Original Article

Insulin resistance in children and adolescents with type 1 diabetes mellitus: relation to obesity


Abstract: Background: Insulin resistance is well recognized both in type 1 diabetes mellitus (T1DM) and in obesity. Studies concerning the relation between insulin resistance and overweight in T1DM have not yet been carried out.

Methods: Degree of overweight [standard deviation score-body mass index (SDS-BMI)] and daily insulin doses per weight (ID/kg), per body surface (ID/m²), and per ideal body weight (ID/IW) were recorded in 4124 children aged between 5 and 20 yr with a duration of T1DM of 4–5 yr and an adequate metabolic control [hemoglobin A1c (HbA1c) < 8.0%]. SDS-BMI was compared between insulin-resistant (ID/kg ≥ 1.0) and insulin-sensitive (ID/kg < 1.0) children. The ID/kg, ID/m², and ID/IW were compared between obese (SDS-BMI > 1.9) and non-obese children. Multivariate linear regression analysis was conducted for the dependent variables ID/kg, ID/m², and ID/IW, including age, gender, SDS-BMI, and HbA1c as independent variables.

Results: The 882 insulin-resistant children did not differ significantly (p = 0.447) with respect to SDS-BMI (median +0.38) compared to the 3242 insulin-sensitive children (median SDS-BMI +0.42). The ID/kg was significantly (p = 0.031) lower in the obese children compared to the non-obese children (median 0.80 vs. 0.83), while ID/m² (median 31.0 vs. 26.2) and ID/IW (median 1.17 vs. 0.85) were significantly (p < 0.001) increased in the obese children. In multivariate linear regression analysis, SDS-BMI was significantly (p < 0.001) associated with an increase in ID/m² and ID/IW and a decrease in ID/kg.

Conclusions: T1DM children with insulin resistance based on ID/kg are not more overweight than insulin-sensitive children with T1DM. ID/m² and ID/IW seem to reflect a better tool than ID/kg to describe the influence of overweight on insulin resistance in T1DM.

Insulin resistance, in addition to insulin deficiency, is well recognized in type 1 diabetes mellitus (T1DM), both at onset and after long diabetes duration (1–6). On the other hand, insulin resistance is common in obesity (7–10), and therefore obesity is discussed as a risk factor not only for type 2 but also for T1DM in children (11, 12). The accelerator hypothesis, first stated in 2001, postulates a shared basis for both type 1 and type 2 diabetes; despite individual predisposition and autoimmunity, insulin resistance is supposed to unmask β-cell insufficiency (13). It has long been known that enhanced weight gain or obesity in infancy may be associated with a higher risk for T1DM in children (14). The physiological basis of this observation is not yet clear. A possible explanation could be that enhanced insulin secretion and relative hyperinsulinism
due to increased demands in obesity favor harmful effects to the β-cells at a critical period in early life (11–13).

If obesity in T1DM leads to insulin resistance, weight reduction may be a treatment modality to improve metabolic control, as weight reduction is associated with an improvement of insulin resistance in obese healthy children (15). There are no data reported so far on the relation between insulin resistance and overweight in T1DM. Therefore, the purpose of this study was to determine whether insulin resistance in T1DM as estimated by insulin dose (ID) per weight (kg) (16–18) is associated with overweight in children and adolescents.

Methods

A computer software based on the FoxPro 6.2 compiler was developed for standardized prospective documentation of children and adolescents with diabetes mellitus [delivery point validation (DPV) system] (19). Besides anthropometric parameters, ID per day, metabolic control (glycosylated hemoglobin), and treatment modalities are documented longitudinally by the software. The software allows standardized patient reports, as well as local aggregation of data and patient selection according to multiple criteria. Anonymized data are transmitted for central multicenter analysis. Each participating center complies with their local data-management guidelines.

One hundred and fifty-six treatment centers for diabetic children and adolescents in Germany participated in this study. This report takes in account the data of 8156 children and adolescents aged between 5 and 20 yr, accumulated in 1980–2003 during the fifth year of the disease. The children with adequate metabolic control [definition hemoglobin A1c (HbA1c) <8.0%] were separately analyzed, as increased HbA1c may reflect poor metabolic control due to non-compliance or due to too small ID in these patients. HbA1c values from different laboratories were mathematically standardized to the Diabetes Control and Complications Trial (DCCT) normal range (4.05–6.05%).

The weight status was recorded as body mass index (BMI) and the BMI-standard deviation score (SDS-BMI) using the LMS method (20): The M- and S-values correspond to the median and coefficient of variation of BMI for German children at each age and gender, whereas the L-value allows for the substantial age-dependent skewness in the distribution of BMI (21). The assumption underlying the LMS method is that after Box-Cox power transformation, the data at each age are normally distributed (20). Obesity was defined according to the BMI 97th percentile using population-specific data according to the definition of obesity by the International Task Force of Obesity (IOTF) (20, 21). The reference population was collected approximately over the same time period as the study population (21).

