Contributions of age, gender and insulin administration to weight gain in subjects with IDDM

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Summary Overweight in insulin-dependent diabetes mellitus (IDDM) has been repeatedly reported, especially in girls during adolescence. Potential pathophysiologic factors include tight metabolic control, insulin dose, treatment regimen, puberty and genetics. A standardized data-base from all IDDM patients treated at our institution was evaluated. IDDM patients with hypothyroidism or celiac's disease as well as all records from the first year of diabetes were excluded, resulting in a total of 427 patients (2454 patient-years) available for analysis. BMI and SD-score for BMI based on the Zurich longitudinal growth study were evaluated. Standardized BMI was higher in pubertal children ($+1.07 \pm 0.06$) compared to prepubertal children ($+0.68 \pm 0.07$; $p < 0.002$). This increase was present both for boys and girls. Increasing overweight during puberty was found irrespective of the age at diagnosis of diabetes (prepubertal or pu-

bertal). The daily dose of insulin and the long-term metabolic control had only a minor impact on the development of overweight. In contrast, in pubertal children, SDS-BMI was significantly higher in patients on intensified insulin regimens (3 or 4 daily injections) compared to patients with 2 injections ($p < 0.05$).

These data demonstrate that both boys as well as girls with IDDM develop overweight during puberty. Multiple injection therapy, not daily dose of insulin or the level of metabolic control achieved, was the main predictor of weight gain. This finding may be explained by increased caloric intake due to the flexibility allowed by intensified treatment. [Diabetologia (1998) 41: 542–547]

Keywords Body mass index, puberty, metabolic control, insulin dose, intensified insulin therapy.

Poor long-term metabolic control has been proven to be a major risk-factor for the development of late complications in IDDM patients [1, 2]. This relationship is also true for paediatric patients during adolescence [3], and no glycaemic threshold has been found for the development of long-term complications [4]. As a consequence, tight metabolic control, as achieved by intensified insulin therapy, is recommended today for most IDDM patients. However,

all intervention studies comparing conventional and intensified insulin therapy have reported a significant weight-gain after switching to multiple injection therapy: In the DCCT, the risk for becoming overweight was 73 % higher in the intensive therapy group [5]. In the Stockholm study, subjects in the intensified treatment group gained on average 4.1 kg over 5 years, compared to no weight-gain in the regular treatment group [2]. This undesirable side-effect has also been reported in adolescent patients [6, 7] and is a major cause of non-compliance especially in female adolescents with diabetes [8, 9]. Development of overweight is often explained by overinsulinization during intensified insulin therapy. Alternative explanations are frequent hypoglycaemic episodes treated by additional food intake, or reduced loss of glucose in the urine. In addition, the nutritional liberation

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; SDS, standard deviation score.

during intensified insulin therapy might lead to increased energy intake in IDDM adolescents. It is of major importance to identify factors related to weight gain in IDDM children and adolescents. Based on a large database from one centre, we therefore investigated the effects of age, gender, insulin dose, injection frequency and metabolic control on body mass index in IDDM patients.

Subjects and methods

Height and weight in IDDM patients were recorded at each visit to our outpatient clinic, using a calibrated stadiometer (mechanical Harpenden stadiometer until 1989, electronic stadiometer Fa Busse, Ulm, Germany, thereafter) and a calibrated gauge. Measurements were documented in a computer system specifically designed for the long-term care of IDDM patients [10]. This program was developed under the auspices of the German Secretary for Health between 1993 and 1995. It is now widely used throughout Germany. The Foxpro database-format (Microsoft München, Germany) is utilized for the current version of this programme. Relevant data were extracted from the database using the dBaseV software (Borland Eschborn, Germany).

