Received: 9 July 2018 | Accepted: 16 July 2018

DOI: 10.1111/pedi.12734

WILEY ISPAD

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents

Jennifer J. Couper[1,2] | Michael J. Haller[3] | Carla J. Greenbaum[4] | Anette-Gabriele Ziegler[5] | Diane K. Wherrett[6] | Mikael Knip[7] | Maria E. Craig[8,9,10]

[1]Department of Diabetes and Endocrinology, Womens and Childrens Hospital, North Adelaide, Australia

[2]Robinson Research Institute, University of Adelaide, Adelaide, Australia

[3]Department of Pediatrics, Division of Endocrinology, University of Florida, Gainesville, Florida

[4]Benaroya Research Institute, Seattle, Washington

[5]Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

[6]Division of Endocrinology, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada

[7]Children's Hospital, University of Helsinki, Helsinki, Finland

[8]Department of Diabetes and Endocrinology, The Children's Hospital at Westmead, Sydney, Australia

[9]Discipline of Pediatrics and Child Health, University of Sydney, Sydney, Australia

[10]School of Women's and Children's Health, University of New South Wales, Sydney, Australia

Correspondence
Jenny J Couper, Department of Diabetes and Endocrinology, Womens and Childrens Hospital, North Adelaide, Australia.
Email: jennifer.couper@adelaide.edu.au

1 | WHAT IS NEW

- "Phases" of diabetes have been renamed as "stages" to align with the new classification of stages 1 to 3
- Tools for prediction of type 1 diabetes, including genetic risk scores
- Updated information on intervention trials, including primary prevention, and at stages 1 and 2 diabetes

2 | RECOMMENDATIONS AND PRINCIPLES

- Individuals with a first-degree relative with type 1 diabetes have an approximately 15-fold increased relative risk of type 1 diabetes[1–3] **A**
- Individuals with two or more islet antibodies are classified as having the first stage of type 1 diabetes[4] and the American Diabetes Association **A**
- The majority of children at risk of type 1 diabetes with multiple islet antibodies progress to diabetes within the next 15 years, compared to ~10% who have a single islet antibody.[5] **A**
- Screening and intervention before the symptoms of type 1 diabetes should be conducted within the context of defined research studies. **E**
- Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counseling and information regarding current prevention studies. **E**
- Features suggesting the diagnosis of type 2 or monogenic rather than type 1 diabetes include but are not limited to a family history of diabetes in first-degree relatives, obesity, acanthosis nigricans, high-risk racial or ethnic group and undetectable islet autoantibodies. **E**

3 | STAGES OF TYPE 1 DIABETES

Type 1 diabetes is characterized by four stages as shown in Figure 1.

Stage 1. Multiple islet antibodies, normal blood glucose, and presymptomatic.

Stage 2. Multiple islet antibodies, raised blood glucose, and presymptomatic.

Stage 3. Islet autoimmunity, raised blood glucose, and symptomatic.

Stage 4. Long standing type 1 diabetes.

4 | RISK

Individuals with a first-degree relative with type 1 diabetes have an approximately 15-fold increased relative life time risk of type

