

Diet, Growth, and the Risk for Type 1 Diabetes in Childhood

A matched case-referent study

AUSTÈ PUNDZIŪTĒ-LYCKĀ, PHD¹
LARS-ÅKE PERSSON, PHD²
GUNILLA CEDERMARK³
AGNETA JANSSON-ROTH⁴

ULLA NILSSON⁵
VERA WESTIN⁶
GISELA DAHLQUIST, PHD¹

OBJECTIVE — To study the association between type 1 diabetes risk and previous intake of energy, accounting for body size and previous intake of nutrients and foods, accounting for the energy intake.

RESEARCH DESIGN AND METHODS — We conducted an incident population-based case-referent study in Stockholm, Sweden, including 99 of 100 eligible 7- to 14-year-old diabetic children and 180 of 200 age-, sex-, and area-matched referent children identified through the Swedish population register. Average daily energy and nutrient intake 1 year before diabetes diagnosis/interview was estimated using the food frequency questionnaire with assessment of consumed food amounts. Mean SD scores of growth measurements taken during the last 4 years before the diagnosis were used. Odds ratios (ORs) were calculated by conditional logistic regression.

RESULTS — Average intake of energy, carbohydrate, fat, and protein was significantly higher among the case subjects as well as mean weight-for-age SD score. Higher energy intake and weight-for-age were both associated with increased diabetes risk after adjustment for each other: OR (95% CI) for medium and high levels of energy intake were 1.33 (0.52–3.42) and 5.23 (1.67–16.38), respectively, and for weight-for-age were 3.20 (1.30–7.88) and 3.09 (1.16–8.22), respectively. High intake of carbohydrates, especially disaccharides and sucrose, increased diabetes risk.

CONCLUSIONS — Higher energy intake and larger body size were independently associated with increased diabetes risk. Of the different nutrients, higher intake of carbohydrates, particularly disaccharides and sucrose, increased the risk. Lifestyle habits leading to higher energy intake and more rapid growth in childhood may contribute to the increase of childhood-onset type 1 diabetes by different mechanisms.

Diabetes Care 27:2784–2789, 2004

Dietary intake of certain nutrients and possible toxic food components is of interest in the search for triggers or promoters of the autoimmune β -cell destruction that may lead to type 1 diabetes (1–3). Studies of infant diet indicated that short breast-feeding duration and early introduction of cow's milk pro-

teins may be causally related to the development of childhood diabetes (4) and progressive β -cell autoimmunity before the age of 4 years (5). Some studies also found that high intake of cow's milk later in childhood is associated with increased risk of diabetes (6,7). In a previous population-based case-referent study, our

group showed a dose-response relationship between the risk of developing childhood diabetes and the frequency of intake of foods rich in protein, carbohydrates, and nitrosamines (8). Moreover, the nutrition-associated risk profiles differed between the age-groups (9). Analyzing prospectively recorded childhood growth data, we have also showed that future diabetic children had a higher linear growth rate several years before the diagnosis compared with age- and sex-matched referents (10). Studies from different populations have confirmed that and also found that children who develop type 1 diabetes are heavier and have higher BMI or weight-for-height both during infancy and later in childhood compared with referent children (11–15). Although genetic predisposition toward rapid growth and susceptibility to hyperinsulinemia may be the underlying causes, differences of energy intake probably play a role in promoting the more rapid growth of the pre-diabetic children. As body size and energy intake are positively associated, there is a need to simultaneously consider previous dietary intake, as well as body size, when studying the risk of type 1 diabetes in childhood.

In the present study, we investigate whether the higher intake of energy 1 year before the diagnosis is associated with an increase in type 1 diabetes risk, taking relative body size into account. The association between the intake of certain nutrients or groups of food with diabetes risk, taking the total energy intake into account, was also studied.