Body mass index ($BMI = \text{weight}/(\text{height})^2$) was used as an index to reflect the height-weight relationship. For each patient, the z-scores (SD-scores) for height, weight and BMI were calculated based on the Zurich longitudinal growth data [11] (normative data for BMI were kindly provided by A. Prader, Zurich). These data have previously been shown to be suitable for children from our region, as demonstrated on a sample of 102 healthy school children [6] and on non-diabetic siblings from patients with diabetes [12]. All measurements from an individual patient within the span of one year were averaged to correct for differences in the number of yearly visits. Therefore, each patient contributed equally to the mean BMI of patients seen within one year. The SAS statistical software package (Carey, N.J., USA) was used for data analysis. As BMI does not necessarily follow a Gaussian distribution in IDDM patients, non-parametrical statistics (Wilcoxon rank-sum test, Spearman coefficient of correlation, multiple regression analysis on ranks) were applied. Statistical evaluation, as well as graphical representation of the data, was performed only for age-groups where at least 30 patients contributed to each subgroup. Data are presented as mean $\pm$ standard error (SE), significant differences were assumed for p values of less than 0.05.

Patients were screened yearly for the presence of anti-gliadin IgA-antibodies (ELISA, LD-Labordiagnostika, Heiden, Germany) as well as thyroid antibodies (TAK, TPO; ELISA, Elias, Freiburg, Germany). If gliadin antibodies were positive, the presence of celiac disease was confirmed or excluded by a small bowel biopsy. In all patients with positive thyroid antibodies, thyroid function tests were performed (thyroxine, free thyroxine index, triiodothyronine, thyroxine-stimulating hormone). Hypothyroid patients were excluded from analysis. From August 1992 HbA_{1c} was determined every 3 months by HPLC (Micro-Column System, Pharmacia, Freiburg, Germany) (normal range: $4.56 \pm 0.55\%$). Up to July 1992, ion exchange chromatography was used for HbA_{1c} measurement (normal range: 4.3 ± 0.5), these values were adjusted to the current method using the SD-score technique [13].

For a total of 511 patients diagnosed with type-I-diabetes, records including measurements of height and weight as well as information on insulin therapy and metabolic control were

Fig. 1. Body mass index in IDDM boys (top panel) and girls (bottom panel) with a duration of diabetes beyond 1 year, related to chronological age. Median (■) as well as 25th (▲) and 75th (▼) percentiles are indicated. For comparison, BMI-values from children included in the Zurich longitudinal growth study are indicated by lines (median: solid line; 25th and 75th percentiles: dotted lines)

available in our database. Prospective longitudinal collection of data started in January 1986, all patients included in the study were seen at our institution between this time-point and December 1996. Additional measurements of height, weight, HbA_{1c} and information on insulin therapy, reflecting the course of diabetes between manifestation and December 1985, were extracted from the patient charts. Therefore, in 193 patients (38% of the total study group), part of the data were collected retrospectively. 84 patients were excluded from analysis for the following reasons: reference data were not applicable because one or both parents were of non-German descent ($n = 49$), coexistent celiac disease ($n = 9$), hypothyroidism ($n = 11$), Down's syndrome ($n = 2$) or insufficient follow-up period ($n = 13$). To exclude the effect of weight-loss during initial metabolic decompensation, and the effect of the remission phase with low exogenous insulin requirement, all records related to the first year of diabetes were excluded. Therefore, data encompassing 2454 patient-years from 427 patients (202 boys, 225 girls) were available for analysis. The mean age at diagnosis of diabetes was 8.2 ± 0.2 years, not different between boys (8.2 ± 0.3 years) and girls (8.1 ± 0.3 years).

Results

As depicted in Fig. 1, BMI in paediatric IDDM patients was higher compared to the reference population even during the prepubertal years. However, following the onset of puberty, BMI increased even further in boys and girls. Standardized BMI-scores allow statistical comparisons between groups. For all 427 subjects, the mean SDS for BMI, weighted with the number of measurements per patient, was $+0.96 \pm$

Fig. 2. Standardized BMI (SD-score) in paediatric IDDM patients related to chronological age (top panel). Median (■) as well as 25th (▲) and 75th (▼) percentiles are indicated, the lines represent a 3rd order spline approximation for better visualisation. In the bottom panel, separate curves representing the median for boys (■) and girls (□) are depicted

