Pediatric Type 1 diabetes: adjunctive therapies, celiac disease and the role of the primary care physician

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If & when should insulin-sensitizing agents be considered in children and/or adolescents with Type 1 diabetes?

■ **Paola Luca & Jill Hamilton**

Why is it that metabolic control can be more challenging for adolescents?

It is well established that metabolic control is more challenging once individuals with Type 1 diabetes (T1D) enter puberty. The Diabetes Control and Complications Trial (DCCT) demonstrated that adolescents' hemoglobin A1c levels were on average 1% higher compared with adults in both the conventional and intensive treatment groups [1]. One possible reason for this is an exaggeration of the normal insulin resistance of puberty, caused by increased growth hormone (GH) levels during this period of development. In adolescents with T1D, GH levels are further elevated owing to lower circulating IGF-I, which in turn is believed to be related to the lack of portal insulin delivery and subsequent lower levels of IGF-binding proteins. This leads to increasing insulin requirements and more rapid weight gain [2]. Furthermore, adolescence is a time when many psychosocial factors, such as increasing independence and decreased adherence to insulin administration and glucose monitoring, contribute to worsening glycemic control.

What adjunctive therapies to insulin are available & what do we know about these?

Several drugs have been evaluated as potential adjunctive therapies to insulin in T1D, including insulin sensitizers (i.e., metformin and thiazolidinediones), recombinant human IGF-I, and drugs that slow gastric emptying and suppress glucagon (i.e., amylin and agents that increase GLP-1).

Of these, only metformin has been studied in detail. Metformin acts as an insulin sensitizer by decreasing hepatic glucose production and to a lesser extent by increasing peripheral insulin sensitivity [3,4]. It has also been studied extensively in adults with Type 2 diabetes, in adolescents with Type 2 diabetes and adolescents with obesity and polycystic ovary syndrome. A recent Cochrane review on metformin added to insulin therapy for adolescents with T1D concluded that there is evidence for its use in adolescents with poorly controlled T1D who show signs of insulin resistance [5]. The review included two randomized controlled trials of metformin 1000 mg twice daily versus placebo for 3 months in adolescents aged 12–20 years with A1c levels between 8 and 11%, and insulin daily dose requirements of >0.9 units/kg/day [5]. Both studies demonstrated a significant improvement in A1c in patients receiving metformin; at the end of one study, A1c was 0.6% lower in the metformin group than in the placebo group and, in one study, A1c decreased by 0.9% in the metformin group and remained unchanged in the placebo group [5]. Fasting glucose levels also improved significantly and mean daily dose of insulin reduced significantly after metformin therapy in one of the studies [3]. Neither study demonstrated a significant change in peripheral insulin sensitivity, BMI or lipid levels between the two groups [5]. Overall, there was no increase in the frequency of gastrointestinal complaints between the two groups; however, mild hypoglycemia occurred more frequently in the metformin group compared with the placebo group [3].

By contrast, use of thiazoladinediones, pioglitazone and rosiglitazone in adolescents with T1D and suboptimal control has not been shown to be effective in improving glycemic control, despite their potential benefit as insulin sensitizers, and

in fact, they may be detrimental given their propensity to induce weight gain [6,7].

Recombinant human IGF-I has also been studied as adjunctive therapy to improve insulin resistance through reduction of endogenous GH via feedback from IGF-I. Higher doses of 40 µg/kg were found to reduce A1c by 0.6% at 12 weeks, but effects were not sustained and concern regarding side effects of jaw pain, edema and potential worsening of retinopathy have led to the drug not being used in this population in the clinical setting [8].

More recently, agents that delay gastric emptying and suppress glucagon have been shown to have therapeutic potential in teenagers with T1D. Exenatide, a long-acting GLP-1 receptor agonist, decreased postprandial hyperglycemia in eight adolescents with T1D with a reduction in insulin doses after injection of either 1.25 or 2.5 µg of the medication [9]. Similarly, pramlintide acetate, a synthetic analog of the β-cell hormone amylin, reduced postprandial hyperglycemia in a small group of adolescents receiving pramlintide for 28 days compared with a control group. A1c values, body weight and insulin dosages significantly improved in the treatment group compared with the control group [10]. The treatment group experienced a mean decrease in A1c of -0.84%, a mean weight change of -0.80 kg and a mean decrease in total daily insulin dose of 13 units. While the use of these agents can theoretically be applied to adolescents with T1D, they are not approved for clinical use in this patient population and require further study.