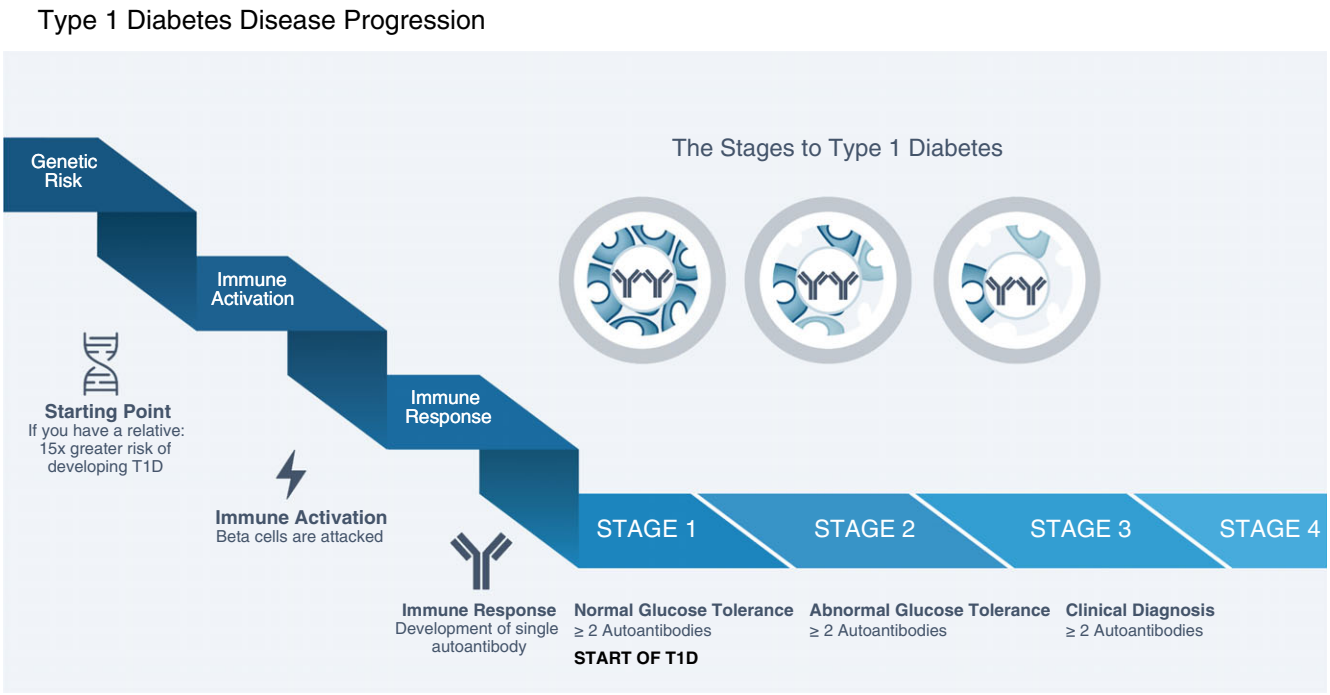

FIGURE 1 The stages of type 1 diabetes (T1D) (DiabetesTrialNet.org). A proportion of individuals who have increased genetic risk of T1D progress at variable rates to immune activation and the development of islet autoimmunity. The development of two or more islet antibodies (stage 1) ultimately progresses to dysglycemia (stage 2) and then to symptomatic T1D (stage 3)

1 diabetes.[1,3,6] However, at least 85% of children who develop type 1 diabetes do not have a family history of type 1 diabetes. The prevalence of type 1 diabetes in the general population by age 20 years is ~0.3%, compared with ~5% of those with a first-degree relative with type 1 diabetes. More than 60 genetic variants have been identified in association with type 1 diabetes by genome-wide association studies.[7] The human leukocyte antigen (HLA) genotype confers approximately half of the genetic risk for type 1 diabetes.[8,9] Specific combinations of DR and DQ alleles at the HLA loci confer increased or decreased risk.[10] The highest risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 which are in strong linkage disequilibrium). In the general population, heterozygotes for DR3/DR4 (DQ2/DQ8) have a 30-fold increased risk of islet autoimmunity and type 1 diabetes.[11] First-degree relatives carrying DR3/DR4 (DQ2/DQ8) have a further increase in risk consistent with a contribution of non-HLA risk loci.[12] The highest non-HLA genetic contribution arises from the INS, PTPN22, CTLA4, and IL2RA genes.[13] Genetic risk scores that also incorporate non-HLA genes improve risk estimates for islet autoimmunity and type 1 diabetes[14,15] and discrete non-HLA genetic markers exist for the risk of progression from islet autoimmunity to clinical type 1 diabetes.[16–18]

5 | IMMUNE ACTIVATION AND ISLET (β-CELL) AUTOIMMUNITY

Stages 1 and 2 refer to the months or years preceding the clinical presentation of type 1 diabetes when two or more islet antibodies to proteins associated with secretory granules in β-cells can be detected as markers of β-cell autoimmunity[19]: glutamic acid decarboxylase 65 autoantibodies (GAD), tyrosine phosphatase-like insulinoma antigen 2 antibodies, insulin autoantibodies, and β-cell-specific zinc transporter 8 autoantibodies.

Islet autoimmunity and β-cell dysfunction begin months to years before the diagnosis of type 1 diabetes. Islet antibodies usually appear in early life whereby over 90% of children who develop type 1 diabetes before puberty have islet antibodies by 5 years. Natural history studies consistently show that nearly all individuals with two or more islet antibodies eventually develop type 1 diabetes, with a rate of diagnosis of ~11% per year among two or more antibody positive patients.[20] The majority of children at risk of type 1 diabetes with two or more islet antibodies progress to diabetes within the next 15 years, compared to a rate of ~10% in those who have a single islet antibody. Progression in children with multiple islet antibodies is faster when seroconversion to islet autoimmunity is before age 3 years and in children with the HLA DR3/DR4-DQ8 genotype.[5] It is important to note that antibodies can also first appear later in childhood. Thus, genetically, at-risk individuals (ie, family members) who do not have antibodies on initial screening in research studies should be tested annually for the development of antibodies until their adult years (DiabetesTrialNet.org).

Loss of β-cell function is often stepwise and non-linear. In addition to immune and genetic markers, the risk of type 1 diabetes may be refined further by the measurement of β-cell function as insulin release in response to an intravenous glucose load (intravenous glucose tolerance test [IVGTT]). Impaired first phase insulin release on IVGTT (defined as an insulin response less than the 10th percentile for age and sex-matched controls) confers a 60% risk of developing type 1 diabetes over the next 5 years.[21] That said, IVGTT does not add prognostic information to the risk of progression; in antibody,

positive first-degree relatives with normal glucose tolerance in the Diabetes Prevention Trial (DPT)-1 trial, the two-hour glucose level on oral glucose tolerance test, demonstrated the greatest accuracy for predicting progression to type 1 diabetes.[22] In those with abnormal glucose tolerance, the combination of 2-hour glucose, peak c-peptide, and area under the curve c-peptide significantly improved the prognostic accuracy compared with a single measure.[23] More sensitive predictors of β-cell function, such as elevations in the serum proinsulin to c-peptide ratio, are under investigation.[24] Interestingly, antibody positive individuals may experience episodes of hypoglycemia likely due to asynchronous release of insulin in response to meals.[25] Consistent with this, continuous glucose monitoring detects increased blood glucose variability before the onset of insulin therapy and before progression to symptomatic dysglycemia.[26,27]