0.05 (mean $\pm$ SE). The onset of puberty was defined according to chronologic age: 12.2 years in boys (average age at development of pubic hair) and 10.4 years in girls (average onset of breast development) [14, 15]. The weighted mean of BMI-SDS for 355 IDDM children observed during the prepubertal years was $+0.68 \pm 0.07$, significantly lower compared to $+1.07 \pm 0.06$ for 222 adolescents observed during the pubertal years ($p < 0.002$, Wilcoxon sign rank test; Fig. 2, top panel; 150 patients were observed both during the prepubertal and the pubertal age). Comparing boys with girls, no significant difference was present for the whole group of 427 patients (males: $+1.02 \pm 0.07$; females: $+0.89 \pm 0.07$; NS). In addition, no significant gender difference was encountered for all age-groups with the exception of the age-range 10–13 years, during which interval diabetic boys were significantly more overweight compared with girls ($p < 0.01$; Fig. 2, bottom panel).

IDDM children were next stratified according to prepubertal or pubertal onset of diabetes. As depicted in Fig. 3, the increase in BMI was identical for both groups. Statistical comparison revealed no significant difference in standardized BMI for all age-groups between 11 and 25 years. Further subdivision according to gender showed again no difference between boys or girls with prepubertal or pubertal age at diagnosis of diabetes (data not shown). As the definition of pubertal onset was based on chronological age, rather than the recording of Tanner stages, the analysis was repeated for patient subgroups of

Fig. 3. Comparison of standardized BMI among paediatric IDDM patients with onset of diabetes before (□, dotted line) or in puberty (■, solid line). Data represent the median of all patients in the respective age-group. For definition of prepubertal or pubertal age at diagnosis of diabetes, see “Results”

“young onset” (< 10 years at manifestation) and “old onset” (> 13 years). Again, no difference with respect to the development of overweight was present (data not shown).

The development of overweight in diabetic subjects is generally attributed to hyperinsulinisation. Insulin requirement in paediatric IDDM patients is highly dependent on age: on average, reported insulin requirement was 0.67 ± 0.02 U/kg for prepubertal and 0.85 ± 0.01 U/kg for pubertal patients. For each age-group, therefore the median insulin requirement per kg of body weight was calculated. BMI in subjects with an insulin requirement above or below this limit was compared (see Fig. 4, top panel). While no difference was present during childhood and early adolescence, in older patients standardized BMI was higher in the subgroup reporting a lower insulin dose per kg of body weight. This difference was significant for patients 17–19 years of age ($p < 0.03$).

Conventional and intensified insulin treatment can be classified according to the number of daily injections. The treatment regime was dependent on chronological age: At age 11, 59% of patients injected insulin twice daily, 21% used 3 and 20% of patients used 4 injections. The respective numbers were 46%–27%–27% for 14-year-old children and 31%–31%–38% for 17-year-old patients. The number of prepubertal children on 3 or 4 injections was too small for statistical comparison. In pubertal children (12–16 years), standardized BMI was significantly higher for intensified treatment compared with children on a 2 injection regimen (p -values between < 0.04 and < 0.003 for the age-groups respectively; Fig. 4, middle panel). No difference was present for adult patients (≥ 17 years).

Metabolic control, as reflected by HbA_{1c}, is a further parameter potentially related to weight gain in IDDM subjects. For all patients, the median of all previously measured HbA_{1c}-values averaged $7.54 \pm 0.22\%$. For each age-group, the median long-

Fig. 4. Standardized BMI-score in IDDM children related to chronological age, stratified according to the daily dose of insulin (top panel), the number of daily insulin injections (middle panel) or the longterm metabolic control achieved (bottom panel)

term HbA_{1c} was used as a cutoff between “good” and “poor” metabolic control. Patients with “poor” long-term metabolic control tended to be more overweight compared with patients with a “good” median HbA_{1c} , however this difference was significant only for the age-group 20 years (see Fig. 4, bottom panel).

Multiple regression analysis was utilized to evaluate simultaneously the effects of treatment and metabolic control on the development of overweight. BMI was used as the dependent parameter, and gender, insulin dose per kg of body weight, number of daily injections of insulin and long-term mean HbA_{1c} were entered as independent variables into the model. The analysis was performed separately for each yearly interval of chronological age. In children younger than 11 years ($n = 130$), none of the above factors had a significant impact on BMI. By contrast, in children 12–17 years of age ($n = 179$ –222), the number of daily injections of insulin was the single most important predictor of BMI (p -values < 0.0001 to < 0.005 for the different age groups). Surprisingly, in adults (≥ 18 years, $n = 126$), the number of injections per day no longer had a significant influence on BMI. Similar results were obtained when multiple regression analysis was performed on ranks or when BMI-SDS was used as the dependent variable.