RESEARCH DESIGN AND METHODS

— The Karolinska Institute Ethics Committee and the Swedish Data Inspection Board approved the study. Incident diabetic case subjects 7–14 years of age at diagnosis, occurring in the Stockholm region in Sweden during 1991–1993, were invited to participate. Case subjects were identified at four pediatric departments, where all children aged 0–14 years with suspected diabetes

From the ¹Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden; the ²Department of Mother's and Children's Health, International Maternal and Child Health, Uppsala University, Uppsala, Sweden; the ³Department of Pediatrics, Danderyd Hospital, Danderyd, Sweden; ⁴Sachs' Children's Hospital at South Stockholm General Hospital, Stockholm, Sweden; the ⁵Pediatric Clinic, St. Görans Hospital, Stockholm, Sweden; and the ⁶Children's Hospital at Huddinge University Hospital, Stockholm, Sweden.

Address correspondence and reprint requests to Austė Pundziūtė-Lyckā, Department of Clinical Sciences, Pediatrics, Umeå University 901 85 Umeå, Sweden. E-mail: austepundziute.lycka@pediatri.umu.se.

Received for publication 29 April 2004 and accepted in revised form 1 September 2004.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2004 by the American Diabetes Association.

are referred. The determination of diabetes type was made on clinical grounds. Analysis of autoantibodies was not performed. One hundred consecutive case subjects were invited and 99 accepted. For each case subject, two referent children matched for age, sex, and geographical region within Stockholm were identified through the official Swedish population register and invited to participate. A total of 180 (90%) referents agreed to participate.

Dietary data

A food frequency questionnaire including 206 different foods and dishes was developed on the basis of previous dietary studies of Swedish children in relevant ages. Evaluation of the dietary history in school children showed satisfactory agreement with 24-h recall for energy and all nutrients included in the current study, although dietary history tended to give higher group mean values (16). Reproducibility of the method was also good—for most nutrients the correlations were moderate to high between two dietary history interviews performed with a 3-month interval (16). Copies of the questionnaire are available from the authors. Interviews were performed by experienced dietitians who received special training on how to avoid bias when asking questions. Children were interviewed together with the primary care taker or both parents regarding the dietary intake 1 year before the diabetes diagnosis or the interview. Mothers were present in all but a few instances. The interview started by mapping the general food habits, meal frequencies, and meals at home, school, and elsewhere and thereafter advanced into meals and general dietary intake. A system of cross-checking to the meal pattern and number of breakfasts, lunches, and dinners per week was used throughout the interview. The interview was also supported by a listing of all of the dishes served at the schools in question during the reference period—in Sweden all children receive free school lunches, and no commercial school cafeterias are available in schools. Consumed amounts were estimated using household measures and pictures of portion sizes. Frequencies and amounts of consumed foods were recorded in the questionnaire. Interviews were performed at the hospital (most case subjects) or at home (some case subjects and all referents). The same dietitian in-

terviewed the case subject and matched referent children. Average individual intake of certain foods or food groups was calculated and expressed as grams per day. Dietary data were transformed into energy and nutrient intake per day using the Swedish Food Data Bank, computerized by the Swedish National Food Administration. Food groups were represented by several items: milk group includes sweet and sour milk, yogurt, cream, and ice-cream; bread group includes dark and white bread, biscuits, and pasta; and nitrosamine-containing foods include different sorts of smoked meat, sausage, and fish.

Growth data

After permission from the parents, prospectively recorded growth data were retrieved from the records at Child Health Clinics and School Health services. Growth data before the diagnosis or interview were available for 77 (78%) case subjects and 148 (82%) referents, with 5.7 and 5.1 measurements per individual on average, respectively ($P = 0.54$). Most of the growth data available covered the school age (from 6 years of age). Growth data were transformed into age- and sex-specific SD scores according to the 1978 Centers for Disease Control/World Health Organization reference (17) used by the EpiNut program (EPI Info, version 6.1; Division of Surveillance and Epidemiology, Centers for Disease Control and Prevention, Atlanta, GA). Calculation of the weight-for-height SD scores in EpiNut is limited to 11.5 years and ≤ 145 cm for males and 10 years and ≤ 137 cm for females; thus, our analyses were limited accordingly. To represent the relative body size of the individual, we calculated an average SD score of measurements taken during the 4-year period preceding the diagnosis or interview. As growth of the case children may be influenced by metabolic disturbances, measurements taken during the last 3 months preceding the diagnosis were excluded from the calculations. We chose to include the data recorded during the last 4-year period in order to make the number of measurements included comparable for children of different age. Seventy-four case subjects and 143 referents had growth data available ($P = 0.37$), with 2.3 and 2.5 measurements on average, respectively ($P = 0.22$).

