Paediatric obesity and type 2 diabetes: strategies for prevention and treatment

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ABSTRACT

The rising pandemic of obesity has caused an increase in the prevalence of type 2 diabetes in children and adolescents worldwide. Between 8% and 43% of children with newly-diagnosed diabetes have type 2 diabetes in the USA, while in Europe currently only 0.5% of the newly-diagnosed cases are classified as type 2. Ethnic factors, pubertal insulin resistance and female gender play a major role. Accelerated weight gain in infants may not only lead to type 2 diabetes later in life, but has also been implicated in the pathogenesis of type 1 diabetes. Therefore, preventive approaches against childhood obesity and type 2 diabetes need to start in the preschool age group. Age-appropriate education programmes for paediatric type 2 diabetes should include elements of programmes for paediatric diabetes as well as those for weight management. Thus, they need to be delivered by a multidisciplinary team.

Psychological approaches focusing on training in flexible control of eating and lifestyle behaviour appear to be more successful than rigid treatment regimens. Oral agents and insulin are frequently needed to reach the glycaemic goals. Most of the therapeutic and educational approaches are not well established in the paediatric age group as studies with sufficient power are lacking. Furthermore, many adolescents with type 2 diabetes have been reported to be lost to follow up from continuous paediatric diabetes care after short disease duration.

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KEY WORDS

paediatric obesity; paediatric type 2 diabetes; children; prevention and treatment of type 2 diabetes; education in type 2 diabetes; education in obesity; accelerator hypothesis

Introduction

Overweight and obesity represent high risk factors for chronic diseases in children, i.e. airway disorders, orthopaedic and cardiovascular problems and, particularly, type 2 diabetes.[1] Genetic and ethnic predisposition, lifestyle factors such as lack of exercise and unhealthy eating habits, and social factors leading to the ingestion of unhealthy, high caloric but cheap food have been implicated in the increasing obesity in children worldwide.[2–4]

A review of six representative studies in the USA in the 1960s and between 1999 and 2002 showed a more than three-fold increase in obesity among six- to 11-year-old children and among 12–19-year-old adolescents.[5,6] The International Obesity Task Force states that at least 155 million school-age children worldwide suffer from overweight or obesity, among them more than 22 million children under five years of age. In other words, this means that worldwide one out of 10 children is overweight.[7,8] With a prevalence of 24% we estimate that around 14 million children in Europe are overweight. Predictions that have been made in the 1980s for 2010 have now already been exceeded.[9] A representative German study performed between 2003 and 2006, including more than 17 500 children from the ages of 0–17 years, reported overweight in 15% and obesity in 6.3% of children and adolescents.[10] From a public health perspective, it is important to note that the trend towards obesity starts as early as age four (Figure 1).[11,12] Within the Bogalusa Heart Study, Freedmann *et al.* found an odds ratio of 12.6 (95% CI 10–16) of a high fasting insulin concentration as a consequence of high fasting blood glucose in overweight individuals (BMI >95th percentile) aged five to 17 years.[9] In the USA, up to 45% of children diagnosed with diabetes were classified as non-type 2 diabetes. The majority of these children were overweight or even obese.[13]

Incidence and prevalence of T2DM in young people

Pinhas-Hamiel and Zeitler[14] have summarised the epidemiological data of type 2 diabetes mellitus (T2DM) from 71 studies between 1979 and 2003, demonstrating a worldwide increase of type 2 diabetes in the paediatric age group over the last two decades (Figure 2). It is in parallel with the obesity epidemic[15] and is occurring at a younger age.[2,14,16] Recent data from the SEARCH for Diabetes in Youth Study demonstrated the importance of ethnic factors. Within the period of one year, increases in the incidence of type 2 diabetes were seen in children aged 10–19 years, from 6% to 15% in a non-Hispanic white group and from 76% to 86% in American-Indians. The highest rise was seen in the group of Hispanic young people with a more than two-fold increase (22% to 46%).[17,18] A similar increase and ethnic influences, albeit on a much lower level, have been reported in the UK.[19]

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Weight gain may play a role in T1DM development as well