ID per day were correlated to weight, to body surface area (body surface in m² = 0.024265 × W0.5378 × H0.3964, where W is the weight in kg and H the height in cm) (22), to ideal body weight (IW), and to SDS-BMI by Pearson correlation. Ideal body weight was defined as the weight corresponding to SDS-BMI of 0 based on the height of the subject. Furthermore, ID per day were correlated to weight, body surface, IW, and SDS-BMI by Pearson correlation in the group of obese children (SDS-BMI >1.9).

The children with adequate metabolic control were divided into three groups according to their weight status:

1. Group I: SDS-BMI <0
2. Group II: SDS-BMI 0–1.9
3. Group III: SDS-BMI >1.9 (obese children)

HbA1c, age, gender, and ID per kilogram weight, per body surface, and per IW were compared in these three groups. Doses of basal insulin per kilogram weight were analyzed in these three groups. Furthermore, the children with adequate metabolic control were divided into three groups according to their ID per weight:

1. Group 1: insulin U/kg/d < 1.0 (insulin-sensitive)
2. Group 2: insulin U/kg/d 1.0–1.8 (low degree of insulin resistance)
3. Group 3: insulin U/kg/d > 1.8 (high degree of insulin resistance)

HbA1c, age, gender, and SDS-BMI were compared in these three groups. The cut-off points of 1.0 and 1.8 were chosen, as they have both been used to define insulin resistance in previous reports (16–18).

Direct multivariate linear regression analyses adjusted for treatment centers were conducted for the dependent variables ID per kilogram weight, per body surface, and per IW, including age, gender, SDS-BMI, HbA1c, and number of insulin injections per day as independent variables in each model in the whole study population, including all children, irrespective of HbA1c levels, and in the group of children and adolescents with adequate metabolic control. Gender and treatment centers were used as classification variables in each model.

The same analyses were performed in children younger than 10 yr, accumulated in 1980–2003 during the fifth year of the disease with adequate metabolic control. The SAS 8.2 statistic software package was used for descriptive data evaluation. Non-parametric statistical tests (Mann–Whitney U-test/ Wilcoxon test) were used. A p-value <0.05 was considered as significant. Data are presented as median (25 and 75 percentile).
Results

4124 children and adolescents demonstrated adequate metabolic control and 4032 had poor metabolic control. The average duration of T1DM was 4.5 yr. The ID and SDS-BMI of the children and adolescents with and without adequate metabolic control are summarized in Table 1. The children with adequate metabolic control were predominately males and demonstrated lower ID per weight, per body surface, and per IW compared to the children with poor metabolic control. The SDS-BMI differed significantly, but only very weakly between the children with and without adequate metabolic control. The children with adequate metabolic control were significantly (p < 0.001) younger (Fig. 1).

In the whole study population of 8156 children and adolescents, ID per day were correlated to weight (r = 0.75, p < 0.001), body surface (r = 0.77, p < 0.001), and IW (r = 0.73, p < 0.001). The correlation between SDS-BMI and ID per day was weak (r = 0.25, p < 0.001). ID per weight displayed a weak, yet significant negative correlation to SDS-BMI (r = -0.10, p = 0.037).

In the group of the 4124 children and adolescents with adequate metabolic control, ID per day were correlated to weight (r = 0.78, p < 0.001), body surface (r = 0.80, p < 0.001), and IW (r = 0.75, p < 0.001), while the correlation between SDS-BMI and ID per day was weak (r = 0.26, p < 0.001). ID per weight displayed a very weak, yet significant correlation to SDS-BMI (r = -0.03, p = 0.037, Fig. 2). In the subgroup of obese children (n = 96), the correlations of ID to weight (r = 0.62; p < 0.001), body surface (r = 0.65; p < 0.001), and IW (r = 0.63; p < 0.001) were lower. In this group, there was no significant correlation between ID and SDS-BMI (r = 0.12, p = 0.246).

The ID per weight was significantly lower in the obese children compared to the non-obese children, while ID per body surface and ID per IW were significantly increased in obese children in the group of the 4124 children and adolescents with adequate metabolic control (Table 2). The doses of basal insulin per weight did not significantly differ between the obese and non-obese children. The obese children did not significantly differ from the non-obese children in terms of age and HbA1c, while obese children were predominately female.