Dietary analysis was possible for 98

matched sets of case and referent children: 78 with 2 and 20 with 1 referent child per case. Analysis including both dietary and growth information was possible for 67 matched sets (67%): 40 with 2 and 27 with 1 referent child per case. There were no significant differences in the intake of energy, protein, fat, and carbohydrates between the children with and without growth information (data not shown).

Statistical analysis

Mean intake of energy and different nutrients and mean SD scores of case subjects and referents were compared using one-way ANOVA. Crude and adjusted ORs for the risk of developing diabetes and 95% CIs were calculated using conditional logistic regression analysis of matched case-referent sets (EGRET, Epidemiological Graphics Estimation and Testing Packages; Statistical and Epidemiological Research, Seattle, WA). For the dietary analyses the variables were dichotomized using the 75th percentile of the distribution in case subjects and referents for the cutoff. ORs associated with high intake (above the 75th percentile) of certain nutrient or food groups were adjusted for the high intake of energy by including both dichotomous variables into the same model (nutrient/food and total energy intake). For the analyses of diet and growth, the intake of energy and average SD scores were grouped into three levels of exposure using the values of the 33rd and 66th percentiles of the distribution for the cutoff.

RESULTS— Of 206 foods and dishes listed on the interview form, both case subjects and referents consumed 77 items on average. The mean frequency of intake and average portion size did not differ significantly between the case and referent children (data not shown), but mean registered amounts of food tended to be slightly higher for the case subjects (32 and 30 g, respectively, $P = 0.08$). The average daily intake of energy, protein, fat, carbohydrates, and selected groups of food was higher among the case subjects compared with the referents (Table 1).

There was a crude association between high intake (above the 75th percentile) of energy, protein, and carbohydrates with increased diabetes risk (Table 2). When analyzing different types of carbohydrates, high intake of disaccharides,

Table 1—Mean daily intake of energy, selected nutrients, and groups of food and mean SD scores of growth measurements taken during the last 4-year period preceding diabetes diagnosis or interview in 7- to 14-year-old Swedish children

	Mean \pm SD		P
	Case subjects	Referents	
Energy and nutrients			
n (male/female)	99 (50/49)	180 (86/94)	
Energy (kcal)	2,751 \pm 876	2,449 \pm 706	0.002
Protein (g)	99 \pm 34	88 \pm 28	0.01
Fat (g)	101 \pm 40	90 \pm 33	0.01
Carbohydrate (g)	358 \pm 116	320 \pm 95	0.01
Monosaccharide (g)	43 \pm 18	41 \pm 17	0.40
Disaccharide (g)	135 \pm 55	116 \pm 43	0.004
Sucrose (g)	80 \pm 40	67 \pm 28	0.01
Groups of food			
Milk (g)	953 \pm 502	838 \pm 636	0.12
Bread (g)	149 \pm 92	121 \pm 85	0.01
Soft drinks (g)	307 \pm 239	312 \pm 237	0.84
Candy (g)	36 \pm 40	25 \pm 22	0.01
Nitrosamine rich (g)	27 \pm 19	24 \pm 16	0.12
Body size			
n (male/female)	75 (38/37)	144 (69/75)	
Weight-for-age	0.54 \pm 0.98	0.25 \pm 0.99	0.04
Height-for-age	0.72 \pm 0.90	0.50 \pm 0.99	0.12
Weight-for-height*	0.22 \pm 0.84	-0.10 \pm 0.87	0.03

*Case subjects $n = 53$, referents $n = 122$.

and sucrose in particular, was associated with increased risk. The association with high intake of carbohydrates, as well as disaccharides and sucrose, remained significant even after the adjustment for high intake of energy (Table 2).