6 | THE ROLE OF THE ENVIRONMENT IN THE PATHOGENESIS OF TYPE 1 DIABETES

The global increase in the incidence of type 1 diabetes over the last 30 years, in parallel with a reduction in the proportion of individuals with high-risk HLA haplotypes,[28–30] confirms the role of the modern environment in its pathogenesis; this is likely through complex gene-environment interactions.[31] There is heightened interest in the interaction of the environment with biological systems (including the microbiome and metabolome), which in turn can regulate immune tolerance. Congenital rubella is a long standing recognized environmental trigger.[32,33] Other putative exposures are enterovirus infections during pregnancy and childhood,[34,35] and the introduction of multiple foreign antigens in the infant diet.[36–38] In at-risk children, concurrent breast milk feeding at the time of cereal introduction may be protective.[37] Omega 3 fatty acids may also have a small protective effect.[39] Vitamin D metabolism may play, as yet, an undetermined role.[40–42] The modern environment provides for excess nutrition in mothers during pregnancy and for rapid growth and weight gain in children in early life with an accompanying reduction in insulin sensitivity. This may accelerate both the development of islet autoimmunity and progression to type 1 diabetes.[43–45] International networks following children at increased genetic risk from pregnancy or birth are investigating these questions.[5,46,47]

7 | PREVENTION OF TYPE 1 DIABETES AND INTERVENTIONS TO PRESERVE β-CELL FUNCTION

Care for children living with other autoimmune diseases, such as juvenile idiopathic arthritis, has shifted from symptom treatment to disease-modifying interventions. This is also an over-riding goal for type 1 diabetes. Interventions to preserve β-cell function involve clinical trials before islet autoimmunity (prestage 1, primary prevention studies), after the development of islet autoimmunity and before the symptoms of diabetes (stages 1 and 2), and soon after clinical diagnosis in recent onset diabetes (stage 3).

Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined research studies. Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to timely counseling and appropriate information about relevant research studies. Families and their at-risk children are generally enthusiastic about entering intervention trials and may benefit from being more prepared if their child is diagnosed with diabetes through participation in follow-up studies.[48] It is our position that unproven treatments that are believed by the medical and research communities to have clinical potential should only be prescribed to patients in the context of carefully monitored clinical trials. The therapeutic value and safety of all treatments and agents must be evaluated rigorously, and human subject (patient) protections must be in place.

8 | PRIMARY PREVENTION TRIALS

Primary prevention trials begin prior to the development of islet autoimmunity, typically in young children at increased genetic risk of type 1 diabetes. Because the majority of genetically identified participants would not be expected to progress to clinical disease, the safety of the intervention must be heavily weighed.

- The BABYDIET study showed no benefit from delaying gluten exposure until 12 months of age in 150 at-risk children.[49]
- The FINDIA study, involving 1104 babies, showed that weaning to a cow's milk formula free of bovine insulin reduced the cumulative incidence of islet autoantibodies by age 3 years in children at genetic risk of type 1 diabetes.[50]
- The international, placebo controlled, randomized TRIGR trial involving 2160 at-risk infants showed no benefit of weaning to an extensively hydrolyzed milk formula on the development of islet autoantibodies by 6 years of age nor the development of type 1 diabetes by 11 years of age.[51–53]
- The Pre-POINT pilot study demonstrated immune response to high-dose oral insulin in a small number of at-risk children.[54] Two studies are further investigating the effects of high-dose oral insulin: one testing whether oral insulin induces an immune response in antibody positive relatives (TrialNet Immune Effects of Oral Insulin Trial; clinicaltrials.gov NCT02580877), and the other testing whether oral insulin results in mucosal tolerance in children in the general population at increased genetic risk, the POINT trial.[55]
- Future primary prevention targets that are being considered include the development of other vaccines that induce immune tolerance in β-cells, an enterovirus vaccine,[56] and use of microbiota and their products (pre- or probiotics) to induce immune-regulation.

9 | INTERVENTION AT STAGES 1 AND 2 OF TYPE 1 DIABETES

These trials intervene after the development of islet autoimmunity, prior to the onset of symptomatic disease. Because those with multiple antibodies will eventually develop clinical disease, intervention can be considered treatment of early type 1 diabetes, as distinct from prevention. Many consider that intervention at this stage will require combination approaches to multiple targets in the pathogenesis of

type 1 diabetes: islet inflammation and autoimmune destruction, β-cell function, and metabolism.

- Type 1 Diabetes TrialNet provides an international network of intervention trials to preserve β-cell function at the different stages.[57,58] The TrialNet Pathway to Prevention study screens and follows relatives of type 1 diabetes probands. Oral Insulin, CTLA-4 Ig (Abatacept), and anti-CD3 monoclonal antibody (Teplizumab) are currently under investigation in stage 1 and stage 2.
- The European Nicotinamide Diabetes Intervention Trial demonstrated—in a placebo controlled randomized trial of 552 participants—that nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk first-degree relatives.[59]
- The National Institute of Health Diabetes Prevention Trials demonstrated that neither low-dose subcutaneous nor oral insulin therapy delayed or prevented the onset of clinical diabetes in high-risk (N = 339) and intermediate-risk (N = 372) relatives, respectively.[21,60] However, in post hoc analysis of those subjects with high insulin autoantibody titers, oral insulin delayed progression to type 1 diabetes.[60] This observation was prospectively retested in the TrialNet Oral Insulin study,[61] which failed to prevent type 1 diabetes in the primary cohort of 389 relatives. However, in a second independent cohort of 55 individuals with reduced first phase insulin release, there was a detectable delay in progression to type 1 diabetes (unpublished data).
- The Australian intranasal insulin trial II involving 110 antibody positive individuals, which also aimed to induce mucosal tolerance,[62,63] showed no benefit in delaying progression to type 1 diabetes.
- The adAPT trial currently in progress will test whether metformin can slow the progression to clinical diabetes in children with islet autoimmunity.[64]
- Autologous cord blood transfusion does not provide benefit in recent onset type 1 diabetes and is now being investigated in islet autoimmune children in the CoRD study.[65]