The incidence of type 1 diabetes mellitus (T1DM) among Finnish children has more than doubled in the past 25 years,[20] with similar increases being reported in other countries.[21] Controversy exists as to whether this is a true increase in the lifetime number with the disease or whether it is a shift towards younger age with many cases of adult-onset type 1 diabetes having been misclassified as type 2 diabetes in previous years.[22,23] It has also been reported that children at onset of type 1 diabetes are often overweight.[24] A retrospective examination over 20 years regarding the prevalence of overweight in 185 white and black children and adolescents (aged on average 10 years) with onset of type 1 diabetes (matched for age, sex and year of onset) could show an increase from 12.6% to 36.8% between January 1979 and December 1998. In the group of prepubertal children (<11 years) the prevalence was already 7.3% in 1979 and by 1998 had increased to 22.2%.[25] A possible underlying mechanism between weight gain and the development of type 1 diabetes could be the need for increased insulin secretion of the infantile pancreas caused by rapid weight gain. Possibly, such hypersecretion could lead to overstraining of 'young' beta-cells inducing an early impairment of islet cells as a result of insulin resistance, leading to early death of insulin-producing cells or increased susceptibility for autoimmunity. Other retrospective studies suggest a causal correlation between obesity and type 1 diabetes, just as in the case for type 2 diabetes. They demonstrated an association of age at onset with the degree of weight gain during the first years of life.[26–28] This hypothesis, linking weight gain and insulin resistance as a cause of type 1 or type 2 diabetes on the basis of different genetic backgrounds, has been put forward as the 'accelerator hypothesis' by Wilkin.[29] Wilkin pointed out that both types of diabetes differ in a more or less accelerated beta-cell death. The death of beta-cells may depend on the presence or absence of the following 'accelerators':

Figure 1. Comparison of the 3rd, 50th, and 95th percentiles between 1999 and 2003 according to two large German cohorts (red lines: CrescNet[11]; blue lines: Kromeyer-Hauschild *et al*.[12]) While the increase is minimal at the 3rd and 50th percentiles, the effect is obvious in the higher BMI range. It shows the strongest impact of altered environmental and lifestyle factors. The increase becomes noticeable from four years of age. (Modified from Keller *et al*.)[11]

