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Other complications and associated conditions with diabetes in children and adolescents

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Impaired growth and development

Monitoring of growth and development and the use of percentile charts is a crucial element in the care of children and adolescents with diabetes.

Increased height at diagnosis of type 1 diabetes has been frequently reported (1–4). The precise mechanism for this and whether or not this increased height is maintained is unclear. Some studies report that poorly controlled patients show a decrease in height standard deviation score over the next few years, whilst better controlled patients maintain their height advantage (3, 4). Others have not shown this relationship with diabetic control (1).

In a recent Australian study, children treated with modern regimens (diagnosed after 1990) maintained their increased height better than children diagnosed before 1991 (2). Although the median HbA_{1c} did not differ significantly, those diagnosed after 1990 had a significantly higher number of insulin injections per day.

Poor gain of height and weight, hepatomegaly (NASH non alcoholic steatosis hepatitis) and late pubertal development (Mauriac syndrome) might be seen in children with persistently poorly controlled diabetes. Insulin insufficiency, celiac disease and other gastrointestinal disorders should be considered in this setting. There is no role for human growth hormone therapy in the poorly growing child with diabetes, unless it is associated with documented growth hormone deficiency.

Once the child or adolescent has reached a satisfactory weight after diagnosis, excessive weight gain may indicate high energy intake, and this may be related to excessive exogenous insulin. Excessive weight gain is more common during and after puberty (5). The Diabetes Control and Complications Trial and other studies have reported increased weight gain as a side effect of intensive insulin therapy with improved metabolic control (6–8). As obesity is a modifiable cardiovascular risk factor, careful monitoring and management of weight gain should be emphasised in diabetes care.

Girls seem to be more at risk of overweight and as well of eating disorders, In association with increased weight is the risk of hyperandrogenism and polycystic ovarian syndrome (9).

As increased doses of insulin are required during the adolescent growth spurt, it is important to remember to reduce the dose, when pubertal development is completed.

Associated autoimmune conditions

Islet cell antibodies (ICA) as well as autoantibodies to insulin, the 65 kDa isoform of glutamic acid decarboxylase (GAD65), and/or the protein tyrosine phosphatase (PTP) related molecules IA-2 (ICA512) and IA-2 β (phogrin) are observed in the overwhelming majority of children *en route* to clinical type 1 diabetes (10, 11).

A higher proportion of children with type 1 diabetes have also other detectable organ-specific autoantibodies (e.g. thyroid, adrenal) than children from the general population.

Family members of children with diabetes are more likely to have autoantibodies and other manifestations of autoimmune disease than the general population (12, 13).

Hypothyroidism

Primary hypothyroidism due to autoimmune thyroiditis occurs in approximately 3–8% (14) or 0.9 per 100 patient years (15) of children and adolescents with diabetes. Antithyroid antibodies have been shown to occur during the first years of diabetes in up to 25% of individuals with diabetes (16–20), and to be predictive for the development of clinical or compensated hypothyroidism (20). Thyroid antibodies are observed more frequently in girls than in boys, often emerging along with pubertal maturation (20).

Clinical features may include the presence of a painless goitre, increased weight gain, retarded growth, tiredness, lethargy, cold intolerance and bradycardia. Diabetic control may not be significantly affected.

Hypothyroidism is confirmed by demonstrating a low free thyroxine and a raised TSH concentration. Compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH.

The treatment is based on replacement with oral L-thyroxine (T₄) sufficient to normalise TSH levels and usually this allows regression of the goitre if present.

Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with diabetes (18, 21), but still more common than in the general population. It may be

due to Grave's disease or the hyperthyroid phase of Hashimoto's thyroiditis.

Hyperthyroidism should be considered if there is unexplained difficulty in maintaining glycaemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement or characteristic eye signs.

Treatment is anti-thyroid drugs such as carbimazole or propylthiouracil. Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to control tachycardia and agitation. Treatment options for persistent or recurrent hyperthyroidism include surgery or radio-active iodine.