10 | INTERVENTION AT STAGE 3 TYPE 1 DIABETES

These trials enroll children generally within 100 days of diagnosis. The aim is to preserve some β-cell function to potentially delay the complications of type 1 diabetes. Cyclosporin transiently preserved β-cell function several decades ago,[66] but was not pursued because of toxicities associated with chronic use. Randomized controlled trials of GAD alum vaccine have produced inconsistent results. Bayesian meta-analysis indicated a high probability that GAD with alum administered twice in stage 3 diabetes reduces the loss of C-peptide by 15% to 20% at 1 year after treatment.[67]

Short-term administration of immune modulation therapies that can delay the loss of β-cell function (rate of decline of C-peptide) in patients with recent onset type 1 diabetes includes the anti-CD3 monoclonal antibodies Teplizumab[68] and otelixizumab, Abatacept (CTLA4-Ig),[69,70] Alefacept,[71]and the anti-CD20 monoclonal antibody, rituximab.[72,73] Children and adolescents were participants in these trials and in general had a better c-peptide response to the intervention than adults.

Combination immune therapy via autologous non-myeloablative hematopoetic stem cell transplant has had the most success in restoring β-cell function in the short term.[74] Trials were designed to deconstruct the therapy with more acceptable risk profiles using antithymocyte globulin (ATG) and granulocyte colony stimulation factor (GCSF). ATG and GCSF combination therapy preserved β-cell function for at least 12 months in a pilot study in established type 1 diabetes, with distinct responders and non-responders.[75] A fully powered, randomized placebo-controlled trial of low-dose ATG vs placebo and low-dose ATG/GCSF vs placebo in new onset type 1 diabetes demonstrated significant reduction in HbA1c in both ATG and ATG/GCSF treated subjects with significant preservation of C-peptide in the low-dose ATG group at 1 year outcome (clinicaltrials.gov identifier NCT02215200).[76]

In contrast, multiple other therapies tested in phase 2 fully powered, randomized placebo controlled trials in recently diagnosed individuals have demonstrated no effect on preservation of β-cell function. These include antigen therapies,[77] anti-inflammatory agents,[78] the GLP-1 agonist sitagliptin in combination with a proton pump inhibitor,[79] the combination of mycophenalate mofitil and daclizumab,[80] and many others. Yet with the certain knowledge that controlling the immune system is essential to preserving β-cell function, multiple other agents are under study or being considered either alone or in combination including agents that are already approved for use in other autoimmune diseases in children. Studies are also testing agents aimed at stimulating β-cell repair and regeneration.

Ultimately, a targeted and combination approach with individualized treatment according to the patient's genetic make-up and other biomarkers of response is likely to be the most effective.[81,82]

11 | CLINICAL PRESENTATION OF TYPE 1 DIABETES

Prospective follow-up of high-risk individuals shows that diagnosis of type 1 diabetes can be made before persistent hyperglycemia and symptoms[21] and that their risk of diabetic ketoacidosis is substantially reduced.[83,84] Individuals with islet autoimmunity who are followed regularly until clinical diagnosis present with lower HbA1c and a lower risk of diabetic ketoacidosis[84–86]. This, taken together with the emerging evidence that children who present with diabetic ketoacidosis have poorer long-term control[87] has provided impetus to justify general population screening programs for islet autoimmunity. Such general population screening programs are in progress in Germany[88] and the United States. They seek to provide evidence of cost effectiveness and benefit and stimulate active intervention strategies in the presymptomatic stages of disease.

A child presenting with a classical history of increasing polyuria, polydipsia, and weight loss over 2 to 6 weeks (stage 3) presents a straightforward diagnosis. However, failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis and an increased risk of diabetic ketoacidosis.[89] Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis; others have a slow onset of symptoms over several months. Clinical presentation of diabetes can range from non-emergency

presentations to severe dehydration, shock, and diabetic ketoacidosis (Table 1).

Urinary "dipstick" testing for glucosuria and ketonuria, or measurement of blood glucose and blood ketones using a bedside glucometer, provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose ≥ 11.1 mmol/L/200 mg/dL) confirms the diagnosis; this should be based on a laboratory glucose oxidase estimation rather than a capillary blood glucose monitor.

If a child has symptoms of diabetes, immediate referral to a center with expertise in the care of such children is mandatory, because prompt diagnosis and treatment of diabetes in children are important in preventing rapid deterioration into ketoacidosis. Severe ketoacidosis if untreated is fatal. Therapy is urgent and referral to specialized services is essential. See Chapter 10—Diabetic Ketoacidosis.[90]

12 | DIFFERENTIATING BETWEEN TYPE 1, TYPE 2 DIABETES, OR MONOGENIC DIABETES AT DIAGNOSIS

Features suggesting the diagnosis of type 2 diabetes rather than type 1 diabetes at diagnosis include:

TABLE 1 Clinical characteristics at presentation of type 1 diabetes

Non-emergency presentations
- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection.
- Perineal candidiasis, especially in prepubertal girls.
- Chronic weight loss or failure to gain weight in a growing child.
- Irritability and decreasing school performance.
- Recurrent skin infections.