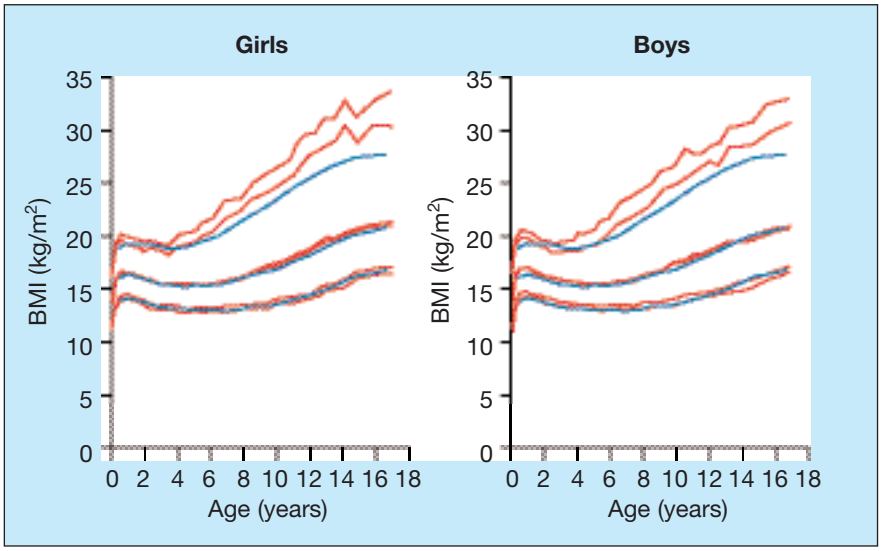
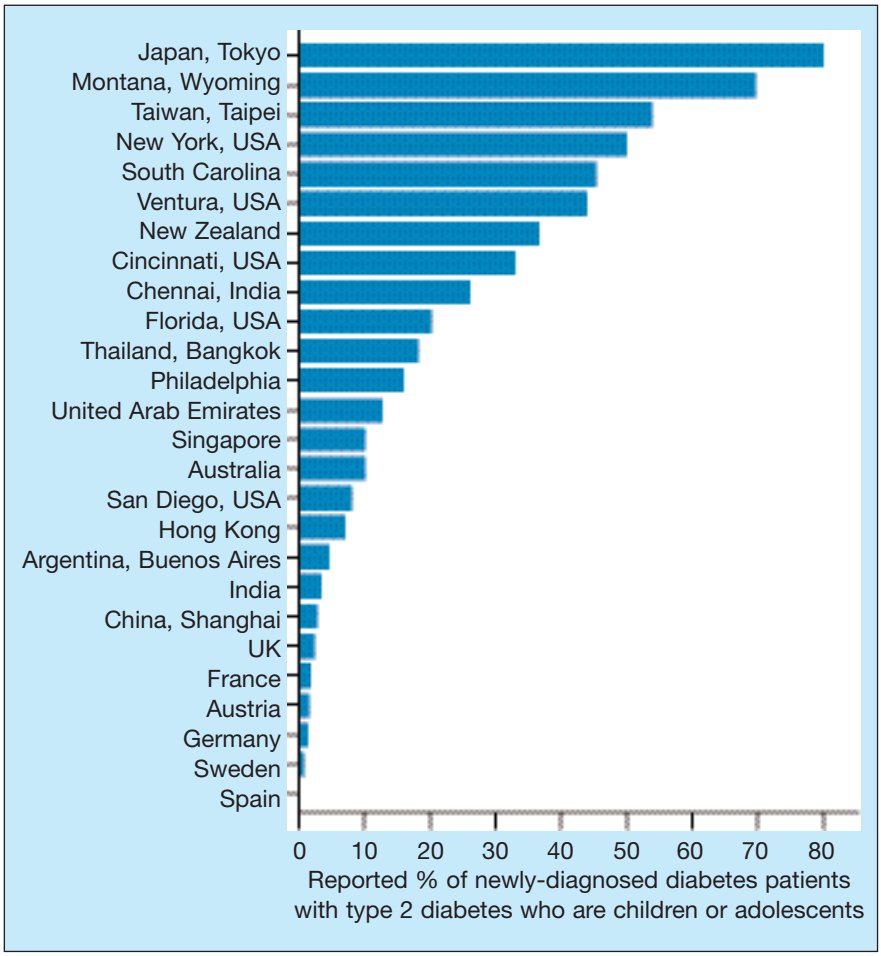


Figure 2. Worldwide differences in the prevalence of type 2 in newly-diagnosed paediatric diabetes patients. (Modified, with recent reports, from Pinhas-Hamiel *et al*.)[14]



genetic predisposition, insulin resistance (associated with weight gain and physical activity) and autoimmunity of beta-cells.[29] Studies in favour of and against this hypothesis have been published,[24,30,31] and further research elucidating the pathophysiology associated with early excessive weight gain in toddlers is needed.

Diagnosis and screening of paediatric T2DM

Type 2 diabetes is a polymorphic chronic disease characterised by dysfunction of insulin secretion or missing effectiveness of insulin. As in adults, type 2 diabetes in adolescents is characterised by a combination of insulin resistance, hyperinsulinaemia, relative insulin deficiency and secretory disorders.[32] Dyslipidaemia and arterial hypertension are also frequent comorbidities with type 2 diabetes in paediatric patients. Acanthosis nigricans or polycystic ovarian syndrome can be a result of the insulin resistance.[33,34] The visceral fat, measured clinically as waist circumference, has consistently been described as a significant predictor of insulin resistance in adulthood.[35,36] Fatty tissue is now understood to be an endocrine organ in itself. On the one hand, it produces adipocytokines that induce a decline of insulin sensitivity and, on the other hand, it secretes adiponectin that has an antihyperglycaemic effect.

Data from the US National Health and Nutrition Examination Surveys from 1988–1994 and 1999–2004 have shown a significant increase of mean waist circumference by 3.7cm among both boys and girls aged between two and 19 years. The comparison of the prevalence of obesity measured by waist circumferences >90th percentile and otherwise measured by BMI >90th percentile pointed to a parallel increase in visceral fat and general body fat for children and adolescents as well.[37] Unfortunately, the association of these findings with insulin resistance have not been examined in this study. However, some years later, Lee and colleagues[38] verified a significant correlation between BMI and waist circumference. In addition, they have found that insulin resistance (defined by elevated fasting insulin, proinsulin and decreased insulin sensitivity) increases while the BMI and waist circumference are rising. Although it is not clear yet if waist circumference or BMI may be a better parameter to identify obese children at particular risk of type 2 diabetes, both parameters should be measured if possible.