Celiac disease

Celiac disease occurs in 1–10% of children and adolescents with diabetes or 0.7 per 100 patient years (15, 22–30). Celiac disease is often asymptomatic (26, 28, 31) and not necessarily associated with poor growth or poor diabetes control (although it should be excluded in such situations). Any child with gastrointestinal signs or symptoms including diarrhoea, abdominal pain, flatulence, dyspeptic symptoms, recurrent aphthous ulceration, unexplained poor growth or anaemia should be investigated. Undiagnosed celiac disease has also been associated with increased frequency of hypoglycaemic episodes and a progressive reduction in insulin requirement over a 12 month period prior to diagnosis (32).

The screening for celiac disease is based on the detection of IgA antiendomysial (EmA) antibodies and IgA antibodies against tissue transglutaminase (tTG). Although experience with a recently introduced assay for tissue transglutaminase (tTG) antibodies suggests that tTG may be more sensitive than EMA (91% vs 86%), the latter is slightly more specific for celiac disease (100% vs 96%) (33). Antigliadin antibodies might be more sensitive for celiac disease than EMA and tTg antibodies in very young children (<2 years), although their specificity remains modest.

IgA deficiency (which is present in 1:500 people) should be excluded when screening for celiac disease by measuring the total IgA level. IgA antibodies may not be detected in IgA deficiency, resulting in a false negative test. If the child is IgA deficient, then IgG antigliadin and IgG tTG antibodies need to be used for screening (34). This is particularly important because celiac disease is more common in those with IgA deficiency than in the general population (1.7% compared with 0.25%) (35).

In the presence of an elevated antibody level, a small bowel biopsy is needed to confirm the diagnosis of celiac disease (MARSH Classification) (36).

A gluten-free diet normalises the bowel mucosa and frequently leads to disappearance of antibodies,

but may not necessarily lead to improved diabetic control (37).

In an asymptomatic child with proven celiac disease gluten-free diet can be considered justified with the aim of reducing the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (i.e. osteoporosis and iron deficiency). Whilst this is a prudent recommendation, there is no literature documenting the long-term benefit of a gluten-free diet in asymptomatic children diagnosed with celiac disease by routine screening. One paediatric case series has shown an increase in height-for-weight following the introduction of gluten-free diet (31). Another demonstrated a non-significant increase in BMI and a non-significant reduction in HbA_{1c} (38). Some studies have demonstrated short term benefits in other patient groups in terms of improved wellbeing and increased bone mineral density (39–41).

The risk of celiac disease is negatively and independently associated with age at onset of diabetes, with a threefold higher risk being seen in children age <4 years than in those age >9 years; (42). It is also more common at diagnosis and in the first five years after diagnosis: in one study using annual EmA screening and biopsy 3.3% were positive at diabetes diagnosis; 3.3% at 1 year, 1.7% at 2 years, 1.7% at 3 years and 0.3% at 5 years (43).

Children with proven celiac disease should be referred to a paediatric gastroenterologist and receive support from a paediatric dietician with experience of gluten-free diets.

Vitiligo

Vitiligo is an acquired pigmentary disorder characterised by a loss of melanocytes resulting in white spots or leukoderma (44). It is a common autoimmune condition associated with type 1 diabetes and is present in about 6% of diabetic children (45). Treatment is difficult and multiple therapies have been tried with little success.

Primary adrenal insufficiency (Addison's disease)

Up to 2% of patients with type 1 diabetes have detectable antiadrenal autoantibodies (16, 46, 47). Addison's disease is occasionally associated with type 1 diabetes in the Autoimmune Polyglandular Syndromes (APS I and II). APS I is associated with mucocutaneous candidiasis and hypoparathyroidism and is caused by a mutation in the Autoimmune regulator gene (AIRE) on chromosome 21q22.3 (48, 49). APS II is more common in adults but is also seen in children in association with autoimmune thyroiditis (50).

The condition is suspected by the clinical picture of frequent hypoglycaemia, unexplained decrease in

insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatraemia and hyperkalaemia.

The diagnosis is based on the demonstration of a low cortisol response to a ACTH test. Treatment with a glucocorticoid is urgent and lifelong. In some cases the therapy has to be supplemented with a mineralocorticoid.

In asymptomatic children with positive adrenal antibodies detected on routine screening, a rising ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency.

The immunodysregulation polyendocrinopathy x-linked syndrome (IPEX) is another rare disorder associated with diabetes in early childhood, severe enteropathy and autoimmune symptoms due to a clear genetic defect (FOX-P3) (51).

