

Diabetes is an increasing global problem, with more than 620 million adults estimated to have diabetes by 2,045, and 90% of cases are likely to be type 2 diabetes (T2D) [1]. This problem has been evident in adults for some time, but only recently has T2D emerged as a pediatric disease [1]. The documented prevalence of T2D in children and adolescents ranges from <2/10,000 cases per non-Hispanic White population to ~12/10,000 cases per American Indian population [2]. However, the incidence of youth-onset T2D (diagnosis of T2D in those ≤25 years of age) is increasing annually by 7.1% in some countries [3], a worrying trend for health-care professionals (HCPs).

Youth-onset T2D creates large personal and societal burdens [2, 4]. For example, children and adolescents with T2D had reduced quality of life at the end of the 60-month SEARCH trial (compared with baseline and with participants with T1D) [5]. As with adult T2D, patients with youth-onset T2D are at risk of serious complications [6]. Microvascular, renal, and neurological complications may be evident 5 years post-diagnosis [4], with more serious complications such as blindness developing within 10 years from diagnosis [2]. These individual burdens combine to create a potentially large societal impact [3], particularly if the disease remains undetected and untreated.

Primary care physicians, general practitioners, and pediatricians see children and adolescents daily for many reasons. These HCPs screen for diabetes regularly, but sometimes patients may be asymptomatic or mildly symptomatic for youth-onset T2D [7, 8], or present with another condition obscuring T2D [4]. While there are classic symptoms and risk factors of youth-onset T2D [8, 9], there are several other manifestations that could indicate whether it is appropriate to screen for this disease (Table 1).

This narrative review includes information on both classic and less well-known indicators, to inform all HCPs of the many different ways in which youth-onset T2D may present in a clinical setting.

Methods

This review was performed through searching PubMed for articles in this field. Of 633 articles found, 69 were selected and included in the review. The detailed methods used are provided in the online supplemental Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000500234).

Results/Discussion

Well-Known Symptoms, Indicators, Risk Factors, and Comorbidities

Similar to adult T2D, the classic symptoms for youth-onset T2D include frequent urination and excessive thirst (online suppl. Table S2) [1, 8, 9]. Symptoms specific to young people include unexplained weight loss, growth impairment, and bed wetting (online suppl. Table S2) [8, 9]. These true diabetes-related symptoms are rather unspecific in nature.

Also similar to adult T2D, lifestyle factors and family history play an important role in the risk of youth-onset T2D (online suppl. Table S2). For example, smoking and reduced physical activity are associated with this disease [1, 10, 11]. In some countries (e.g., the United States), low socioeconomic status is associated with an increased risk of youth-onset T2D [2, 8, 12, 13] but, in others (e.g., China), children from more affluent families are more likely to have this disease [8]. Family history of T2D [12], ethnicity/race [3, 13], exposure to diabetes in utero [13], and children born small or large for gestational age [8, 12, 14] are other well-known risk factors for all T2D types [1, 8, 14].

There are 2 comorbidities with well-established links to youth-onset T2D: metabolic syndrome and obesity (online suppl. Table S2) [1, 15]. Although obesity is one of the metabolic syndrome parameters, its link with youth-onset T2D has been investigated separately (e.g., [16, 17]). Children and adolescents from the United Kingdom who were within the obesity category had a 4.3 greater risk of T2D compared with their normal-weight peers [16]. A similar increased risk for children with obesity was also found in a prospective study of American Indians, where the relative risk of developing T2D ranged from 2.3 to 7.4, depending on gender, age, and degree of overweight [17]. Due to this association, a consortium of leading pediatric obesity centers in the United States published guidelines recommending that all children with obesity be screened regularly for T2D using a fasting glucose test [18].

Less-Known Comorbid Associations with Youth-Onset T2D

In addition to the well-characterized indicators and symptoms associated with youth-onset T2D, there are other comorbidities and complications that are less well known to primary HCPs (Table 1). Drawing on our expertise in pediatric endocrinology, gastroenterology, hepatology, and nutrition, we highlight conditions that

Table 1. Less-known comorbidities and indicators of youth-onset T2D likely to be encountered in primary care