Discussion

In contrast to the textbook view that IDDM patients are generally of normal weight, overweight in this group of patients is increasingly recognized and related to intensified insulin treatment and good metabolic control [2, 5]. This phenomenon has also been demonstrated for paediatric patients [12, 16]. In our patient group, the most pronounced elevation of BMI was observed during adolescence, however, even in prepubertal children BMI was increased compared to the control group. In a recent study including non-diabetic siblings from paediatric IDDM patients, we reported a mean BMI-SDS of $+0.28$ for these healthy control subjects with the same genetic background [12]. The slightly increased BMI even in young IDDM children might therefore reflect a secular trend in height-weight relationship, or a genetic background of overweight in families with IDDM children. In fact, tall stature and rapid weight gain have been identified as risk-factors for the development of IDDM [17, 18].

It is a general belief in paediatric diabetology that overweight is more pronounced in IDDM girls compared with boys, a notion which seems to be supported by some studies [19–21] but contradicted by others [22, 23]. Unfortunately, the statistical methods applied in these studies are often insufficient. Based on our large sample of paediatric IDDM patients, followed and documented at our institution, we clearly found that age- and sex-standardized BMI is no higher in girls compared with boys. In contrast, at the onset of puberty, a higher degree of overweight is present in boys, confirming the previous report by Clarkson et al. [22]. BMI values objectively reflect the anthropometric aspect of overweight, however, in our society overweight is a more prominent stigma for girls compared with boys, explaining why diabetes care providers are much more exposed to female patients suffering from excessive weight gain.

Several hypotheses have been put forward to explain why overweight is primarily encountered in patients on intensified insulin treatment with good metabolic control: reduced loss of glucose in the urine, increased energy intake due to dietary flexibility with multiple injection regimens, altered basal energy expenditure or the necessity to consume additional carbohydrates due to more frequent hypoglycaemic episodes have been suggested as pathogenetic factors. In a previous study, we examined body composition using bioelectrical impedance measurements in IDDM adolescents [24]. We found that overweight in this group of patients is caused by an increase in muscle mass, while fat mass was similar to age-adjusted control subjects. Peripheral hyperinsulinaemia, in conjunction with elevated growth hormone values and high circulating glucose concentrations, might explain this anabolic effect of diabetes. In diabetic

animals, increasing amounts of insulin infused through the physiologic range resulted in a 40% increase in daily food intake and a rapid gain in body weight [25].

Both hyperinsulinisation as well as intensified insulin treatment have been considered to cause excessive weight-gain in IDDM adolescents. Using multiple regression analysis, we therefore elucidated the contributions of these factors. High insulin dose and good metabolic control had no significant effect on BMI in this age-group. In contrast, multiple injection therapy was strongly associated with high BMI. Intensified conventional therapy with multiple daily insulin injections allows considerable flexibility of dietary habits, this is likely to lead to increased food consumption and subsequent overweight. Our finding, that not tight metabolic control, but the use of multiple injection therapy is the main factor associated with overweight, is clearly in contradiction of the notion that frequent hypoglycaemia and subsequent additional food intake are responsible for overweight. In several studies on intensified insulin regimen, the prevalence of severe hypoglycaemic episodes is inversely correlated to metabolic control [1, 2, 3], however this point is controversial.

Our results that the number of insulin injections, rather than the total insulin dose, is important for overweight during adolescence may contrast with the general view of many paediatric diabetologists, but is in agreement with several reports in the literature [20, 26]. It is therefore likely that additional food intake made possible by flexible insulin treatment regimens is causing overweight in IDDM adolescents. This pathophysiologic explanation is supported by a recent study from Finland, demonstrating that the daily energy intake in adolescent girls with diabetes is higher compared with control subjects [8]. As patients on two daily injections gain weight as well – however at a slower pace –, and as in adults multiple injection therapy is no longer the main factor related to overweight, the other explanations for overweight in IDDM mentioned are likely to contribute as well. It has to be kept in mind that both the insulin doses and the number of daily injections were reported by the patients, and some noncompliance cannot be excluded definitively. The difference between children and adolescents/young adults with IDDM may partly be explained by differences in insulin sensitivity or physical activity between adolescent and adult patients [27, 28].