Lipodystrophy (lipoatrophy and lipohypertrophy)

Lipoatrophy is now seen infrequently with the use of human insulin. Recent case reports have described lipoatrophy also occurring in pump patients treated with lispro insulin and in patients treated with Lantus (52–54) it is still a rare side effect.

Lipohypertrophy is a frequent complication of insulin therapy. It has been found in up to 48% of those with type 1 diabetes and has associated with higher HbA_{1c}, more injections and longer duration but not the needle length (55–57).

Non-rotation of injection sites has been consistently reported as an independent risk factor for lipohypertrophy (55, 57). Not only is it unsightly, but insulin may be absorbed erratically and unpredictably from these areas (58, 59).

Necrobiosis lipoidica diabetorum

These are well circumscribed, raised reddish lesions sometimes progressing to central ulceration, usually seen in the pre-tibial region. The reported prevalence in children varies from 0.06% to 10% (45, 60). The aetiology is not clearly understood. Necrobiosis lipoidica diabetorum has been associated with underlying microvascular complications (61, 62). A wide variety of treatments have been used over the years in adults including: topical, systemic or intra-lesional steroids, aspirin, cyclosporin, mycophenolate, becaplermin, excision and grafting, laser surgery, hyperbaric oxygen, topical granulocyte-macrophage colony-stimulating factor and photochemotherapy with topical PUVA (63–70). None has been proven useful in controlled clinical trials and many of these treatments have significant side effects.

Limited joint mobility

Limited joint mobility (LJM) is the earliest clinically apparent long-term complication of type 1 diabetes in childhood. It is a bilateral painless, but obvious, contracture of the finger joints and large joints, associated with tight waxy skin. Following its initial description associated with short stature, and early microvascular complications, it was recognized to be a common feature of both type 1 and type 2 diabetes, with a wide range of limitation, affecting ~30% of youngsters and correlating with diminished stature (71, 72). Changes begin in the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and extend radially with involvement of the distal interphalangeal joints as well. Involvement of larger joints includes particularly the wrist and elbow, but also ankles and cervical and thoracolumbar spine. The limitation is only mildly disabling even when severe.

A simple examination method is to have the patient attempt to approximate palmar surfaces of the interphalangeal joints (73). Passive examination is essential to confirm that inability to do so is due to LJM. With rare exception, LJM appears after the age of 10 years. The interval between the detection of mild LJM and progression to moderate or severe changes in those who progress beyond mild changes, ranges from a few months to four years, following which stabilization occurs (72).

Skin biopsy specimens have shown active fibroblasts and extensive collagen polymerization in the rough endoplasmic reticulum (74). The biochemical basis for LJM is likely glycation of protein with the formation of advanced glycation end products (AGE). This results in increased stiffness of the periarticular and skin collagen with decreased range of motion. Fluorescence of skin collagen, reflecting the accumulation of stable end products of the glycation reaction, with increased cross-linking, dehydration, and condensation of collagen, increases linearly with age but with abnormal rapidity in type 1 diabetes, correlating with the presence of retinopathy, nephropathy, and LJM (75).

LJM is associated with a 3–4 fold risk for retinopathy, nephropathy, and neuropathy (72, 76, 77). Although cross-sectional studies showed no relationship to diabetes control as measured by HbA1c, longitudinal study of average HbA1c from onset of diabetes showed that for every unit increase in average HbA1c, there was an approximately 46% increase in the risk of developing LJM (78).

There has been a >4 fold reduction in frequency of LJM between the mid-70s and mid-90s, in children (79) and a lesser decline in adults (80), with a marked decrease in severity in the fewer children who are affected, most likely the result of improved glucose control during this era.

Oedema

Generalised oedema due to water retention is a rare complication of insulin therapy. Oedema may be seen during establishment of improved glycaemic control after prolonged periods of poor metabolic control, particularly if there has been significant omission of insulin (81, 82). The oedema spontaneously resolves over a period of days to weeks with continued good glycaemic control.