Comorbidities	Blood test results	Detailed medial history
– *Dermatology:* AN [7, 12, 19–21, 24, 44, 46, 68], granuloma annulare [21, 22], NLD [20–22], scleredema [20] – *Gynecology:* PCOS [7, 23, 24, 44, 46], irregular menses [25, 26], oligomenorrhea [23], vulvovaginitis [28] – *Hepatology:* NAFLD/hepatic steatosis [11, 29, 30, 44] – *Mental health/psychiatry [34]:* psychosis [36], depression [5, 35], autism spectrum disorder [33], binge eating [37, 38], ADHD [32] – *Genetic syndromes:* WBS [41], TS [39, 40], lipodystrophy [42], others [39] – *Other:* periodontitis [43]	– Inflammation markers/hormone levels/hepatokines [45, 50–53] – Alanine aminotransferase [69] – PEDF [54] – Vitamin D levels [45, 55]	– Use of antipsychotic medications [34, 58, 59], specifically atypical antipsychotics [60, 61] – Use of antidepressants [62] – Use of statins, when no dyslipidemia present [63] – Abnormal sleep patterns [37, 64]

ADHD, attention-deficient/hyperactivity disorder; AN, acanthosis nigricans; NAFLD, nonalcoholic fatty liver disease; NLD, necrobiosis lipoidica diabeticorum; PCOS, polycystic ovary syndrome; PEDF, pigment epithelium derived factor; T2D, type 2 diabetes; TS, turner syndrome; WBS, Williams-Beuren syndrome.

normally result in a referral to another specialty, but that may also indicate youth-onset T2D. These conditions with under-recognized links to youth-onset T2D are usually related to 5 specialties.

Dermatology

Some skin conditions may be an indicator of the presence of T2D in children and adolescents. The most common of these is acanthosis nigricans (AN), which is skin hyperpigmentation affecting the armpits, neck folds, flexor skin muscles, and umbilicus [19–21] (Fig. 1). AN has been demonstrated as a reliable marker for insulin resistance in children and adolescents with obesity, and the percentage with AN and insulin resistance or T2D is related to ethnicity, varying from 3% in Caucasians to 73% in Hispanics [19]. Other diabetes-associated dermatological conditions are rare in children, but could be warning indicators. These include granuloma annulare [21, 22], necrobiosis lipoidica diabeticorum [20–22], and scleredema [20]. Granuloma annulare consists of small circular patches of pink/purple skin, up to 5 cm in diameter, and necrobiosis lipoidica diabeticorum causes yellow-brown skin plaques with an atrophied center [22]. Scleredema presents as pitting on the neck and surrounding areas [20]. Further studies are needed to investigate if these dermatology conditions are true risk factors of youth-onset T2D, or simply coincidental to its complications [22].

Such dermatological presentations are possibly the result of persistent hyperglycemia and hyperinsulinemia in youth-onset T2D, leading to vascular basement membrane changes and alterations to the insulin-like growth factor-1 signaling pathway [20]. Signaling alterations due to T2D may also trigger production of lymphokines and activation of collagenase [21]. Such changes in signaling could disrupt cellular growth and differentiation, eventually causing visible changes to the skin [20].

Gynecology

Within 2 years postmenarche, menstruation should be regular, and any persistent irregularity may result in a referral to a gynecologist. If the patient has hyperandrogenism, chronic oligomenorrhea, and polycystic ovarian morphology, she is likely to be diagnosed with polycystic ovary syndrome (PCOS) [23]. Visible manifestations of PCOS include hirsutism, acne, and hair loss [23] (Fig. 1). Although the link between PCOS and development of adult T2D is well established, data surrounding youth-onset T2D are limited [23].

In pediatric studies, PCOS was reported as a comorbidity with newly diagnosed T2D in 1.1 and 15.6% of children and adolescents (Aboriginal and Caucasian, respectively) [24]. This high percentage of patients with both PCOS and T2D in certain ethnic groups demonstrates the possible usefulness of PCOS in identifying girls at risk of youth-onset T2D.

Oligomenorrhea, a PCOS symptom [23], also correlates with youth-onset T2D in those up to 24 years of age [25]. Adolescent girls (14–19 years of age) with at least