In contrast to the usual clinical signs of type 1 diabetes in children, polyuria and polydipsia are mild or even missing and the patients are diagnosed with glucosuria without ketonuria, impaired glucose tolerance, and pronounced overweight.[13,34] In particular, there is less or no reduction in weight in the history, and diabetes-specific antibodies

Table 1. Differentiating between different forms of diabetes in children. (Modified from Reinehr[34])

	Type 1 diabetes	Type 2 diabetes	Maturity-onset diabetes of the young (MODY)
Relative frequency in Caucasian populations	>90%	<10%	1–3%
Age at diagnosis	Children and adolescents	Adolescents above age 10	MODY 2: children MODY 3: adolescents
Obesity	Corresponding to background population	Frequent	Corresponding to background population
Gender	Boys = girls	Girls > boys	Boys = girls
Family history	2–4% type 1 diabetes	75–100% type 2 diabetes	90% MODY
Ethnic background	Predominantly Caucasian	Afro-Americans, Hispanics, native Americans, Asians	
Beta-cell autoimmunity	85–98%	Rare	Unlikely
Insulin, C-peptide	Low	High	Low
Onset	Rapid	Insidious	Variable
Ketoacidosis	Frequent	Rare	Unlikely
Associated diseases	Hashimoto thyroiditis Coeliac disease	Acanthosis nigricans Polycystic ovary syndrome Metabolic syndrome	

Table 2. ADA recommendations for screening for type 2 diabetes in obese adolescents[13]

First criteria:
- BMI > 85th/ 90th percentile for age and gender or
- Body weight for height >85th/90th percentile or
- Body weight >120% of ideal for height

Plus any two of the following risk factors:
- Family history of type 2 diabetes in first- or second-degree relatives race/ethnicity (American-Indian, African-American, Hispanic, Asian/Pacific Islander)
- Signs/symptoms of insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, polycystic ovary syndrome)

are usually not detected at onset of the disease.[32] A total of 74–100% of children with type 2 diabetes have a positive family history of type 2 diabetes.[13] Currently, approximately 70%[39] of the genes involved in the development of type 2 diabetes in obese individuals have been described. A strong protective or triggering genetic influence could be the explanation for the varying prevalence distribution of type 2 diabetes in different ethnic populations living under comparable living conditions. A higher prevalence is found among African-Americans, native American-Indians and Asian-Indians living in the USA than among the European population having the same lifestyle. As a possible link between diabetes risk and ethnic factors, higher insulin levels were found in seven- to 11-year-old African-American children compared to matched white children.[40,41]

The lack of clinical signs of type 2 diabetes in paediatric patients raises the question as to whether screening programmes would be feasible. Eventually, future advances may offer the possibility of genetic screening although many ethical issues need to be resolved. Population-based urinary glucose screening programmes in school children have been performed successfully in Japan, where type 2 diabetes is more frequent than type 1 diabetes in paediatric patients.[42] Further studies are necessary to determine the practical relevance of measuring waist circumference as a predictor of the risk of developing type 2 diabetes.

In most populations, screening should be targeted to high risk groups of children who are overweight and have a positive family history. According to the American Diabetes Association (ADA) guidelines,[13] screening should be started in the 10th year of life in the context of preventive medical check-up, as cases of type 2 diabetes before puberty are very rare. Screening should include HbA_{1c}, fasting blood glucose after a fasting time of at least eight hours, and two-hour postprandial blood glucose measurement. The World Health Organization[43] recommends performing an oral glucose tolerance test. The ADA recommends biennial screening on the basis of body weight and risk factors (Table 2). A recent nationwide survey in the Netherlands reviewing close to 1000 newly-diagnosed paediatric diabetes patients in the Dutch Paediatric Surveillance Unit showed a discrepancy between the number of patients with type 2 diabetes diagnosed by paediatricians in daily practice and those diagnosed according to the ADA criteria. Moreover, a considerable amount of reported patients were misclassified. Finally, 2.4% of patients were classified as (very likely) type 2 diabetes.[44] Such diagnostic difficulties may remain until genetic testing becomes available.