High intake (above the 75th percentile) of milk, bread, and candy was associated with increased risk of type 1 diabetes (Table 2). There was no association with high intake of soft drinks. The intake of milk was high among the study participants: one-third of children consumed over 1,000 g milk/day. When adjusted for the total energy intake, only high intake of bread remained a significant risk factor (Table 2). High intake of foods containing nitrosamines was not associated with increased risk of diabetes (OR 1.29 [95% CI 0.71–2.37]).

Mean SD scores of measurements taken during the 4-year period preceding the diagnosis or interview tended to be higher for the diabetic compared with the referent children (Table 1). Compared with the lowest category, the risk of diabetes increased if the mean previous weight-for-age SD scores were in the medium or high categories (Table 3, model 1). Similar association was found with

previous height-for-age and weight-for-height. ORs (95% CI) were 2.38 (1.01–5.58) for medium and 2.32 (1.00–5.38) for high height-for-age. For weight-for-height the corresponding ORs were 3.83 (1.19–12.30) and 4.09 (1.23–13.63), respectively. The increase in risk was, how-

ever, not linear, as ORs in the medium and high categories were of the same magnitude. The association was similar in boys and girls (data not shown).

There was a crude association between high intake of energy and increased diabetes risk (Table 3, model 1). When adjusted for each other by including into the same model, both higher previous relative weight and high intake of energy were associated with increased risk for type 1 diabetes, suggesting an independent effect (Table 3, model 2).

CONCLUSIONS— This study indicates that among the 7- to 14-year-old children, higher intake of energy 1 year before the diabetes diagnosis, perhaps especially in the form of disaccharides and sucrose, is associated with increased risk of diabetes. Previous findings (10–15) of a larger body size as a risk determinant of childhood-onset diabetes were confirmed. In this study we were also able to show that higher energy intake and higher relative body weight seem to be independently associated with diabetes risk. As diet may play different roles in different age-groups (9), the selected age interval limits the possibility to draw inferences outside the 7- to 14-year range.

The main results on dietary intake are in accordance with our previous larger, nationwide study based on mailed food frequency questionnaires (8). In that study the frequency of intake of foods rich in protein, fat, and carbohydrate, includ-

Table 2—Association between high intake (>75th percentile) of selected nutrients and groups of food and the risk of type 1 diabetes in 7- to 14-year-old Swedish children: results of univariate (crude ORs) and bivariate analyses (ORs adjusted for high intake of energy) in 98 matched sets of case subjects and referents

Nutrient or type of food	Crude	Adjusted for energy intake
	OR (95% CI)	OR (95% CI)
Energy	1.95 (1.04–3.65)	
Protein	2.47 (1.30–4.72)	2.28 (0.95–5.51)
Fat	1.51 (0.84–2.70)	1.10 (0.54–2.23)
Carbohydrate	2.90 (1.50–5.58)	3.06 (1.24–7.56)
Monosaccharide	1.56 (0.87–2.79)	1.37 (0.75–2.52)
Disaccharide	2.52 (1.40–4.55)	2.36 (1.14–4.93)
Sucrose	2.44 (1.35–4.42)	2.16 (1.15–4.05)
Milk	1.99 (1.09–3.62)	1.66 (0.88–3.22)
Bread	2.22 (1.19–4.14)	1.93 (1.00–3.69)
Soft drinks	1.04 (0.60–1.81)	0.91 (0.51–1.63)
Candy	1.83 (0.99–3.36)	1.73 (0.93–3.21)

*Case subjects $n = 53$, referents $n = 122$.