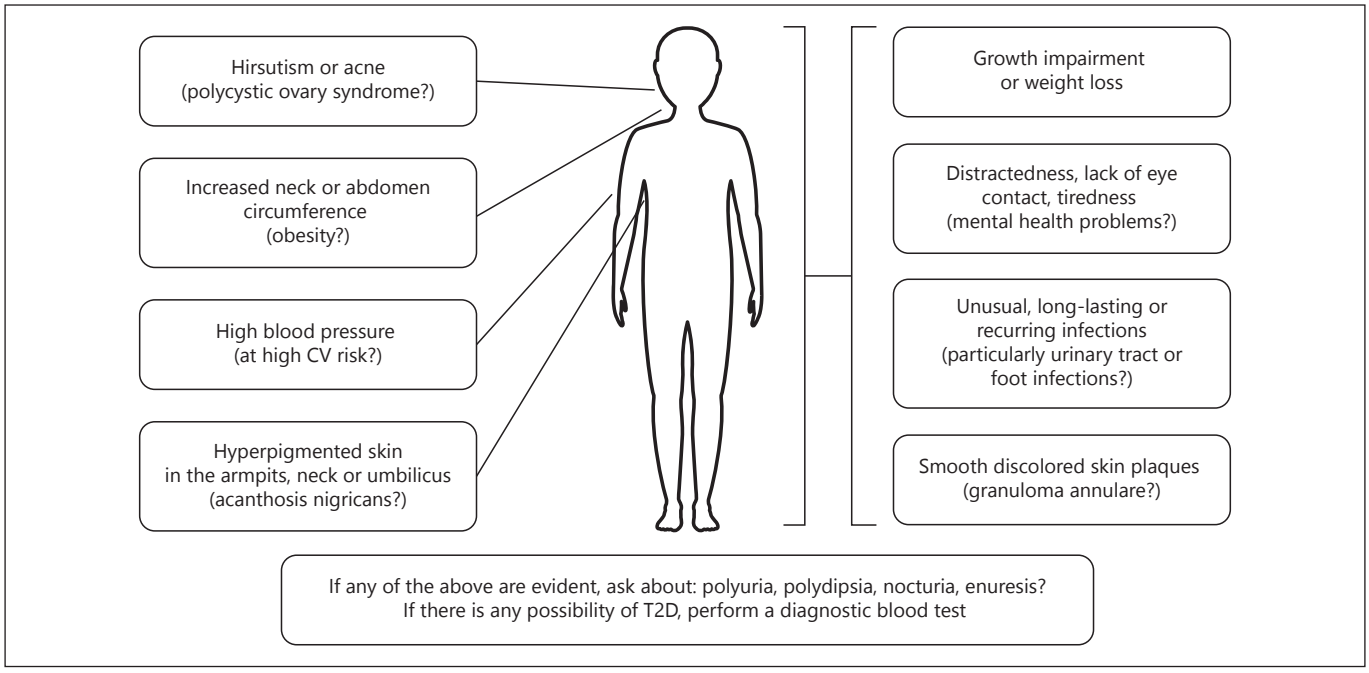

Fig. 1. Symptoms and comorbidities during a physical exam indicating that youth-onset T2D may be present. CV, cardiovascular; T2D, type 2 diabetes.

3 delayed menstrual cycles were 6.5 times more likely to develop impaired fasting glucose and T2D when they were young adults (19–24 years of age) than those who never had a delayed cycle [25]. Similarly, the broad symptom of irregular menses was present in 20.5% of girls with T2D, which appeared higher than prevalence rates for healthy populations [26]. Any indication of individual PCOS symptoms should prompt a primary care professional to explore if youth-onset T2D may also be present [23, 25].

In adolescent girls with such conditions, there are high testosterone levels compared with those without PCOS/irregular menses [26, 27]. Such increases in testosterone may be due to systemic insulin resistance, which alters both ovarian androgen and sex hormone-binding globulin production [26]. Lipotoxicity may also play a role in the pathway linking PCOS with T2D [23].

Vulvovaginitis is another gynecological condition that may be related to youth-onset T2D, as cases have been reported in patients 13–16 years of age who were subsequently found to have youth-onset T2D [28]. Although a susceptibility to certain infections can accompany chronic hyperglycemia [9], this association may be overlooked in gynecological infections. When a girl presents with such an infection, the HCP should consider the presence of T2D.

Hepatology

Liver disease may have many underlying causes, but it is associated with adult and youth-onset T2D [29]. In 2016, Newton et al. [29] published the first multicenter study in children and adolescents with nonalcoholic fatty liver disease (NAFLD) assessing the prevalence of prediabetes and T2D. Children with prediabetes and T2D were at 2 and 3 times (respectively) greater risk of nonalcoholic steatohepatitis than the normal-glucose group [29]. These data reflect an earlier study, which also measured liver triglyceride content and showed that children with T2D were twice as likely to have hepatic steatosis compared with weight-matched normoglycemic controls [11]. Data from a third study showed that 18.2% of pediatric patients had T2D when they were diagnosed with NAFLD [30]. These 3 studies indicated that NAFLD is associated with youth-onset T2D. Physical symptoms of NAFLD are relatively nonspecific, and include headache, irritability, muscle aches, and abdominal swelling [31].