Treatment options in paediatric T2DM

Several treatment options are available for the paediatric age group (Table 3). The complex nature of paediatric type 2 diabetes necessitates management by a multidisciplinary team. Clinic visits are recommended every two to four weeks initially and then in longer intervals for diabetes follow up as an individual in outpatient care. In contrast, weight management education is usually performed as peer-group education. Therefore, the treatment approach should combine individual diabetes education[45] with group education (Table 4). As in adults, the aim of paediatric type 2 diabetes treatment is the reduction of the risks of comorbidity and long-term complications.[13] It is likely that we can extrapolate

Table 3. Treatment options for paediatric type 2 diabetes

Treatment	Reduction of hyperglycaemia	Improvement of beta-cell function	Improvement of insulin resistance	Recommended in guidelines	Approval	Comment
Diet and exercise	Yes	No	Yes	Yes	Yes	–
Insulin	Yes	No	No	Yes	Yes	Weight gain
Metformin	Yes	No	Yes	Yes	Yes	Few side effects
Sulfonylurea	Yes	Yes	No	Yes	No	Risk of hypoglycaemia
Thiazolidinediones	Yes	?	Yes	No	No	Weight gain, no long-term data
Arcarbose	?	No	No	??	No	Flatulence
Orlistat	?	No	No	??	No	Unacceptable side effects
Bariatric surgery	Yes	No	Yes	???	–	Case reports

Table 4. Multidisciplinary group education programme for obese adolescents in Hannover, and additional topics for diabetes

Combining a paediatric weight management programme with type 2 diabetes education	
Method	• Selection criteria and diagnostic process – BMI >97th percentile (age- and gender-dependent) – Child needs to be motivated to participate – Pre-selection examination by psychologist and physician – Physical fitness assessment • Structure – Maximum 12 participants per group – One-year programme with weekly sessions • Team – Physician, psychologist, sports therapist, dietitian
Standardised education programme topics	• Exercise – Exercising safely – Body awareness, coordination, power, endurance – Physical exercise and games • Food – Basic knowledge ('food-pyramid', amounts, servings) – Training in eating behaviour – Shopping, cooking, eating meals together • Psychosocial – Social interaction, acceptance of yourself, self-perception – Role-playing • Family – Parenting skills and family resources – Nutrition and activities • Health – Definition, background, treatment and consequences of obesity – Long-term complications
Additional modules for type 2 diabetes	• Exercise – Hypoglycaemia (when using insulin or hypoglycaemic agents) • Food – Carb-counting • Psychosocial – Talking about diabetes with peers – Career choices and relationships – Legal issues • Family – Self-efficacy and gaining independence from the parental home • Health – Diabetes treatment, self-monitoring – Ongoing care and check-up – Future perspectives in relationship to late complications – Alcohol, smoking, drugs – Sexuality, contraception, family planning, diabetes risks of children

from the results of the adult United Kingdom Prospective Diabetes Study that each 1% reduction in mean HbA_{1c} can reduce the diabetes-related complications by about 21%. Thus, the treatment programme needs to combine the medical approach – reducing blood glucose levels (fasting plasma glucose <126mg/dl [<7mmol/L]) and HbA_{1c} (<7%) – with the lifestyle/behaviour modification programmes that are successfully used for the weight management of obese adolescents.[32,46] Initial studies indicate an early appearance of late complications in patients with paediatric-onset type 2 diabetes,[47] requiring intense efforts from the onset of the disease.