Table 3—Previous intake of energy and relative body weight as risk factors for type 1 diabetes in 7- to 14-year-old Swedish children: crude (model 1) and adjusted ORs (model 2) in 67 sets of case subjects and age- and sex-matched referents

Exposure level		Model 1: crude OR (95% CI)	Model 2: adjusted OR (95% CI)
Energy	Low (<33rd)	1.00	1.00
	Medium (33–66th)	1.49 (0.60–3.72)	1.33 (0.52–3.42)
	High (>66th)	5.21 (1.69–16.12)	5.23 (1.67–16.38)
Weight-for-age	Low (<33rd)	1.00	1.00
	Medium (33–66th)	2.76 (1.19–6.38)	3.20 (1.30–7.88)
	High (>66th)	2.81 (1.15–6.86)	3.09 (1.16–8.22)

Adjustment was done by including energy intake and average weight-for-age SD score into the same model.

ing mono- and disaccharides, were found to be risk factors in addition to foods rich in nitrosamine. The latter association could not be confirmed clearly in the present study, perhaps due to lower power. Contrary to our previous findings (8), but in agreement with other reports (6,7), high intake of cow's milk was associated with increased risk of diabetes in the present study, although the association was no longer significant after the adjustment for the high energy intake.

It is unlikely that the precision of growth data retrieved from Child Health Clinics and Schools would systematically differ between the case subjects and referents. To decrease the impact of possible measurement errors, we used a mean SD score of several measurements and excluded the measurements taken during the last 3 months preceding the diagnosis, when growth of the pre-diabetic children may be influenced by the metabolic disturbances. Unfortunately, growth data were not available for 25 (25%) case subjects and 37 (21%) referents ($P = 0.37$). Still, our conclusions of larger body size as a risk factor for childhood-onset diabetes should be reliable.

Only subjects with information available on both diet and growth were included into the analyses of energy intake and relative weight (67 of 98 matched datasets). However, as the dietary intake did not differ significantly between the children with and without growth data, the result should not be biased. Further, dietary data for one of the referents were missing in 20 matched sets. In the extreme situation, the missing referents may have had a distribution of the exposure close to that of the case subjects. However, when sucrose and energy distribution of case subjects was randomly

ascribed to the missing referents, the ORs were lower but still statistically significant (data not shown).

Although the determination of diabetes type was made on clinical grounds, we do not believe that misclassification would be of concern. Only 31 (0.5%) type 2 diabetic case subjects were found in Sweden among ~6,000 prevalent case subjects aged 0–18 years in 2001 (18). In the current study, three (3.9%) case subjects and three (2.0%) referents would be classified as obese according to a recently suggested international definition (19), also supporting the diagnosis of type 1 diabetes.

We did not have information about the pubertal stage of the study participants. However, this should not confound the conclusions regarding dietary intake. The referent group is population based and large enough to expect random distribution of pubertal stages among the children of different ages. Adjustment for the relative weight-for-age, a proxy of the pubertal development, hardly changed the effect of high energy intake.

The dietary history method faces specific difficulties in childhood. It may be difficult for the parent to estimate the dietary intake of the child, as she/he is eating not only at home but also at school or at daycare and younger children have a limited ability to cooperate in the interview themselves. The development of the current questionnaire was based on previous experience, and evaluation of the method showed that it performed satisfactorily in school children regarding both reliability and reproducibility (16). The reliability of retrospective evaluation of the diet 1 year earlier is, however, not known; therefore caution is necessary for the interpretation of the results. Much

emphasis was placed on the training of the interviewers on how to avoid a biased way of asking questions, and the same dietitian interviewed case subjects and matched referents. An interviewer bias resulting in a differential misclassification would probably primarily be reflected by a higher number of food items listed or by reported larger portion sizes. The differences observed between the case subjects and referents were, however, mainly a result of differences in the selection of foods and not in the number of food items or portion sizes.