Recommendations

- Monitoring of growth and physical development and the use of growth charts is an essential element in the continuous care of children and adolescents with type 1 diabetes.
- Screening of thyroid function by analysing circulating TSH and antibodies is recommended at the diagnosis of diabetes and, thereafter, every second year in asymptomatic individuals without goitre or in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise.
- Screening for celiac disease should be carried out at the time of diagnosis, annually for the first five years and every second year thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of celiac disease or the child has a first-degree relative with celiac disease.
- Children with type 1 diabetes detected to have celiac disease on routine screening, should be referred to a paediatric gastroenterologist and on confirmation of the diagnosis receive support from a paediatric dietician with experience of gluten-free diets.
- Routine clinical examination should be undertaken for skin and joint changes. Regular screening by laboratory or radiological methods is not recommended. There is no established therapeutic intervention for lipodystrophy, necrobiosis lipoidica or limited joint mobility.

References

1. BOGNETTI E, RIVA MC, BONFANTI R, MESCHI F, VISCARDI M, CHIUMELLO G. Growth changes in children and adolescents with short-term diabetes. *Diabetes Care* 1998; 21: 1226–1229.
2. DONAGHUE KC, KORDONOURI O, CHAN A, SILINK M. Secular trends in growth in diabetes: are we winning? *Archives of Disease in Childhood*. 2003; 88: 151–154.
3. GUNCZLER P, LANES R. Poor metabolic control decreases the growth velocity of diabetic children. *Diabetes Care* 1999; 22: 1012.
4. HOLL RW, GRABERT M, HEINZE E, SORGO W, DEBATIN KM. Age at onset and long-term metabolic control affect height in type-1 diabetes mellitus. *European Journal of Pediatrics*. 1998; 157: 972–977.