Table 1. SDS-BMI, gender, and IDs of 4124 children and adolescents with T1DM and adequate metabolic control (HbA1c < 8%) and 4032 children and adolescents with T1DM and poor metabolic control (HbA1c ≥ 8%) (data as median and interquartile range or percentage)

<table>
<thead>
<tr>
<th></th>
<th>Adequate metabolic control</th>
<th>Poor metabolic control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>53% males</td>
<td>49% males</td>
<td>0.002</td>
</tr>
<tr>
<td>SDS-BMI</td>
<td>+0.41 (-0.12 to +0.93)</td>
<td>+0.47 (+0.03 to +0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ID (U/kg/d)</td>
<td>0.83 (0.70-0.98)</td>
<td>0.91 (0.77-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ID (U/m²/d)</td>
<td>26.7 (21.4-32.9)</td>
<td>30.8 (25.7-35.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ID (U/ideal body weight in kg/d)</td>
<td>0.89 (0.74-1.06)</td>
<td>0.99 (0.84-1.14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HbA1c, hemoglobin A1c; ID, insulin dose; SDS-BMI, standard deviation score-body mass index; T1DM, type 1 diabetes mellitus.
Insulin-resistant children were significantly older compared to insulin-sensitive children (Table 3), while insulin-resistant children did not significantly differ in terms of weight (SDS-BMI) in the group of the 4124 children and adolescents with adequate metabolic control. There were significant, but only weak, differences for gender and no significant differences for HbA1c when patients with different degrees of insulin resistance were compared.

ID per weight, per body surface, and per IW were significantly influenced by age, degree of overweight (SDS-BMI), gender, metabolic control (HbA1c), and number of insulin injections per day using multivariate linear regression analyses adjusted for treatment centers in the group of the 4124 children and adolescents with adequate metabolic control (Table 4). In these multivariate linear regression analyses, increasing overweight (SDS-BMI) was associated with a decrease in ID per kilogram weight and an increase in ID per IW and per body surface.

Performing the same analyses in children younger than 10 yr with adequate metabolic control (n = 1464) or in the whole study population of children and adolescents, including all children and adolescents irrespective of HbA1c levels (n = 8156), demonstrated the same findings (data not shown) as for children and for adolescents aged 5–20 yr with adequate metabolic control.

### Discussion

This is the first study analyzing the impact of overweight on insulin resistance in children with T1DM. Euglycemic–hyperinsulinemic clamp studies are the gold standards to measure insulin resistance. However, there is some justification for the ID of T1DM patients as an assessment of insulin resistance, which is used in clinical practice. In healthy subjects, insulin secretion is closely linked to insulin sensitivity such that any change in insulin action is carefully balanced by an increased insulin production. Thus, insulin action and secretion interact upon each other. Therefore, the requirement of exogenous insulin in patients with T1DM is dependent of the insulin sensitivity in target tissues, despite any residual β-cell function. Usually, an average ID did not change with diabetes duration after 2–3 yr (16, 18), pointing to complete β-cell failure by this time point. In the unlikely case of residual function in β-cells 4–5 yr after the onset of diabetes, this effect can be suspected to be minimal. Therefore, the IDs in our patients with duration of T1DM from 4 to 5 yr reflect almost exclusively insulin sensitivity.

In our study, there was a weak negative relation between insulin resistance measured as ID per kilogram weight and degree of overweight expressed as SDS-BMI in multivariate analysis. Furthermore, the insulin-resistant children were not more overweight...
than the insulin-sensitive children. The missing positive relation between ID per weight and degree of overweight is in concordance with two other small studies using identical cut-off points for insulin resistance (16, 18). These results are surprising, as insulin resistance is a prominent feature of obesity (8) based on euglycemic–hyperinsulinemic clamp studies, not only in adults, but also in children (9, 10).

It can be appreciated that insulin sensitivity spans a wide range even among healthy individuals (23). A too low cut-off point to define insulin resistance as an explanation for our results seems unlikely, as values >1.0 U/kg/d in T1DM patients are often considered to be insulin resistant (16, 17, 24). A study in conventionally treated children with T1DM demonstrated the 95th percentile of ID at 1.2 U/kg/d in prepubertal children and 1.8 U/kg/d in pubertal children (18). Even the children with a high degree of insulin resistance (>1.8 U/kg/d) were not more overweight than the insulin-sensitive children in our study.

Our data suggest that obese T1DM children do not have an increased risk for insulin resistance. In concordance with this finding, a severe degree of insulin resistance was evident in normal weight T1DM (1); insulin sensitivity was decreased in euglycemic–hyperinsulinemic clamp after 1 yr of insulin treatment in adult T1DM patients (25, 26). Using a combined insulin–glucose tolerance test, as many as half of the patients suffering from T1DM were found to be insulin resistant (3).