What adjunctive therapy can be recommended to adolescent patients in the clinic?

For adolescents with poorly controlled T1D and signs of insulin resistance (insulin doses >1 unit/kg/day, increasing weight gain ± acanthosis nigricans), metformin would be the only adjunctive therapy recommended outside of a research setting. Metformin has been the most studied adjunctive therapy, and there is substantial clinical experience with metformin outside of T1D in pediatric and adult populations that demonstrate its safety. Prior to usage, it is imperative to ensure that the adolescent is adherent to the high doses of insulin prescribed, has not had significant episodes of ketoacidosis and is counseled about the potential side effects. Dosage should be titrated slowly to a maximum of 1000 mg twice daily, taken with meals to minimize gastrointestinal side effects, and frequent blood glucose monitoring is needed to monitor for hypoglycemia. Insulin doses may need to be reduced with the addition of metformin. If no improvements on maximal doses are seen after a 3 month period, treatment is unlikely to be of further benefit and can be discontinued. Larger studies carried out over longer periods of time are required to determine the long-term efficacy of metformin in this clinical situation. This is especially relevant as secular trends of overweight and obesity contribute to increasing numbers of teenagers with T1D and obesity-related insulin resistance.

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Is there an optimal approach for screening & treatment of celiac disease in Type 1 diabetes?

■ **Farid H Mahmud**

What is celiac disease & how is it related to diabetes?

Celiac disease (CD) is an autoimmune enteropathy characterized by immune-mediated damage to the small intestinal mucosa triggered by ingestion of gluten – a ubiquitous ingredient in our modern diet, found in wheat, barley and rye [1]. Shared genetic determinants help explain the increased prevalence of CD in Type 1 diabetes (T1D) [2]. CD is five- to ten-fold more prevalent in individuals with

T1D compared with the general population (0.7–1.0% baseline population prevalence) [3,4]. Although sampling methods and diagnostic criteria differ among studies, rates of biopsy-proven CD in pediatric T1D have been found to range from 0.64 to 16.4% [5]. Furthermore, CD can be associated with significant short- and long-term health risks, including symptoms related to gastrointestinal malabsorption (malnutrition, failure to thrive, diarrhea, abdominal distension and pain), as well as nongastrointestinal symptoms such as short stature, pubertal delay, vitamin and mineral deficiencies and impaired bone mineralization [1,5]. Recent epidemiological evidence from Europe and the USA also describe increased mortality rates in patients with serology positive, undiagnosed CD [6,7].

Should we screen all T1D patients for CD?

Empirically, the high prevalence rate and concerns about complications, coupled with sensitive and specific serologic testing to detect CD, do support a rationale for universal screening of T1D populations, as recommended by multiple diabetes organizations, including the International Society for Pediatric and Adolescent Diabetes and the American Diabetes Association [8–10].

In the context of T1D, the question is more complicated. In symptomatic patients, screening and treatment with a gluten-free diet (GFD) does offer clear benefits and improvements in actual and perceived health. In patients without symptoms, the putative benefits and potential harm of screening and treatment with a GFD are less clear.

Why can it sometimes be difficult to diagnose CD in children?

The literature regarding the prevalence and nature of symptoms in patients presenting with both CD and T1D generally describes 'classic' presentations of CD. This includes gastrointestinal and growth-related symptoms that may also include unexplained hypoglycemic episodes attributed to malabsorption. Using these criteria, asymptomatic patients have been reported between 20–80% and our clinical experience has shown that close to 50% of our patients with T1D did not present with symptoms or growth attenuation in our diabetes clinic nor at the time of gastrointestinal evaluation [5,10,11]. The reality is that symptoms of CD can be subtle as children may be less likely to show overt growth failure, but can have weight and height measures at a lower growth percentile and complain of nonspecific symptoms, including anorexia and lassitude [5,12,13]. Some patients are also overweight or obese at diagnosis, as 11.2% of children with CD had a BMI greater than the 90th percentile in a recent USA study. These features highlight the complex clinical spectrum of CD, but the reality is that a sizable proportion of patients who screen positive for CD are clinically well at diagnosis [14].