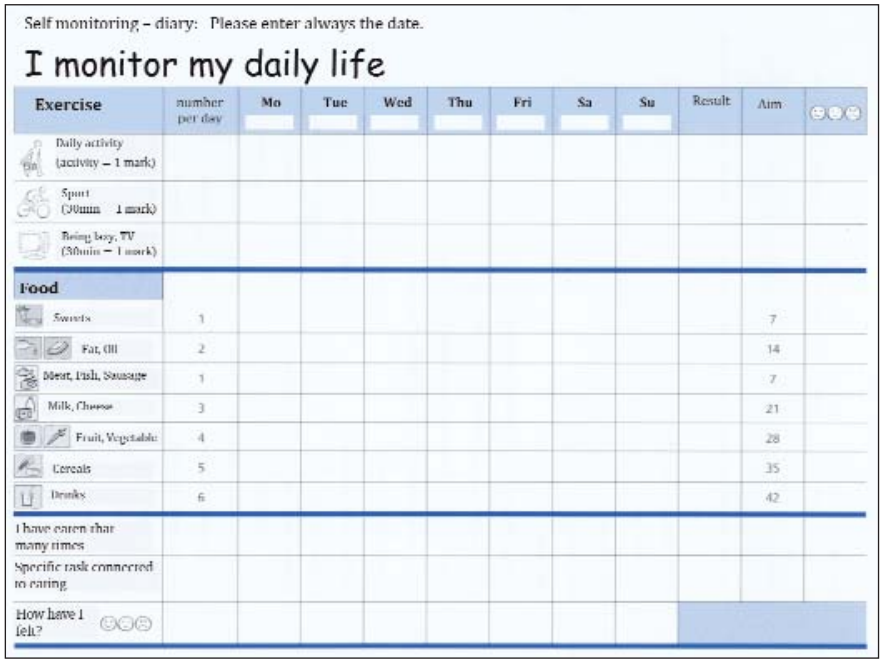
Psychological aspects

The targets for weight management in children and adolescents with type 2 diabetes correspond to those of other obese adolescents. Although a rapid reduction in weight may be desirable in order to reduce the intensity of antidiabetic treatment, the eventual goal has to be a stable long-term weight reduction (i.e. reduction of fat mass). In the context of the whole family and the peer group, a sustainable change in eating behaviour and lifestyle needs to be achieved. The concept of flexible control (Table 5) has been proven to be superior to restrictive strategies which frequently lead to relapses.[48] The establishment of effective strategies of self-monitoring is an integral part of success for the long term (Figure 3). Implementing the frequent use of logbooks for activities and food intake with self-monitoring of blood glucose requires ongoing motivation and feedback on the part of the multidisciplinary team. As with any intervention, it is important to avoid unwanted psychological side effects of weight management. It has been reported that 70% of obese adolescents have anxiety or depression and 17% are afflicted by an eating disorder.[49] Thus, careful psychological evaluation appears necessary for the early recognition and treatment of psychological conditions before entering a peer-group programme for weight management. It has been shown that the rate of psychological

Table 5. Characteristics of flexible control as a basis for lifestyle counselling in paediatric type 2 diabetes

- Restrained eating behaviour
  - Moderate restrictions
  - Long-term weight control
- Control of physical exercise
  - Increase in everyday activity
  - Reduction in inactivity per week
- Self-monitoring
  - Training logbook

Figure 3. Example of a logbook to monitor daily activities and food intake to be used in a weight management programme for obese children with type 2 diabetes. (Adapted from Die Konsensusgruppe Adipositasschulung)[55]


Self monitoring – diary: Please enter always the date.

I monitor my daily life

Exercise	number per day	Mo	Tue	Wed	Thu	Fri	Sa	Su	Result	Aim	☺☺☺
Daily activity (activity – 1 mark)											
Sport (30min – 1 mark)											
Being busy, TV (30min – 1 mark)											
Food											
Sweets	1									7	
Fat, Oil	2									14	
Meat, Fish, Sausage	1									7	
Milk, Cheese	3									21	
Fruit, Vegetable	4									28	
Cereals	5									35	
Drinks	6									42	
I have eaten that many times											
Specific task connected to eating											
How have I felt? ☺☺☺											

disorders in adolescents with type 1 diabetes was three times higher than that in a non-diabetic control group matched for age, gender and socio-economic status.[50] Similar studies for paediatric type 2 diabetes are not available so far.