5. HOLL RW, HEINZE E, SEIFERT M, GRABERT M, TELLER WM. Longitudinal analysis of somatic development in paediatric patients with IDDM: genetic influences on height and weight. *Diabetologia* 1994; 37: 925–929.
6. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N.Engl.J.Med.* 1993; 329: 977–986.
7. HOLL RW, GRABERT M, SORGO W, HEINZE E, DEBATIN KM. Contributions of age, gender and insulin administration to weight gain in subjects with IDDM. *Diabetologia* 1998; 41: 542–547.
8. THON A, HEINZE E, FEILEN KD, HOLL RW, SCHMIDT H, KOLETZKO S, WENDEL U, NÖTHJUNGE J. Development of height and weight in children with diabetes mellitus: report on two prospective multicentre studies, one cross-sectional, one longitudinal. *European Journal of Pediatrics* 1992; 151: 258–262.
9. CODNER E, SOTO N, LOPEZ P, TREJO L, AVILA A, EYZAGUIRRE FC, INIGUEZ G, CASSORLA F. Diagnostic criteria for polycystic ovary syndrome and ovarian morphology in women with type 1 diabetes mellitus. *J.Clin.Endocrinol.Metab* 2006; 91: 2250–2256.
10. ATKINSON MA, EISENBARTH GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 2001; 358: 221–229.
11. EISENBARTH GS, GOTTLIEB PA. Autoimmune polyendocrine syndromes. *N.Engl.J.Med.* 2004; 350: 2068–2079.
12. SOUGIOULTZOGLU F, FALORNI A, KASSI G, BROZZETTI A, KARAMITSOS D, KOLIAKOS GG. Coincidence of high antiislet and antithyroid autoantibody titres in first-degree relatives of patients with type 1 diabetes. *Exp.Clin.Endocrinol.Diabetes* 2005; 113: 85–89.
13. SUMNIK Z, KOLOUSKOVA S, MALCOVA H, VAVRINEC J, VENHACOVA J, LEBL J, CINEK O. High prevalence of celiac disease in siblings of children with type 1 diabetes. *Eur.J.Pediatr.* 2005; 164: 9–12.
14. HANSEN D, BENNEDBAEK FN, HOIER-MADSEN M, HEGEDUS L, JACOBSEN BB. A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes. *Eur.J.Endocrinol.* 2003; 148: 245–251.
15. GLASTRAS SJ, CRAIG ME, VERGE CF, CHAN AK, CUSUMANO JM, DONAGHUE KC. The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and celiac disease and microvascular complications. *Diabetes Care* 2005; 28: 2170–2175.
16. DE BLOCK CE, DE LEEUW IH, VERTOMMEN JJ, ROOMAN RP, DU CAJU MV, VAN CAMPENHOUT CM, WEYLER JJ, WINNOCK F, VAN AUTREVE J, GORUS FK, THE BELGIAN DR. Beta-cell, thyroid, gastric, adrenal and celiac autoimmunity and HLA-DQ types in type 1 diabetes. *Clinical & Experimental Immunology* 2001; 126: 236–241.
17. HOLL RW, BOHM B, LOOS U, GRABERT M, HEINZE E, HOMOKI J. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Effect of age, gender and HLA type. *Hormone Research* 1999; 52: 113–118.
18. KONTIAINEN S, SCHLENZKA A, KOSKIMIES S, RILVA A, MAENPAA J. Autoantibodies and autoimmune diseases in young diabetics. *Diabetes Research* 1990; 13: 151–156.
19. KORDONOURI O, KLINGHAMMER A, LANG EB, GRUTERS-KIESLICH A, GRABERT M, HOLL RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. *Diabetes Care* 2002; 25: 1346–1350.
20. KORDONOURI O, HARTMANN R, DEISS D, WILMS M, GRUTERS-KIESLICH A. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. *Arch.Dis.Child* 2005; 90: 411–414.
21. UMPIERREZ GE, LATIF KA, MURPHY MB, LAMBETH HC. Stentz: Thyroid Dysfunction in Patients With Type 1 Diabetes: A longitudinal study. *Diabetes Care* 2003; 26: 1181–1185.
22. AKTAY AN, LEE PC, KUMAR V, PARTON E, WYATT DT, WERLIN SL. The prevalence and clinical characteristics of celiac disease in juvenile diabetes in Wisconsin. *Journal of Pediatric Gastroenterology & Nutrition* 2001; 33: 462–465.
23. CALERO P, RIBES-KONINCKX C, ALBIACH V, CARLES C, FERRER J. IgA anti gliadin antibodies as a screening method for nonovert celiac disease in children with insulin-dependent diabetes mellitus. *Journal of Pediatric Gastroenterology & Nutrition*. 1996; 23: 29–33.
24. CARLSSON AK, AXELSSON IE, BORULF SK, BREDBERG AC, LINDBERG BA, SJOBERG KG, IVARSSON SA. Prevalence of IgA-antiendomysium and IgA-anti gliadin autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children and adolescents. *Pediatrics* 1999; 103: 1248–1252.
25. CRONE J, RAMI B, HUBER WD, GRANDITSCH G, SCHOBERT E. Prevalence of Celiac Disease and Follow-up of EMA in Children and Adolescents With Type 1 Diabetes Mellitus. *Journal of Pediatric Gastroenterology & Nutrition* 2003; 37: 67–71.
26. DE V, I, GHIRLANDA G, GASBARRINI G. Prevalence of celiac disease in type I diabetes: a multicentre study. *Acta Paediatrica Supplement*. 1996; 412: 56–57.
27. HANSEN D, BENNEDBAEK FN, HANSEN LK, HOIER-MADSEN M, HEGEDU LS, JACOBSEN BB, HUSBY S. High prevalence of celiac disease in Danish children with type I diabetes mellitus.[comment]. *Acta Paediatrica* 2001; 90: 1238–1243.
28. NOT T, TOMMASINI A, TONINI G, BURATTI E, POCECCO M, TORTUL C, VALUSSI M, CRICHIUTTI G, BERTI I, TREVISIOL C, AZZONI E, NERI E, TORRE G, MARTELOSSI S, SOBAN M, LENHARDT A, CATTIN L, VENTURA A. Undiagnosed celiac disease and risk of autoimmune disorders in subjects with Type I diabetes mellitus. *Diabetologia* 2001; 44: 151–155.
29. SMITH CM, CLARKE CF, PORTEOUS LE, ELSORI H, CAMERON DJ. Prevalence of celiac disease and longitudinal follow-up of anti gliadin antibody status in children and adolescents with type 1 diabetes mellitus. *Pediatric Diabetes*. 2000; 1(4): 199–203.
30. WESTMAN E, AMBLER GR, ROYLE M, PEAT J, CHAN A. Children with celiac disease and insulin dependent diabetes mellitus—growth, diabetes control and dietary intake. *Journal of Pediatric Endocrinology & Metabolism* 1999; 12: 433–442.