Questions also exist surrounding the natural history of undiagnosed CD in asymptomatic diabetes patients and if the outcomes of those identified by screening are similar to those who are clinically identified by the presence of symptoms. It also remains unclear whether asymptomatic patients experience long- and/or short-term health-related benefits from following a GFD.

Is there an optimal approach to screening in this patient population?

The Canadian Diabetes Association guidelines are unique in their recommendation that screening should only be offered to symptomatic subjects and expands symptomotology beyond gastrointestinal and growth impairment to include fatigue and unexplained hypoglycemia [15]. However, practically it can be difficult to determine which patient is symptomatic, as most busy diabetes clinics do not routinely screen for many of the myriad of CD-related symptoms and a universal screening program for CD allows for appropriate identification. In addition, for adult patients, if clinicians overlook minor glycemic index symptoms or ascribe them to complications of longstanding diabetes, then a practice of routine testing may pick up these symptomatic patients. We try to avoid CD testing immediately at diagnosis in subjects without overt symptoms, as the perception that teaching both GFD and diabetes-related dietary management at onset can be difficult. Frequency of rescreening at intervals of 2–3 years seems reasonable.

Should all patients, symptomatic or not, be recommended a GFD?

Our approach has been to discuss treatment with all patients, regardless of symptomotology, with a GFD. This is based upon data with regard to clinically relevant outcomes with some improvements noted regarding growth parameters and decreased hypoglycemia, although observed changes in HbA1c while on the GFD are inconclusive. Clinicians should be aware that CD is associated with decreased bone mineral density, and that childhood and adolescence is a key period for bone mass accrual; this may represent the most insidious complication impacting CD and T1D patients. In our clinic, we have evaluated rates of GFD adherence at 70% and also reported a minimal impact of this double diagnosis on measures of quality of life, but with significant parental concerns about their child's socialization [16]. However, it is not surprising that many TID patients and families struggle with the limited availability and higher food costs associated with the GFD, as well as the prospect of managing two chronic conditions.

In asymptomatic patients who elect not to adopt a GFD, alternative approaches may need to be explored. A recent nonrandomized study prospectively followed pediatric subjects with diabetes and CD for 2 years, and observed no significant adverse outcomes in screen-positive patients who delayed therapy for 2 years, although reduced bone density and lower vitamin D levels were found in some subjects with persistently high serology [15]. Adopting such an approach would entail a complete clinical evaluation of all CD-related complications (including anemia, impaired calcium, vitamin D and bone density) with close evaluation for evidence of hypoglycemia and growth to ensure that these are normal. Patients and families would also be advised about the risks of this approach, as untreated CD is associated with numerous complications that will require frequent surveillance as there is some emerging data in adults with CD and T1D suggestive of

higher diabetes complication rates (retinopathy and nephropathy) and longer term morbidities [17,18]. It is also difficult to comment on long-term consequences of such an approach.

How should we diagnose & manage CD in children with diabetes?

Given the higher prevalence of CD and the variability of symptoms than can present as part of this multisystem disease, it is recommended to screen patients with T1D. If symptomatic, then a GFD should be suggested. If a patient who is screen-positive presents in the absence of a complete symptom assessment, treatment remains complex and will remain so in the absence of well-designed prospective studies that evaluate the risks and benefits of GFD treatment for CD in the T1D population, as they pertain to clinically relevant outcomes.

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When should primary care physicians consider Type 1 diabetes in children & young people (as a means of preventing diabetic ketoacidosis & its consequences)?

■ **Juliet Usher-Smith**

Why is the primary care physician important? What is their role in the diagnosis of Type 1 diabetes in children?

Primary care physicians play a central role in the diagnosis of Type 1 diabetes in children and young people. They are often the first point of contact for parents and children, with over 80% of children who develop diabetes seen in primary care prior to diagnosis [1], and children diagnosed at their first visit to a doctor have a threefold decreased risk of developing diabetic ketoacidosis (DKA) [2]. By recognizing DKA when it has already developed, and promptly referring for treatment, primary care physicians are also in a position to minimize the consequences of DKA.