Emergency presentations (diabetic ketoacidosis or hyperosmolar hyperglycemia)[90]:
- Moderate to severe dehydration.
- Frequent vomiting and in some cases, abdominal pain, which may be misdiagnosed as gastroenteritis.
- Continuing polyuria despite the presence of dehydration.
- Weight loss due to fluid loss and loss of muscle and fat.
- Flushed cheeks due to ketoacidosis.
- Acetone detected on the breath.
- Hyperventilation of diabetic ketoacidosis (Kussmaul respiration), characterized by an increased respiratory rate and large tidal volume of each breath, which gives it a sighing quality.
- Disordered sensorium (disoriented, semicomatose, or rarely comatose).
- Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis).
- Hypotension (a very late sign and rare in children with diabetic ketoacidosis).

Diagnostic difficulties that may delay diagnosis
- Very young children may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency and because the diagnosis was not considered earlier.
- The hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis) and in the case of asthma treated with glucocorticoids that exacerbate the severity of hyperglycemia.
- Abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon.
- Polyuria and enuresis may be misdiagnosed as a urinary tract infection.
- Polydipsia may be thought to be psychogenic.
- Vomiting may be misdiagnosed as gastroenteritis or sepsis.

- Overweight or obesity
- Age greater than 10 years
- Strong family history of type 2 diabetes
- Acanthosis nigricans
- High-risk racial or ethnic groups
- Undetectable islet autoantibodies

The overweight epidemic in many countries has resulted in up to one-third of children presenting with overweight or obesity at diagnosis of type 1 diabetes,[91–93] with accompanying insulin resistance. Raised islet autoantibodies confirm the diagnosis of type 1 diabetes and the need for insulin therapy. It is noteworthy that some racial or ethnic groups have a higher risk of DKA at presentation of type 1 diabetes.

13 | PARTIAL REMISSION OR HONEYMOON PHASE IN TYPE 1 DIABETES

In approximately 80% of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment[94]; this reflects partial β-cell recovery with increased insulin secretion and improved peripheral insulin sensitivity before the decline in insulin production begins.[95,96] Parents and children with type 1 diabetes should be counseled that the remission phase of diabetes is transient and does not indicate total remission of diabetes. At present, no therapy is known to restore β-cell function for an extended period of time. Nevertheless, any preservation of β-cell function decreases the risk of developing vascular complications and the risk of severe hypoglycemia,[97,98] so this remains an important research goal.

Some have defined partial remission as an insulin requirement of <0.5 units per kg of body weight per day and HbA1c <7%.[94] The phase commences within days or weeks of the start of insulin therapy and may last for weeks to years. However, an unusually prolonged "honeymoon phase" should alert the treating physician to the possibility of a form of monogenic diabetes such as MODY or milder manifestation of genes commonly responsible for NDM (see chapter on Monogenic Forms of Diabetes). During this period, blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. Ketoacidosis at presentation,[99] and younger age at diabetes onset, reduces the likelihood of a remission phase.[100,101]

14 | CHRONIC PHASE OF LIFELONG DEPENDENCE ON INSULIN

The progression from the partial remission phase into the chronic phase of dependence on exogenous insulin is usually a gradual decrease in residual β-cell function. The rate of loss of c-peptide production is similar in children and adolescents, and faster than that in adults; few children and adolescents have significant residual β-cell function by 4 years after clinical diagnosis.[102] However, ultrasensitive c-peptide assays show that a small amount of long-term endogenous insulin production persists in up to 75% of patients[103]; the presence

of persistent c-peptide in long standing disease is much less in those diagnosed as children as compared to diagnosis as an adult.[104]

Conflict of interest

The authors have declared no conflicts of interest.

ORCID

Jennifer J. Couper http://orcid.org/0000-0003-4448-8629
Maria E. Craig http://orcid.org/0000-0001-6004-576X