To minimize the possibility of disease-dependent recall bias and to help remember the situation 1 year earlier, the interview started by mapping general food habits and meal patterns. A system of cross-checking to the meal pattern as well as to a listing of the dishes served at the schools in question during the reference period was used throughout the interview. In Sweden all children receive free school lunches, and no commercial school cafeterias are available in schools. The families of case children were interviewed in the hospital shortly after receiving dietary instructions in association with diabetes diagnosis, which may have influenced their recall of the dietary intake, particularly regarding "harmful" foods containing rapidly absorbed sugars. Thus, the possibility of disease-dependent recall bias cannot be excluded, and some caution is needed in the interpretation of the results regarding dietary intake, especially the association of the high intake of disaccharides and sucrose with increased diabetes risk. It may also be possible that our findings reflect the natural course of diabetes development. It has been shown in the Diabetes Prevention Trial (20) that hypoglycemia may occur in the pre-diabetic individuals during the last few years before diabetes diagnosis. Also in our study, irregular insulin secretion and hypoglycemic episodes before the diagnosis of diabetes could have led to a higher intake of specifically sucrose and other sources of disaccharides.

Even keeping all possible shortcomings in mind, our data may have important implications for understanding the causes of childhood-onset type 1 diabetes. The autoimmune destruction of the β -cell is probably a slow process, ongoing for several years before the clinical onset (21), and may be initiated early in life (2,22). Still, not all individuals who show signs of au-

toimmunity to the β -cell will develop clinical diabetes (23,24). Increased body mass and other factors overloading the β -cells by increased insulin demand may accelerate the autoimmune destruction and make the disease overt earlier and in a larger number of susceptible individuals, as suggested by the accelerator hypothesis (2,25). Hyperglycemia increases the expression of GAD autoantigen on the β -cell surface and may upregulate the ongoing autoimmune process (26). Moreover, in vitro cytokine toxicity is increased in hyperglycemic milieu and may trigger β -cell death due to apoptosis (27). Higher intake of energy, especially in the form of rapidly absorbed sugars, would directly stimulate more insulin secretion and increase the immediate workload to the β -cells. In the long-term perspective, higher intake of energy in childhood would promote both more rapid linear growth and accumulation of fat tissue. The resulting reduced tissue sensitivity to insulin, due to increased growth hormone secretion (28), increased fat mass, and decreased physical activity, would require more insulin secretion and overload the β -cells.

In conclusion, our study supports the idea that higher energy intake, as well as a larger relative body size, which implies more growth in both length and fat mass, may accelerate the ongoing β -cell destruction and lead to an earlier clinical presentation of diabetes (2,25). Overnutrition in childhood may contribute to the increasing incidence of childhood-onset type 1 diabetes reported from many countries all over the world (29), which also seems to correlate with estimates of wealth (30).

Acknowledgments—This project was supported by grants from the Swedish Medical Research Council (project number 07531), the Swedish Diabetes Association, and the Västerbotten's County Council.

This study has been published in the abstract volume of the 18th Congress of International Diabetes Federation, Paris, 24–29 August 2003.

We sincerely thank the families for participation.

References

1. Dahlquist G: Nutritional factors. In *Causes of Diabetes*. Leslie RD, Ed. New York, John Wiley & Sons, 1993, p. 125–132
2. Dahlquist G: Environmental risk factors