To date, there is no prospective longitudinal study that investigated if NAFLD precedes or follows development of youth-onset T2D, but some evidence suggests that NAFLD comes first [29]. Systemic insulin resistance may be important in the pathology of both diseases. It is unknown why some adolescents manifest in-

sulin resistance as NAFLD first and then develop youth-onset T2D, whereas in others this happens in the opposite order.

Mental Health/Psychiatry

Outside the psychiatry and mental health specialties, not many HCPs may be aware that links exist between certain mental health disorders and youth-onset T2D. Patients with psychosis, depression, autism, binge eating, and attention-deficit/hyperactivity disorder may be at increased risk of youth-onset T2D [5, 32–38].

Genetic Syndromes

There are also links between youth-onset T2D and certain genetic syndromes. Analysis of a German, Austrian, and Swiss database showed that diabetes is linked with Down's syndrome, Turner syndrome, and Prader-Willi syndrome [39]. The link between Turner syndrome and youth-onset T2D was strengthened by a case-controlled, cross-sectional study [40]. Williams-Beuren syndrome and lipodystrophy have also been associated with youth-onset T2D [41, 42]. As these genetic syndromes are very diverse, there is no known common underlying pathology linking them to T2D [39].

Other

Other comorbidities may also be linked to youth-onset T2D, but have yet to be investigated in detail. For example, while it is known that patients with T2D are at risk of periodontitis, there is now evidence that patients with periodontitis are at risk of T2D [43]. Chronic periodontitis is typically seen as inflammation of the gingival margin and can lead to destruction of the bone and ligaments supporting the teeth [43]. This relationship has yet to be explicitly investigated in pediatrics [43].

Early Diabetes-Related Complications that Might be Mistaken for a Primary Diagnosis

Patients with youth-onset T2D may initially present to HCPs with symptoms of an early complication such as disturbed vision, unusual foam in urine, numbness in the extremities, or shortness of breath. These early complications include retinopathy [6], albuminuria/nephropathy [6, 12, 24, 44], neuropathy [6], or endothelial dysfunction [45], leading to macrovascular disease [6].

Even in children and adolescents, T2D leads to severe complications [6]. For some of these (microalbuminuria, hypertension, neuropathy, and mortality), the risk is increased with youth-onset T2D versus T1D [6]. Such complications may be evident within 2–5 years of T2D diagnosis [4, 46], but they have also been recorded at diagnosis [24], making it important for HCPs to be aware of the overlap between the occurrence of the complication and the diagnosis of youth-onset T2D.

Chance Investigative Findings in Medical Assessments that Could Signal Youth-Onset T2D

As mentioned, T2D alters cellular signaling and a blood test may detect differences in certain chemicals prior to physical symptoms (Table 1). First, oxidized lipids [47], lipoprotein-associated phospholipase A2 [48], and proprotein convertase subtilisin/kexin type 9 [49] can be altered in patients with undiagnosed youth-onset T2D. Proprotein convertase subtilisin/kexin type 9 was only measured at an elevated level in females (not males) with youth-onset T2D compared with normal weight, no-diabetes controls [49].

Second, inflammation may link some comorbidities and T2D. Some inflammation markers that predict microvascular disease could be linked with dyslipidemia and T2D [45]. A hyperactive immune system in children and adolescents with T2D may play a role in the development of T2D [50].

Liver-derived hormones (hepatokines) and adipose-derived hormones (adipokines) may be linked to T2D. Leptin levels were lower, and fibroblast growth factor 21 and feutin higher, in those with obesity and youth-onset T2D versus weight-matched controls, possibly reflecting the increased insulin resistance in those patients [51–53].

Other blood tests that may indicate youth-onset T2D include pigment epithelium-derived factor [54] and vitamin D [45, 55] levels. Increased pigment epithelium-derived factor levels have been associated with AN in adolescents with obesity [56], and it may be that its levels increase in blood before AN is evident. The presence of micronuclei indicates oxidative damage of DNA and could be a marker of youth-onset T2D [57]. Due to the disparate nature of this list, it is uncertain if these play a role in the pathogenesis of T2D or result from its presence.