REFERENCES

1. Pociot F, Norgaard K, Hobolth N, Andersen O, Nerup J. A nationwide population-based study of the familial aggregation of type 1 (insulin--dependent) diabetes mellitus in Denmark. Danish Study Group of Diabetes in Childhood. *Diabetologia*. 1993;36(9):870-875.
2. Nisticò L, Iafusco D, Galderisi A, et al. Emerging effects of early environmental factors over genetic background for type 1 diabetes susceptibility: evidence from a Nationwide Italian Twin Study. *J Clin Endocrinol Metab*. 2012;97(8):E1483-E1491.
3. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR. Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *N Engl J Med*. 1984;311(3):149-152.
4. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015;38(10):1964-1974.
5. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. 2013;309(23):2473-2479.
6. Harjutsalo V, Reunanen A, Tuomilehto J. Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. *Diabetes*. 2006;55(5):1517-1524.
7. Barrett JC, Clayton DG, Concannon P, et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet*. 2009;41(6):703-707.
8. Noble JA, Valdes AM, Cook M, Klitz W, Thomson G, Erlich HA. The role of HLA class II genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families. *Am J Hum Genet*. 1996;59(5):1134-1148.
9. Lambert AP, Gillespie KM, Thomson G, et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. *J Clin Endocrinol Metab*. 2004;89(8):4037-4043.
10. Nguyen C, Varney MD, Harrison LC, Morahan G. Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms. *Diabetes*. 2013;62(6):2135-2140.
11. Erlich H, Valdes AM, Noble J, et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. *Diabetes*. 2008;57(4):1084-1092.
12. Aly TA, Ide A, Jahromi MM, et al. Extreme genetic risk for type 1A diabetes. *Proc Natl Acad Sci U S A*. 2006;103(38):14074-14079.
13. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. *Lancet*. 2016;387(10035):2331-2339.
14. Winkler C, Krumsiek J, Buettner F, et al. Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. *Diabetologia*. 2014;57(12):2521-2529.
15. Steck AK, Wong R, Wagner B, et al. Effects of non-HLA gene polymorphisms on development of islet autoimmunity and type 1 diabetes in a population with high-risk HLA-DRDQ genotypes. *Diabetes*. 2012;61(3):753-758.
16. Bonifacio E, Krumsiek J, Winkler C, Theis FJ, Ziegler AG. A strategy to find gene combinations that identify children who progress rapidly to type 1 diabetes after islet autoantibody seroconversion. *Acta Diabetol*. 2014;51(3):403-411.
17. Steck AK, Xu P, Geyer S, et al. Can non-HLA single nucleotide polymorphisms help stratify risk in TrialNet relatives at risk for type 1 diabetes? *J Clin Endocrinol Metab*. 2017;102(8):2873-2880.
18. Oram RA, Patel K, Hill A, et al. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care*. 2016;39(3):337-344.
19. Watkins RA, Evans-Molina C, Blum JS, Dimeglio LA. Established and emerging biomarkers for the prediction of type 1 diabetes: a systematic review. *Transl Res*. 2014;164:110-121.
20. Bonifacio E. Predicting type 1 diabetes using biomarkers. *Diabetes Care*. 2015;38(6):989-996.
21. DPT-1 Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Eng J Med*. 2002;346(22):1685-1691.
22. Xu P, Wu Y, Zhu Y, et al. Prognostic performance of metabolic indexes in predicting onset of type 1 diabetes. *Diabetes Care*. 2010;33(12):2508-2513.
23. Xu P, Beam CA, Cuthbertson D, et al. Prognostic accuracy of immunologic and metabolic markers for type 1 diabetes in a high-risk population: receiver operating characteristic analysis. *Diabetes Care*. 2012;35(10):1975-1980.
24. Sims EK, Chaudhry Z, Watkins R, et al. Elevations in the fasting serum proinsulin-to-C-peptide ratio precede the onset of type 1 diabetes. *Diabetes Care*. 2016;39(9):1519-1526.
25. Diabetes Prevention Trial—Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. 2002;346(22):1685-1691.
26. Steck AK, Dong F, Taki I, Hoffman M, Klingensmith GJ, Rewers MJ. Early hyperglycemia detected by continuous glucose monitoring in children at risk for type 1 diabetes. *Diabetes Care*. 2014;37(7):2031-2033.
27. Van Dalem A, Demeester S, Balti EV, et al. Relationship between glycaemic variability and hyperglycaemic clamp-derived functional variables in (impending) type 1 diabetes. *Diabetologia*. 2015;58(12):2753-2764.
28. Gillespie KM, Bain SC, Barnett AH, et al. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. *Lancet*. 2004;364(9446):1699-1700.
29. Fourlanos S, Varney MD, Tait BD, et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. *Diabetes Care*. 2008;31(8):1546-1549.
30. Hermann R, Knip M, Veijola R, et al. Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes--indication of an increased environmental pressure? *Diabetologia*. 2003;46(3):420-425.
31. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *Lancet*. 2016;387(10035):2340-2348.
32. McIntosh ED, Menser MA. A fifty-year follow-up of congenital rubella. *Lancet*. 1992;340(8816):414-415.
33. Takasu N, Ikema T, Komiya I, Mimura G. Forty-year observation of 280 Japanese patients with congenital rubella syndrome. *Diabetes Care*. 2005;28(9):2331-2332.
34. Yeung G, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus—a systematic review of molecular studies. *Br Med J*. 2011;342:d35.
35. Allen DW, Kim KW, Rawlinson WD, Craig ME. Maternal virus infections in pregnancy and type 1 diabetes in their offspring: systematic review and meta-analysis of observational studies. *Rev Med Virol*. 2018;28(3):e1974.
36. Akerblom HK, Virtanen SM, Ilonen J, et al. Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. *Diabetologia*. 2005;48(5):829-837.
37. Norris JM, Barriga K, Klingensmith G, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA*. 2003;290(13):1713-1720.
38. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA*. 2003;290(13):1721-1728.
39. Norris JM, Yin X, Lamb MM, et al. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. *JAMA*. 2007;298(12):1420-1428.