- in human type 1 diabetes: an epidemiological perspective. *Diabetes Metab Rev* 11: 37–46, 1995
3. Åkerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M: Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet* 115:18–29, 2002
4. Gerstein HC: Cow's milk exposure and type I diabetes mellitus: a critical overview of the clinical literature. *Diabetes Care* 17:13–19, 1994
5. Kimpimäki T, Kupila A, Hamalainen AM, Kukko M, Kulmala P, Savola K, Simell T, Keskinen P, Ilonen J, Simell O, Knip M: The first signs of beta-cell autoimmunity appear in infancy in genetically susceptible children from the general population: the Finnish Type 1 Diabetes Prediction and Prevention Study. *J Clin Endocrinol Metab* 86:4782–4788, 2001
6. Verge CF, Howard NJ, Irwig L, Simpson JM, Mackerras D, Silink M: Environmental factors in childhood IDDM: a population-based, case-control study. *Diabetes Care* 17:1381–1389, 1994
7. Virtanen SM, Laara E, Hyppönen E, Reijonen H, Räsänen L, Aro A, Knip M, Ilonen J, Åkerblom HK, the Childhood Diabetes in Finland Study Group: Cow's milk consumption, HLA-DQB1 genotype, and type 1 diabetes: a nested case-control study of siblings of children with diabetes. *Diabetes* 49:912–917, 2000
8. Dahlquist GG, Blom LG, Persson LA, Sandström AI, Wall SG: Dietary factors and the risk of developing insulin dependent diabetes in childhood. *BMJ* 300: 1302–1306, 1990
9. Dahlquist G, Blom L, Lönnberg G: The Swedish Childhood Diabetes Study: a multivariate analysis of risk determinants for diabetes in different age groups. *Diabetologia* 34:757–762, 1991
10. Blom L, Persson LA, Dahlquist G: A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 35:528–533, 1992
11. Johansson C, Samuelsson U, Ludvigsson J: A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 37:91–94, 1994
12. Hyppönen E, Kenward MG, Virtanen SM, Piitulainen A, Virta-Autio P, Tuomilehto J, Knip M, Åkerblom HK, the Childhood Diabetes in Finland (DiMe) Study Group: Infant feeding, early weight gain, and risk of type 1 diabetes. *Diabetes Care* 22: 1961–1965, 1999
13. Bruining GJ, Netherlands Kolibrie Study Group of Childhood Diabetes: Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2 (Letter). *Lancet* 356:655–656, 2000
14. Hyppönen E, Virtanen SM, Kenward

- MG, Knip M, Åkerblom HK: Obesity, increased linear growth, and risk of type 1 diabetes in children. *Diabetes Care* 23: 1755–1760, 2000
15. The EURODIAB Substudy 2 Study Group: Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. *Diabetes Care* 25:1755–1760, 2002
16. Persson LA, Carlgren G: Measuring children's diets: evaluation of dietary assessment techniques in infancy and childhood. *Int J Epidemiol* 13:506–517, 1984
17. Dibley MJ, Goldsby JB, Staehling NW, Trowbridge FL: Development of normalized curves for the international growth reference: historical and technical considerations. *Am J Clin Nutr* 46:736–748, 1987
18. Zachrisson I, Tibell C, Bang P, Örtqvist E: Prevalence of type 2 diabetes among known cases of diabetes aged 0–18 years in Sweden (Abstract). *Diabetologia* 46 (Suppl. 2):A66, 2003
19. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH: Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 320:1240–1243, 2000
20. Diabetes Prevention Trial Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002
21. Atkinson MA, Eisenbarth GS: Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 358:221–229, 2001
22. Kimpimäki T, Kulmala P, Savola K, Kupila A, Korhonen S, Simell T, Ilonen J, Simell O, Knip M: Natural history of beta-cell autoimmunity in young children with increased genetic susceptibility to type 1 diabetes recruited from the general population. *J Clin Endocrinol Metab* 87:4572–4579, 2002
23. Landin Olsson M, Palmer JP, Lernmark Å, Blom L, Sundkvist G, Nyström L, Dahlquist G: Predictive value of islet cell and insulin autoantibodies for type 1 (insulin-dependent) diabetes mellitus in a population-based study of newly-diagnosed diabetic and matched control children. *Diabetologia* 35:1068–1073, 1992
24. Knip M: Natural course of preclinical type 1 diabetes. *Horm Res* 57 (Suppl. 1):6–11, 2002
25. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922, 2001
26. Björk E, Kampe O, Karlsson FA, Pipeleers DG, Andersson A, Hellerström C, Eizirik DL: Glucose regulation of the autoantigen GAD65 in human pancreatic islets. *J Clin Endocrinol Metab* 75:1574–1576, 1992
27. Mandrup Poulsen T: The role of interleukin-1 in the pathogenesis of IDDM. *Dia-*

- betologia* 39:1005–1029, 1996
28. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR: Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 48:2039–2044, 1999
29. Green A, Patterson CC: Trends in the incidence of childhood-onset diabetes in Europe 1989–1998. *Diabetologia* 44 (Suppl. 3):B3–B8, 2001
30. Patterson CC, Dahlquist G, Soltesz G, Green A: Is childhood-onset type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. *Diabetologia* 44 (Suppl. 3):B9–B16, 2001