Less-Known Indicators of Youth-Onset T2D within Medical Histories

When taking a detailed medical history of children or adolescents, HCPs should be alert to the less-known risk factors for youth-onset T2D (Table 1).

A number of studies have analyzed large databases to uncover trends in medications and risk of developing youth-onset T2D [34, 58–63]. Antipsychotic medications, specifically atypical antipsychotics, and antidepressants may increase the risk of developing youth-onset

T2D. When adolescents are treated with antipsychotics for ≥3 months, they are at 1.8 times increased risk of developing T2D compared with nontreated patients with similar psychiatric diagnoses [34]. Similarly, in those currently using antidepressants, there is a 1.9 times increased risk of developing T2D compared with those who had formerly used such medications [62].

Statin use by children without dyslipidemia increased their risk of youth-onset T2D [63]. In children with dyslipidemia prior to statin treatment, there was no such increased risk [63]. These data are from an insurance claims database [63], so no data were available as to why children without dyslipidemia were prescribed statins.

Another less-known indicator of youth-onset T2D is a disrupted sleep pattern, examined in a few studies [37, 64, 65]. Sleep duration was found to be inversely associated with body mass index, insulin resistance, and fasting glucose [64], and daytime sleepiness in girls was associated with binge-eating, placing them at greater risk of youth-onset T2D [37]. Finally, while no direct association was found between obstructive sleep apnea and youth-onset T2D, there was an association between obstructive sleep apnea and plasma C-reactive protein in children, indicating that it may be involved in T2D development [65]. These sleep-disruption studies indicate these patients may also be at risk of T2D.

Diagnostic Tests for Youth-Onset T2D

If a patient presents with classic T2D symptoms or more than one of the indicators (online suppl. Table S2, Table 1, and Fig. 1), a diagnostic blood test is needed [8, 14, 66], followed by a type-distinguishing test [8]. Symptoms of diabetes plus random plasma glucose concentration ≥11.1 mmol/L (200 mg/dL), or glycated hemoglobin (HbA_{1c}; ≥6.5%, 48 mmol/mol), or fasting plasma glucose (FPG; ≥7.0 mmol/L, 126 mg/dL), or 2 h plasma glucose during an oral glucose tolerance test (≥11.1 mmol/L, 200 mg/dL) may be used for diagnosing diabetes of either type [9, 14]. There is, however, debate as to the suitability of HbA_{1c} [14, 67], particularly the precise value to use, with some suggesting that lower than the 6.5% currently recommended in adults should be used [67]. For its durability and lack of fasting requirement, the American Diabetes Association recommends HbA_{1c} as one of the diagnostic criteria of youth-onset T2D [14, 66].

Even if children and adolescents do not have classic (online suppl. Table S2) or physical symptoms (Fig. 1), the American Diabetes Association recommends that they should be screened if they are overweight for their age and have at least one of the following:

– Family history of T2D in a close relative;

– Race/ethnicity is Native American, African American, Latino, Asian American, or of Pacific Islander descent;

– Maternal history of diabetes when the child was in utero [14].

However, the International Society of Pediatric and Adolescent Diabetes cautions that screening may be cost-effective only in specific situations, such as research settings [8].

Once it is established that a child or adolescent has diabetes, further tests are needed to determine the type [8, 9]. Distinguishing between the 2 types in pediatric patients can be difficult, due to overlap in initial symptoms and the growing obesity problem [2, 9]. Although children with youth-onset T2D rarely present prior to puberty [8], differentiating diabetes type solely based on age at diagnosis should never be considered. Measurement of diabetes autoantibodies (glutamic acid decarboxylase 65, tyrosine phosphatase-link insulinoma, and β-cell-specific zinc transporter 8) is recommended to confirm the diabetes type [9], but it is costly [8]. Definitively identifying the diabetes type has important implications for the treatment and education needed [8, 9].

Conclusion

Many diverse comorbidities are associated with youth-onset T2D, including those typically seen by dermatologists, gynecologists, and hepatologists. All primary HCPs need to look beyond the symptoms for which a child or adolescent initially attends a clinic appointment to determine if youth-onset T2D may also be present.

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Statement of Ethics

The authors have no ethical conflicts to disclose, as this is a review, and did not need to obtain consent from patients. Novo Nordisk funded the medical writing support for this review but, other than reviewing for medical accuracy, had no input into this manuscript.

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Author Contributions

All authors conceived this review, contributed to the search terms, examined the search results, and advised on the precise topics to be included. They reviewed the outline and subsequent drafts and approved the final draft for submission.

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