40. Tizaoui K, Kaabachi W, Hamzaoui A, Hamzaoui K. Contribution of VDR polymorphisms to type 1 diabetes susceptibility: systematic review of case-control studies and meta-analysis. *J Steroid Biochem Mol Biol*. 2014;143C:240-249.
41. Simpson M, Brady H, Yin X, et al. No association of vitamin D intake or 25-hydroxyvitamin D levels in childhood with risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY). *Diabetologia*. 2011;54(11):2779-2788.
42. Raab J, Giannopoulou EZ, Schneider S, et al. Prevalence of vitamin D deficiency in pre-type 1 diabetes and its association with disease progression. *Diabetologia*. 2014;57(5):902-908.
43. Couper JJ, Beresford S, Hirte C, et al. Weight gain in early life predicts risk of islet autoimmunity in children with a first-degree relative with type 1 diabetes. *Diabetes Care*. 2009;32(1):94-99.
44. Fourlanos S, Narendran P, Byrnes GB, Colman PG, Harrison LC. Insulin resistance is a risk factor for progression to type 1 diabetes. *Diabetologia*. 2004;47(10):1661-1667.
45. Ferrara CT, Geyer SM, Liu YF, et al. Excess BMI in childhood: a modifiable risk factor for type 1 diabetes development? *Diabetes Care*. 2017;40(5):698-701.
46. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Ann N Y Acad Sci*. 2008;1150:1-13.
47. Penno MA, Couper JJ, Craig ME, et al. Environmental Determinants of Islet Autoimmunity (ENDIA): a pregnancy to early life cohort study in children at-risk of type 1 diabetes. *BMC Pediatr*. 2013;13(1):124.
48. Smith LB, Liu X, Johnson SB, et al. Family adjustment to diabetes diagnosis in children: can participation in a study on type 1 diabetes genetic risk be helpful? *Pediatr Diabetes*. 2018;19(5):1025-1033.
49. Hummel S, Pflüger M, Hummel M, Bonifacio E, Ziegler AG. Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. *Diabetes Care*. 2011;34(6):1301-1305.
50. Vaarala O, Ilonen J, Ruohtula T, et al. Removal of bovine insulin from cow's milk formula and early initiation of beta-cell autoimmunity in the FINDIA Pilot Study. *Arch Pediatr Adolesc Med*. 2012;166(7):608-614.
51. Akerblom HK, Krischer J, Virtanen SM, et al. The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study: recruitment, intervention and follow-up. *Diabetologia*. 2011;54(3):627-633.
52. Knip M, Akerblom HK, Becker D, et al. Hydrolyzed infant formula and early β-cell autoimmunity: a randomized clinical trial. *JAMA*. 2014;311(22):2279-2287.
53. Knip M, Åkerblom HK, Al Taji E, et al. Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes: the TRIGR randomized clinical trial. *JAMA*. 2018;319(1):38-48.
54. Bonifacio E, Ziegler AG, Klingensmith G, et al. Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the pre-POINT randomized clinical trial. *JAMA*. 2015;313(15):1541-1549.
55. Ziegler AG, Danne T, Dunger DB, et al. Primary prevention of beta-cell autoimmunity and type 1 diabetes—the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) perspectives. *Mol Metab*. 2016;5(4):255-262.
56. Larsson PG, Lakshmikanth T, Laitinen OH, et al. A preclinical study on the efficacy and safety of a new vaccine against Coxsackievirus B1 reveals no risk for accelerated diabetes development in mouse models. *Diabetologia*. 2015;58(2):346-354.
57. Skyler JS, Greenbaum CJ, Lachin JM, et al. Type 1 Diabetes TrialNet—an international collaborative clinical trials network. *Ann N Y Acad Sci*. 2008;1150:14-24.
58. Battaglia M, Anderson MS, Buckner JH, et al. Understanding and preventing type 1 diabetes through the unique working model of TrialNet. *Diabetologia*. 2017;60(11):2139-2147.
59. Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet*. 2004;363(9413):925-931.
60. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the diabetes prevention trial--type 1. *Diabetes Care*. 2005;28(5):1068-1076.
61. Skyler JS. Update on worldwide efforts to prevent type 1 diabetes. *Ann N Y Acad Sci*. 2008;1150:190-196.
62. Fourlanos S, Perry C, Gellert SA, et al. Evidence that nasal insulin induces immune tolerance to insulin in adults with autoimmune diabetes. *Diabetes*. 2011;60(4):1237-1245.
63. Harrison LC, Honeyman MC, Steele CE, et al. Pancreatic beta-cell function and immune responses to insulin after administration of intranasal insulin to humans at risk for type 1 diabetes. *Diabetes Care*. 2004;27(10):2348-2355.
64. Wilkin T, Greene S, McCrimmon R. Testing the accelerator hypothesis: a new approach to type 1 diabetes prevention (adAPT 1). *Diabetes Obes Metab*. 2016;18(1):3-5.
65. Han MX, Craig ME. Research using autologous cord blood—time for a policy change. *Med J Aust*. 2013;199(4):288-299.
66. Bougneres PF, Carel JC, Castano L, et al. Factors associated with early remission of type I diabetes in children treated with cyclosporine. *N Engl J Med*. 1988;318(11):663-670.
67. Beam CA, MacCallum C, Herold KC, et al. GAD vaccine reduces insulin loss in recently diagnosed type 1 diabetes: findings from a Bayesian meta-analysis. *Diabetologia*. 2017;60(1):43-49.
68. Vudattu NK, Herold KC. Treatment of new onset type 1 diabetes with teplizumab: successes and pitfalls in development. *Expert Opin Biol Ther*. 2014;14(3):377-385.
69. Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;378(9789):412-419.
70. Orban T, Bundy B, Becker DJ, et al. Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment. *Diabetes Care*. 2014;37(4):1069-1075.
71. Rigby MR, Harris KM, Pinckney A, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. *J Clin Invest*. 2015;125(8):3285-3296.
72. Pescovitz MD, Greenbaum CJ, Bundy B, et al. B-lymphocyte depletion with rituximab and β-cell function: two-year results. *Diabetes Care*. 2014;37(2):453-459.
73. Hagopian W, Ferry RJ Jr, Sherry N, et al. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protege trial. *Diabetes*. 2013;62(11):3901-3908.
74. Couri CE, Oliveira MC, Stracieri AB, et al. C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA*. 2009;301(15):1573-1579.
75. Haller MJ, Gitelman SE, Gottlieb PA, et al. Antithymocyte globulin plus G-CSF combination therapy leads to sustained immunomodulatory and metabolic effects in a subset of responders with established type 1 diabetes. *Diabetes*. 2016;65(12):3765-3775.
76. Haller MJ, Schatz DA, Skyler JS, et al. Low-dose anti-thymocyte globulin (ATG) preserves β-cell function and improves HbA. *Diabetes Care*. 2018;dc180494.
77. Wherrett DK, Bundy B, Becker DJ, et al. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. *Lancet*. 2011;378(9788):319-327.
78. Moran A, Bundy B, Becker DJ, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. *Lancet*. 2013;381(9881):1905-1915.
79. Griffin KJ, Thompson PA, Gottschalk M, Kyllo JH, Rabinovitch A. Combination therapy with sitagliptin and lansoprazole in patients with recent-onset type 1 diabetes (REPAIR-T1D): 12-month results of a multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol*. 2014;2(9):710-718.
80. Gottlieb PA, Quinlan S, Krause-Steinrauf H, et al. Failure to preserve beta-cell function with mycophenolate mofetil and daclizumab combined therapy in patients with new- onset type 1 diabetes. *Diabetes Care*. 2010;33(4):826-832.
81. Brooks-Worrell B, Palmer JP. Prevention versus intervention of type 1 diabetes. *Clin Immunol*. 2013;149(3):332-338.