31. SAUKKONEN T, VAISANEN S, AKERBLOM HK, SAVILAHTI E, Childhood Diabetes in Finland Study Group. Celiac disease in children and adolescents with type 1 diabetes: a study of growth, glycaemic control, and experiences of families. *Acta Paediatrica* 2002; 91: 297–302.
32. MOHN A, CERRUTO M, LAFUSCO D, PRISCO F, TUMINI S, STOPPOLONI O, CHIARELLI F. Celiac disease in children and adolescents with type I diabetes: importance of hypoglycemia. *Journal of Pediatric Gastroenterology & Nutrition* 2001; 32: 37–40.
33. TESEI N, SUGAI E, VAZQUEZ H, SMECUOL E, NIVELONI S, MAZURE R, MORENO ML, GOMEZ JC, MAURINO E, BAI JC. Antibodies to human recombinant tissue transglutaminase may detect celiac disease patients undiagnosed by endomysial antibodies. *Alimentary Pharmacology & Therapeutics* 2003; 17: 1415–1423.
34. LENHARDT A, PLEBANI A, MARCHETTI F, GERARDUZZI T, NOT T, MEINI A, VILLANACCI V, MARTELOSSI S, VENTURA A. Role of human-tissue transglutaminase IgG and anti-gliadin IgG antibodies in the diagnosis of celiac disease in patients with selective immunoglobulin A deficiency. *Dig.Liver Dis.* 2004; 36: 730–734.
35. CATALDO F, MARINO V, BOTTARO G, GRECO P, VENTURA A. Celiac disease and selective immunoglobulin A deficiency. *J Pediatr* 1997; 131: 306–308.
36. MARSH MN, CROWE PT. Morphology of the mucosal lesion in gluten sensitivity. *Baillieres Clin.Gastroenterol.* 1995; 9: 273–293.
37. AMIN R, MURPHY N, EDGE J, AHMED ML, ACERINI CL, DUNGER DB. A longitudinal study of the effects of a gluten-free diet on glycemic control and weight gain in subjects with type 1 diabetes and celiac disease. *Diabetes Care* 2002; 25: 1117–1122.
38. ACERINI CL, AHMED ML, ROSS KM, SULLIVAN PB, BIRD G, DUNGER DB. Celiac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. *Diabetic Medicine* 1998; 15: 38–44.
39. CORAZZA GR, DI SARIO A, CECCHETTI L, JORIZZO RA, DI STEFANO M, MINGUZZI L, BRUSCO G, BERNARDI M, GASBARINI G. Influence of pattern of clinical presentation and of gluten-free diet on bone mass and metabolism in adult celiac disease. *Bone* 1996; 18: 525–530.
40. FABIANI E, CATASSI C, VILLARI A, GISMONDI P, PIERDOMENICO R, RATSCH IM, COPPA GV, GIORGI PL. Dietary compliance in screening-detected celiac disease adolescents. *Acta Paediatrica Supplement* 1996; 412: 65–67.
41. MUSTALAHTI K, COLLIN P, SIEVANEN H, SALMI J, MAKI M. Osteopenia in patients with clinically silent celiac disease warrants screening. *Lancet* 1999; 354: 744–745.
42. CERUTTI F, BRUNO G, CHIARELLI F, LORINI R, MESCHI F, SACCHETTI C. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. *Diabetes Care* 2004; 27: 1294–1298.
43. LARSSON K, CARLSSON A, CEDERWALL E, JONSSON B, NEIDERUD J, JONSSON B, LERNMARK A, IVARSSON SA, Skane Study Group. Annual screening detects celiac disease in children with type 1 diabetes. *Pediatric Diabetes*. 2008; 9(4 Pt 2): 354–9.