What are the main challenges of diagnosing diabetes in primary care?

Whilst biochemical diagnosis of diabetes is straightforward, as with other serious, but rare illnesses in children, differentiating the occasional child with diabetes from the large number with minor undifferentiated illnesses is challenging. The annual age-adjusted incidence of Type 1 diabetes varies over 350-fold, from 0.1/100,000/year in China to 40.9/100,000/year in Finland [3]. Even in those areas with the highest incidence, a primary care physician responsible for the care of 2000 patients can therefore expect to see a child presenting

with diabetes approximately once every 10 years, or three to four times throughout their medical career. Spotting these children is made more difficult by the fact that the symptoms are often not mentioned by parents and children, and can be nonspecific and overlap with those of many other minor illnesses. However, once considered, the diagnosis can be made relatively easily in primary care. It does not require access to specialist diagnostic services (e.g., imaging for suspected malignancy) and the availability of point-of-care tests for hyperglycemia, ketonemia, glycosuria and ketonuria mean that the diagnosis can be made in a single consultation. The difficult step in making the diagnosis in primary care is, therefore, considering the condition.

When should physicians consider diabetes?

For some children, this is relatively straightforward. A child presenting with polyuria, polydipsia and weight loss is likely to prompt most primary care physicians to consider diabetes. However, these symptoms are often not mentioned by parents or children and are not always the trigger for consultation. Many of the diagnostic errors made around the diagnosis of diabetes in children also involve either misinterpreting symptoms (e.g., polyuria misdiagnosed as urinary tract infection) or exclusively treating concomitant diseases (e.g., otitis media or respiratory tract infections) that may precipitate diabetes [4,5]. Primary care physicians should, therefore, be aware of the range of presenting symptoms of diabetes and the need to ask directly about other symptoms, even if an alternative diagnosis is already suspected.

Unfortunately, no studies have looked at the symptoms of children with new-onset diabetes presenting to primary care. Our experience therefore comes from secondary care, where symptoms are likely to be more pronounced and the diagnosis already considered in many cases [6–8].

The most common symptoms at presentation in all ages are polyuria and polydipsia, occurring in between 66 and 97% of children. Weight loss is the next most common, affecting up to 95%, and fatigue (10–70%), polyphagia (30%) and abdominal pain (25%) are also seen across all age groups. Constipation, secondary to chronic dehydration, is an additional important symptom (10%) in children under 5 years and nocturnal enuresis in a previously toilet-trained child (up to 90%) is the earliest symptom of diabetes in children over the age of 4 years. In addition to the classic symptoms of polyuria, polydipsia and weight loss, children presenting with constipation, abdominal pain or new-onset enuresis should therefore prompt consideration of diabetes. The symptoms in younger children can also be subtle and difficult to distinguish from other acute illnesses. Decompensation due to dehydration and acidosis develops more quickly in this age group, so primary care physicians should have a higher index of suspicion in young children presenting nonspecifically unwell.

When should physicians consider DKA?

In addition to these symptoms of diabetes, primary care physicians also need to be aware of the symptoms of DKA, as up to 80% of children develop DKA by the time of diagnosis. Studies comparing symptom pattern and frequency between children with Type 1 diabetes who develop DKA and those who do not show a difference in the frequency of enuresis, nocturia, polyuria or polydipsia [1], but children with DKA present more frequently with vomiting, abdominal pain, dyspnoea weakness, anorexia, changes in mental status and weight loss [6,9–12]. As parents and children often neglect to mention polyuria or polydipsia, these symptoms can lead to DKA being misdiagnosed as acute abdomen, gastroenteritis, acute asthma or pneumonia. Febrile illness is also a risk factor for DKA [2], therefore it is crucial to ask specifically about polyuria and polydipsia when children present with any of these other symptoms. DKA at diagnosis is also more common in children under 5 years of age, those from ethnic minority groups, without medical insurance and with a lower BMI [2], so physicians should be particularly alert for those risk factors in these children. Finally, DKA is a state of dehydration and so diabetes should be considered in any child presenting with features of dehydration (poor skin turgor, prolonged capillary refill time, dry mucous membranes, sunken eyes, oliguria and, ultimately, shock).

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