Our data do not support the idea that overinsulinisation is a major cause of overweight in adolescent patients. If at all, there was a tendency towards higher BMI in patients using lower doses of insulin per kg of body weight, especially in the older age-groups. However, this finding has to be interpreted with some caution, as only the insulin dose reported by the patients can be evaluated. Skipping insulin shots is frequent

among adolescents with diabetes [29], and is intentionally used by some patients to induce weight loss [30, 9]. The hypothesis that overeating due to frequent hypoglycaemic episodes contributes to weight-gain is contradicted by our data: lower HbA_{1c}-values – potentially associated with a higher frequency of severe hypoglycaemic episodes – are not associated with weight gain [1, 3]. However, recent reports have challenged the view that tight metabolic control is invariably accompanied by a higher frequency of severe hypoglycaemic episodes [31, 32].

We conclude from our data, that excess caloric intake made possible by multiple injection therapy represents the major factor contributing to overweight in IDDM adolescents. This interpretation is in line with recent psychological studies indicating that classical as well as atypical eating disorders are encountered with a higher frequency especially in female adolescents and young adults with diabetes [33, 34]. Interestingly, body dissatisfaction and unhealthy weight-control practices – which are often unsuccessful – are prevalent not only among adolescents with diabetes, but also among adolescents with other chronic diseases like asthma, attention deficit disorder, physical disabilities or seizure disorder [35]. As this phenomenon does not seem to be limited to adolescents with nutrition-related chronic illnesses, problems with developmental issues like identity formation, conforming to social norms within the peer group, independence from parents etc. may be the cause of eating disorders and overeating, leading to overweight in chronically ill adolescents.

As overweight has both negative psychological and medical consequences, it remains a major goal of paediatric diabetology to prevent this side-effect of modern therapeutic approaches to IDDM. In our view, the advantages of multiple injection regimen (better metabolic control, increased flexibility) are not to be put into question. However, education related to intensified insulin therapy has to be combined with specific dietary and psychological counselling on the avoidance of weight gain.