Pharmacological treatment

Currently, only one oral medication is approved for use in adolescents with type 2 diabetes who are older than 10 years. Metformin lowers blood glucose levels by reducing hepatic glucose production and by increasing muscle glucose uptake. A randomised placebo-controlled multicentre trial involving 82 adolescents with type 2 diabetes treated twice daily with 1000mg metformin resulted in a reduction in mean HbA_{1c} values compared to the placebo group (7.5% *vs* 8.6%). Additionally, the metformin-treated subjects could reduce their weight by about -1.5kg compared to the placebo group (-0.9kg). In some cases, gastrointestinal side effects have been reported.[51] For this reason, the treatment of young patients with metformin should be started slowly with 500mg daily at bedtime for one week, then increased to 500mg twice a day, with further increases by 500mg a day each week as needed up to a maximum recommended daily dosage of 2550mg. Other oral agents have been tested in children as well,[52] but most of them are still off-label (Table 3). If lifestyle intervention and oral treatment have not been successful in reaching glycaemic targets, patients will require a combination therapy with insulin.[8] Despite these efforts, the prognosis for paediatric type 2 diabetes is poor.[47] As these children often come from an unstable psychosocial background it is not surprising that a recent analysis of a paediatric diabetes database revealed that 60% of these children were lost to follow up less than one year after diagnosis.[53] Thus, from a public health perspective, great efforts should be put into preventing paediatric type 2 diabetes.

Prevention of paediatric T2DM

In an analysis of 15 papers published since 2000, Gittelsohn and Kumar reported that a sufficient number of intervention programmes for children of school age have been developed. These programmes may lead to successful weight reduction allowing secondary prevention of paediatric obesity and thereby prevention of type 2 diabetes.[54] In Germany, a nationwide syllabus for a weight management programme for eight- to 16-year-old children has been developed (Table 4, top panel).[55] In the past four years, 170 families have been treated in our centre on an outpatient basis. Upon entering the programme, 10% of obese children had comorbidities, such as acanthosis nigricans, hyperinsulinism, hypertriglyceridaemia or hypercholesterolaemia. Weight reduction through structured, multidisciplinary intervention allows the successful correction of many of these comorbidities.[56] Two major programmes are currently underway in the US which may serve as a model for other programmes if successful. The HEALTHY trial is a multi-site, three-year middle school intervention programme with a focus on changing school food services, physical education and activities to encourage healthy behaviours.[57] The TODAY trial is a five-year multicentre trial to evaluate the treatment options for type 2 diabetes in youth, including a comprehensive lifestyle change programme. In this trial, the 800 overweight children with type 2 diabetes will be randomised in three intervention arms: metformin, metformin + rosiglitazone, and lifestyle behavioural counselling.[58]

In the Hannover centre, preventive approaches aim at a much younger age group. As a significant number of children are already obese when they reach school age,[59] we are currently conducting a randomised cross-over trial of behavioural intervention in the kindergarten ('fit von klein auf' [fit children]).[60] Unhealthy lifestyles prohibiting balanced meals in families and increasing time spent watching TV are closely linked to obesity

Key points

- As a consequence of the obesity epidemic, type 2 diabetes has emerged recently as a problem among adolescents and young adults, particularly in populations with a high prevalence of obesity
- Preventive approaches against childhood obesity and type 2 diabetes should be targeted to high risk groups and start in the preschool age group
- Treatment approaches in paediatric type 2 diabetes include training programmes for family lifestyle modification and frequently need pharmacotherapy with oral agents and/or insulin
- Psychological approaches focusing on training in flexible control of eating and lifestyle behaviour appear to be more successful than rigid treatment plans

and start at kindergarten age.[61,62] At this time, it may be more productive to involve the parents in the intervention programmes. Childhood obesity is closely linked to parental overweight.[63,64] The risk of becoming obese in adulthood is 71% for a seven-year-old boy, if the parents are obese. In contrast, if the parents have a normal weight, the risk of obesity in adulthood is reduced to 37% for the same boy.[65] Thus, to avoid paediatric type 2 diabetes interventions must start at the preschool age, involve the whole family and be targeted to the high risk groups. Although there is widespread public awareness of the problem, many initiatives for obesity prevention and paediatric type 2 diabetes treatment lack a scientific basis. Carefully planned intervention studies with sufficient power to scientifically prove effectiveness are urgently needed in order to identify successful preventive strategies as well as treatment approaches for paediatric type 2 diabetes.

Conflict of interest statement

There are no conflicts of interest.

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