44. HANDA S, DOGRA S. Epidemiology of childhood vitiligo: a study of 625 patients from north India. *Pediatric Dermatology* 2003; 20: 207–210.
45. VERROTTI A, CHIARELLI F, AMERIO PL, MORGESE G. Skin diseases in children with type 1 diabetes mellitus. *Journal of the European Academy of Dermatology and Venereology* 1995; 4: 41–43.
46. FALORNI A, LAURETI S, NIKOSHKOV A, PICCHIO ML, HALLENGREN B, VANDEWALLE CL, GORUS FK, TORTOIOLI C, LUTHMAN H, BRUNETTI P, SANTEUSANIO F. 21-hydroxylase autoantibodies in adult patients with endocrine autoimmune diseases are highly specific for Addison's disease. *Belgian Diabetes Registry. Clinical & Experimental Immunology* 1997; 107: 341–346.
47. PETERSON P, SALMI H, HYOTY H, MIETTINEN A, ILONEN J, REIJONEN H, KNIP M, AKERBLOM HK, KROHN K. Steroid 21-hydroxylase autoantibodies in insulin-dependent diabetes mellitus. Childhood Diabetes in Finland (DiMe) Study Group. *Clinical Immunology & Immunopathology* 1997; 82: 37–42.
48. AALTONEN J, BJORSES P, SANDKUIJL L, PERHEENTUPA J, PELTONEN L. An autosomal locus causing autoimmune disease: autoimmune polyglandular disease type I assigned to chromosome 21. *Nat.Genet.* 1994; 8: 83–87.
49. AHONEN P, MYLLARNIEMI S, SIPILA I, PERHEENTUPA J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N.Engl.J.Med.* 1990; 322: 1829–1836.
50. DITTMAR M, KAHALY GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. *J.Clin.Endocrinol.Metab* 2003; 88: 2983–2992.
51. CHATILA TA, BLAESER F, HO N, LEDERMAN HM, VOULGAROPOULOS C, HELMS C, BOWCOCK AM. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic dysregulation syndrome. *J.Clin.Invest* 2000; 106: R75–R81.
52. AMPUDIA-BLASCO FJ, GIRBES J, CARMENA R. A case of lipoatrophy with insulin glargine: long-acting insulin analogs are not exempt from this complication. *Diabetes Care* 2005; 28: 2983.
53. AMPUDIA-BLASCO FJ, HASBUM B, CARMENA R. A New Case Of Lipoatrophy With Lispro Insulin In Insulin Pump Therapy: Is there any insulin preparation free of complications? *Diabetes Care* 2003; 26: 953.
54. GRIFFIN ME, FEDER A, TAMBORLANE WV. Lipoatrophy Associated With Lispro Insulin in Insulin Pump Therapy: An old complication, a new cause? *Diabetes Care* 2001; 24: 174.
55. HAUNER H, STOCKAMP B, HAASTERT B. Prevalence of lipohypertrophy in insulin-treated diabetic patients and predisposing factors. *Experimental & Clinical Endocrinology & Diabetes* 1996; 104: 106–110.
56. KORDONOURI O, LAUTERBORN R, DEISS D. Lipohypertrophy in young patients with type 1 diabetes. *Diabetes Care* 2002; 25: 634.
57. SAEZ-DE-IBARRA L, GALLEGO F. Factors related to lipohypertrophy in insulin-treated diabetic patients: Role of educational intervention. *Practical Diabetes International* 1998; 15: 9–11.