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References

1. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986
2. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U (1992) Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): The Stockholm diabetes intervention study (SDIS) after 5 years. *J Int Med Res* 233: 101–108
3. Diabetes Control and Complications Trial Research Group (1994) Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. *J Pediatr* 125: 177–188
4. Diabetes Control and Complications Trial Research Group (1996) The absence of a glycemic threshold for the development of long-term complications. *Diabetes* 45: 1289–1298
5. The Diabetes Control and Complications Trial Research Group (1995) Adverse events and their association with treatment regimens in the diabetes control and complications trial. *Diabetes Care* 18: 1415–1427
6. Thon A, Heinze E, Feilen KD et al. (1992) Development of height and weight in children with diabetes mellitus. *Eur J Pediatr* 15: 258–262
7. Gregory JW, Wilson AC, Greene SA (1992) Body fat and overweight among children and adolescents with diabetes mellitus. *Diabetic Med* 9: 344–348
8. Pietiläinen KH, Virtanen SM, Rissanen A, Rita H, Mäenpää J (1995) Diet, obesity, and metabolic control in girls with insulin-dependent diabetes mellitus. *Arch Dis Child* 73: 398–402
9. Polonsky WH, Aponte JE, Anderson BJ, Jacobson AM, Lohrer PA, Cole CF (1994) Insulin omission in women with IDDM. *Diabetes Care* 17: 1178–1185
10. Holl RW, Grabert M, Schweiggert F, Heinze E (1993) A computer program for prospective documentation in patients with type-1 diabetes mellitus. *Diab Stoffw* 3: 232–238
11. Prader A, Largo RH, Molinari L, Issler C (1989) Physical growth of Swiss children from birth to 20 years of age. *Helvetica Paediatrica Acta* 52: 1–125
12. Holl RW, Seifert M, Grabert M, Heinze E (1994) Longitudinal analysis of somatic development in paediatric patients with diabetes mellitus type I. *Diabetologia* 37: 925–929
13. Heinze E, Vetter U, Thon A, Kohne E (1983) Is there a risk-free haemoglobin A1 concentration in type I diabetics? *Dtsch Med Wochenschr* 108: 1632–1634
14. Largo RH, Prader A (1983) Pubertal development in Swiss boys. *Helvetica Paediatrica Acta* 38: 211–228
15. Largo RH, Prader A (1983) Pubertal development in Swiss girls. *Helvetica Paediatrica Acta* 38: 229–243
16. Dorchy H, Roggemans MP, Willem D (1997) Glycated hemoglobin and related factors in diabetic children and adolescents under 18 years of age. *Diab Care* 20: 2–6
17. Blom L, Persson LA, Dahlquist G (1992) A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 35: 528–533
18. Songer TJ, LaPorte RE, Tajima N et al. (1986) Height at diagnosis of insulin-dependent diabetes in patients and their non-diabetic family members. *BMJ* 292: 1419–1422
19. duCaju MVL, Rooman RP, op de Beeck L (1995) Longitudinal data on growth and final height in diabetic children. *Pediatr Res* 38: 607–611
20. Danne T, Ender I, Kordonouri O, Weber B (1997) Factors influencing height and weight development in children with diabetes. *Diabetes Care* 20: 281–285
21. Bognetti E, Macellaro P, Novelli D, Meschi F, Ciralli F, Chiumello G (1995) Prevalence and correlates of obesity in insulin dependent diabetic patients. *Arch Dis Child* 73: 239–242
22. Clarson C, Daneman D, Ehrlich RM (1985) The relationship of metabolic control to growth and pubertal development in children with insulin-dependent diabetes. *Diabetes Res* 2: 237–241
23. Hjelt K, Braendholt V, Kamper J, Vestermark S (1983) Growth in children with diabetes mellitus. *Dan Med Bull* 30: 28–33
24. Bartz J, Sulzbach U, Heinze E, Teller WM, Holl RW (1997) Body composition in type 1 diabetes mellitus: bioimpedance measurements in 274 diabetic children, juveniles and young adults. *Dtsch Med Wochenschr* 122: 815–819
25. Willing AE, Walls EK, Koopmans HS (1990) Insulin infusion stimulates daily food intake and body weight gain in diabetic rats. *Physiol Behav* 48: 893–898
26. Pitukcheewanont P, Alemzadeh R, Jacobs WR, Jones BH, Eberle AJ (1995) Does glycemic control affect growth velocity in children with insulin-dependent diabetes mellitus? *Acta Diabetol* 32: 148–152
27. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV (1986) Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 315: 215–219
28. Arslanian S, Nixon PA, Becker D, Drash AL (1990) Impact of physical fitness and glycemic control on in vivo insulin action in adolescents with IDDM. *Diabetes Care* 13: 9–15
29. Weissberg-Benchell J, Wirtz P, Glasgow AM, Turek J, Tynan WD, Ward J (1995) Adolescent diabetes management and mismanagement. *Diabetes Care* 18: 77–82
30. Stancin T, Link DL, Reuter JM (1989) Binge eating and purging in young women with IDDM. *Diabetes Care* 12: 601–603
31. Verrotti A, Chiarelli F, Blasetti A, Bruni E, Morgese G (1996) Severe hypoglycemia in insulin-dependent diabetic children treated by multiple injection insulin regimen. *Acta Diabetol* 33: 53–57
32. Bott S, Bott U, Berger M, Mühlhauser I (1997) Intensified insulin therapy and the risk of severe hypoglycaemia. *Diabetologia* 40: 926–932
33. Rubin RR, Peyrot M (1992) Psychosocial problems and interventions in diabetes. *Diabetes Care* 15: 1640–1657
34. Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D (1997) Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med* 336: 1849–1854
35. Neumark-Sztainer D, Story M, Resnick MD, Garwick A, Blum RW (1995) Body dissatisfaction and unhealthy weight-control practices among adolescents with and without chronic illness: A population-based study. *Arch Pediatr Adolesc Med* 149: 1330–1335