82. Ludvigsson J. Combination therapy for preservation of beta cell function in type 1 diabetes: new attitudes and strategies are needed! *Immunol Lett*. 2014;159(1–2):30-35.
83. Elding Larsson H, Vehik K, Bell R, et al. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. *Diabetes Care*. 2011;34(11):2347-2352.
84. Steck AK, Larsson HE, Liu X, et al. Residual beta-cell function in diabetes children followed and diagnosed in the TEDDY study compared to community controls. *Pediatr Diabetes*. 2017;18(8):794-802.
85. Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. *Pediatr Diabetes*. 2012;13(4):308-313.
86. Triolo TM, Chase HP, Barker JM, DPT-1 Study Group. Diabetic subjects diagnosed through the Diabetes Prevention Trial-Type 1 (DPT-1) are often asymptomatic with normal A1C at diabetes onset. *Diabetes Care*. 2009;32(5):769-773.
87. Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. *Diabetes Care*. 2017;40:1249-1255.
88. Raab J, Haupt F, Scholz M, et al. Capillary blood islet autoantibody screening for identifying pre-type 1 diabetes in the general population: design and initial results of the Fr1da study. *BMJ Open*. 2016;6(5):e011144.
89. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. *BMJ*. 2011;343:d4092.
90. Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes*. 2009;10-(Suppl 12):118-133.
91. Kapellen TM, Gausche R, Dost A, et al. Children and adolescents with type 1 diabetes in Germany are more overweight than healthy controls: results comparing DPV database and CrescNet database. *J Pediatr Endocrinol Metab*. 2014;27(3–4):209-214.
92. Islam ST, Abraham A, Donaghue KC, et al. Plateau of adiposity in Australian children diagnosed with type 1 diabetes: a 20-year study. *Diabet Med*. 2014;31:686-690.
93. Phelan H, Clapin H, Bruns L Jnr, et al. The Australasian Diabetes Data Network (ADDN): first national audit data on children and adolescents with type 1 diabetes. *Med J Aust*. 2017;206(3):121-125.
94. Lombardo F, Valenzise M, Wasniewska M, et al. Two-year prospective evaluation of the factors affecting honeymoon frequency and duration in children with insulin dependent diabetes mellitus: the key-role of age at diagnosis. *Diabetes Nutr Metab*. 2002;15(4):246-251.
95. Akirav E, Kushner JA, Herold KC. Beta-cell mass and type 1 diabetes: going, going, gone? *Diabetes*. 2008;57(11):2883-2888.
96. Shields BM, McDonald TJ, Oram R, et al. C-peptide decline in type 1 diabetes has two phases: an initial exponential fall and a subsequent stable phase. *Diabetes Care*. 2018;41(7):1486-1492.
97. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med*. 1998;128(7):517-523.
98. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003;26(3):832-836.
99. Böber E, Dündar B, Büyükgebiz A. Partial remission phase and metabolic control in type 1 diabetes mellitus in children and adolescents. *J Pediatr Endocrinol Metab*. 2001;14(4):435-441.
100. Bowden SA, Duck MM, Hoffman RP. Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. *Pediatr Diabetes*. 2008;9(3 Pt 1):197-201.
101. Mortensen HB, Hougaard P, Swift P, et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care*. 2009;32(8):1384-1390.
102. Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ, Group TDTS. Fall in C-peptide during first 4 years from diagnosis of type 1 diabetes: variable relation to age, HbA1c, and insulin dose. *Diabetes Care*. 2016;39(10):1664-1670.
103. Oram RA, Jones AG, Besser RE, et al. The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia*. 2014;57(1):187-191.
104. Davis AK, DuBose SN, Haller MJ, et al. Prevalence of detectable C-peptide according to age at diagnosis and duration of type 1 diabetes. *Diabetes Care*. 2015;38(3):476-481.

How to cite this article: Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. 2018;19(Suppl. 27):20–27. https://doi.org/10.1111/pedi.12734