58. JOHANSSON UB, AMSBERG S, HANNERZ L, WREDLING R, ADAMSON U, ARNQVIST HJ, LINS PE. Impaired absorption of insulin aspart from lipohypertrophic injection sites. *Diabetes Care* 2005; 28: 2025–2027.
59. THOW JC, JOHNSON AB, MARSDEN S, TAYLOR R, HOME PD. Morphology of palpably abnormal injection sites and effects on absorption of isophane(NPH) insulin. *Diabetic Medicine* 1990; 7: 795–799.
60. DE SILVA BD, SCHOFIELD OMOV, WALKER JD. The prevalence of necrobiosis lipoidica diabetorum in children with type 1 diabetes. *British Journal of Dermatology* 1999; 141: 593–594.
61. KELLY WF, NICHOLAS J, ADAMS J, MAHMOOD R. Necrobiosis lipoidica diabetorum: association with background retinopathy, smoking, and proteinuria. A case controlled study. *Diabetic Medicine* 1993; 10: 725–728.
62. VERROTTI A, CHIARELLI F, AMERIO P, MORGESE G. Necrobiosis lipoidica diabetorum in children and adolescents: a clue for underlying renal and retinal disease. *Pediatric Dermatology* 1995; 12: 220–223.
63. BOYD AS. Tretinoin treatment of necrobiosis lipoidica diabetorum. *Diabetes Care* 1999; 22: 1753–1754.
64. D'ARGENTO V, CURATOLLI G, FILOTICO R, FOTI C, VENA GA. Cyclosporin A in the treatment of necrobiosis lipoidica diabetorum. *Journal of Dermatological Treatment* 1997; 8: 123–125.
65. EVANS AV, AHERTON DJ. Recalcitrant ulcers in necrobiosis lipoidica diabetorum healed by topical granulocyte-macrophage colony-stimulating factor. *British Journal of Dermatology* 2002; 147: 1023–1025.
66. LING TC, THOMSON KF, GOULDEN V, GOODFIELD MJ. PUVA therapy in necrobiosis lipoidica diabetorum. *Journal of the American Academy of Dermatology* 2002; 46: 319–320.
67. MORENO-ARIAS GA, CAMPS-FRESNEDA A. Necrobiosis lipoidica diabetorum treated with the pulsed dye laser. *Journal of Cosmetic & Laser Therapy* 2001; 3: 143–146.
68. NGUYEN K, WASHENIK K, SHUPACK J. Necrobiosis lipoidica diabetorum treated with chloroquine. *Journal of the American Academy of Dermatology* 2002; 46: S34–S36.
69. STEPHENS E RJGP. Becaplermin and necrobiosis lipoidica diabetorum: results of a case control pilot study. *Journal of Diabetes & its Complications* 2001; 15: 55–56.
70. TIDMAN M. Management of necrobiosis lipoidica. *Clinical & Experimental Dermatology* 2002; 27: 328–337.
71. GRGIC A, ROSENBLOOM AL, WEBER FT, GIOR-DANO B, MALONE JI, SHUSTER JJ. Joint contracture—common manifestation of childhood diabetes mellitus. *J.Pediatr.* 1976; 88: 584–588.
72. ROSENBLOOM AL, SILVERSTEIN JH, LEZOTTE DC, RILEY WJ, MACLAREN NK. Limited joint mobility in diabetes mellitus of childhood: natural history and relationship to growth impairment. *J.Pediatr.* 1982; 101: 874–878.
73. ROSENBLOOM AL, SILVERSTEIN JH, LEZOTTE DC, RICHARDSON K, MCCALLUM M. Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. *N.Engl.J.Med.* 1981; 305: 191–194.
74. HANNA W, FRIESEN D, BOMBARDIER C, GLADMAN D, HANNA A. Pathologic features of diabetic thick skin. *J.Am.Acad.Dermatol.* 1987; 16: 546–553.
75. MONNIER VM, VISHWANATH V, FRANK KE, ELMETS CA, DAUCHOT P, KOHN RR. Relation between complications of type I diabetes mellitus and collagen-linked fluorescence. *N.Engl.J.Med.* 1986; 314: 403–408.
76. GARG SK, CHASE HP, MARSHALL G, JACKSON WE, HOLMES D, HOOPS S, HARRIS S. Limited joint mobility in subjects with insulin dependent diabetes mellitus: relationship with eye and kidney complications. *Archives of Disease in Childhood* 1992; 67: 96–99.
77. STARKMAN HS, GLEASON RE, RAND LI, MILLER DE, SOELDNER JS. Limited joint mobility (LJM) of the hand in patients with diabetes mellitus: relation to chronic complications. *Ann.Rheum.Dis.* 1986; 45: 130–135.
78. SILVERSTEIN JH, GORDON G, POLLOCK BH, ROSENBLOOM AL. Long-term glycemic control influences the onset of limited joint mobility in type 1 diabetes. *J.Pediatr.* 1998; 132: 944–947.
79. INFANTE JR, ROSENBLOOM AL, SILVERSTEIN JH, GARZARELLA L, POLLOCK BH. Changes in frequency and severity of limited joint mobility in children with type 1 diabetes mellitus between 1976-78 and 1998. *Journal of Pediatrics* 2001; 138: 33–37.
80. LINDSAY JR, KENNEDY L, ATKINSON AB, BELL PM, CARSON DJ, MCCANCE DR, HUNTER SJ. Reduced prevalence of limited joint mobility in type 1 diabetes in a U.K. clinic population over a 20-year period. *Diabetes Care* 2005; 28: 658–661.
81. HIRSHBERG B, MUSZKAT M, MAROM T, SHALIT M. Natural course of insulin edema. *Journal of Endocrinological Investigation* 2000; 23: 187–188.
82. WHEATLEY T, EDWARDS OM. Insulin oedema and its clinical significance: metabolic studies in three cases. *Diabetic Medicine* 1985; 2: 400–404.