Discrepancies between reported and administered ID may have influenced the results of our study. Furthermore, underreporting is a known phenomenon in obesity (27). As ID were calculated on the reported consumption of carbohydrate units in intensive insulin treatment, this may have led to an underestimation of ID in our obese diabetic children. On the other hand, the dose of basal insulin, which is administered independently of eating, tended to be smaller in the obese compared to the non-obese children. Furthermore, inadequate ID seems unlikely as an explanation for the missing association between insulin resistance and obesity in the children with adequate metabolic control as an indirect hint for good compliance.

Probably, the children in our study were too young and their diabetes and obesity duration were too short to reflect the consequences of insulin resistance. On the other hand, insulin resistance was detected already at onset of T1DM, both in adults (1) and in newly diagnosed children by euglycemic–hyperinsulinemic clamp (28). Furthermore, the impact of obesity on glucose metabolism is described to be independent of the duration of obesity (8).

As insulin resistance occurs only in some obese subjects, multigenic influence factors are discussed (29). The genetic environment associated with T1DM may be preventive for insulin resistance in obesity. Furthermore, other factors leading to insulin resistance may cover the effect of overweight. For instance, insulin-resistant children were older and more likely to be females in our study. The children with poor metabolic control were older, tended to be females, and received greater ID compared to the children with adequate metabolic control. The poor metabolic control may be caused by insulin resistance, but the results in the subgroup of children with poor metabolic control have to be interpreted very cautiously, as poor metabolic control could be caused by non-compliance or inadequate insulin dosage leading to underestimation of required ID. The effects of age and gender in our study are in concordance with many studies, demonstrating that girls are less insulin-sensitive than boys (28, 30–32) and that puberty induces insulin resistance (4, 33) even in children with diabetes (16, 18, 28). Increasing growth hormone secretion is considered to be the cause for this effect of puberty (34).

A potential limitation of our study is the fact that the stage of puberty was not always documented. On the
other hand, age reflects an indirect measurement of pubertal stage, being aware that children enter puberty at different ages but usually in the same age spans. Furthermore, there were no different findings in our study analyzing only children younger than 10 yr presumably being prepubertal. However, multivariate regression analyses adjusted for gender and age demonstrated a negative correlation between degree of overweight and ID per weight.

The missing positive relation between degree of overweight and ID per weight may be caused by the surrogate measurement of SDS-BMI for overweight. An increase in muscle tissues, which leads to an improvement of insulin sensitivity (35–37), is accompanied with an increase in SDS-BMI. Furthermore, some studies demonstrated that insulin sensitivity was negatively related to body composition and body fat distribution, but not to weight (38–40).

Probably, the assessment of ID per weight (16–18, 24) may not be an adequate method to describe insulin resistance in obese children and adolescents with T1DM. From a mathematical point of view, the negative relation between ID per weight and SDS-BMI probably reflects a statistical artifact, as body weight enters in the denominator of the insulin-sensitivity index and in the nominator of the obesity index. From a physiological point of view, insulin sensitivity should ideally be related to lean body mass, because glucose uptake occurs predominantly in lean tissues (23–26, 41). Approximately, 75% of glucose uptake is localized to skeletal muscle and only 4% or less to fat tissue (42). Using ID per IW as a surrogate measure for lean body weight demonstrated an approximate 40% increase of ID in obese children as a hint for insulin resistance. Furthermore, ID per body surface, which should be less dependent on fat mass compared to ID per weight (24), was increased in obese children compared to normal weight children in our study, both in univariate and in multivariate analysis. According to this, the insulin resistance of newly diagnosed T1DM children and adolescents was related to BMI in clamp studies when normalized to lean body mass (28).

Our children with T1DM tended to be more overweight as demonstrated by a positive median SDS-BMI compared to the reference population (43), which was collected in the same time period. This may reflect an indirect hint for the accelerator hypothesis dealing with the phenomenon that onset of T1DM appears in earlier ages parallel to an increase of overweight (13, 14).

In summary, the ID per weight seems to be the accurate way to calculate ID for practical use, as insulin requirement correlated very well to weight and there were only very small differences in doses between normal weight and obese children. The ID per body surface and the ID per IW seem to reflect a better tool than the ID per weight to describe the influence of overweight on insulin resistance in T1DM and should be calculated additionally to the insulin per weight ratio in obese children or if insulin resistance is suspected.

Acknowledgements

Insulin resistance and obesity in T1DM

References

34. Acerbini CL, Chidiamba TD, Edge JA, Dunger DB. Both insulin resistance and insulin clearance in children and young adults with type 1 (insulin-dependent)


