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Diagnosis and treatment of obese children with insulin resistance

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Chapter 8

Conclusions and perspectives on diagnosis and treatment of obese children with insulin resistance

Summary and conclusions

Introduction and background

Last decades, the prevalence of childhood obesity is rising, with rates up to 17.4% in the U.S. [1]. In the Netherlands, the prevalence of childhood obesity varied in 2010 from 1.8% in native boys to 8.4% in boys of Turkish descent [2]. For children standard deviation scores (SDS), z-scores, or percentiles are used to the define overweight and obesity [3-5]. Cut-off values used in the Netherlands are BMI-SDS > 1.1 (BMI > p85) for overweight and BMI-SDS > 2.3 (BMI > p95) for obesity [6].

Childhood obesity is a strong predictor for obesity in adulthood. Odds ratios for obese children to become obese adults varied from OR 1.3 for obese children aged 1-2 years to an OR of 22.3 for obese children aged 10-14 years [7, 8]. Besides psychological consequences, childhood obesity has multiple somatic consequences, affecting almost all organ tracts. Cardiovascular and metabolic consequences are common, including hypertension, dyslipidemia, endothelial dysfunction, insulin resistance (IR) and type 2 diabetes mellitus (T2DM) [9-11]. IR is described as an early sign in the development of metabolic and cardiovascular consequences in obesity [12-14]. Although insulin resistance is related to obesity, not all obese children are insulin resistant, and not all insulin resistant children are obese [15]. However, insulin resistance levels do increase with the level of overweight [16, 17].

Prevalence, diagnosis and follow up of children with insulin resistance

In view of the increasing incidence of obesity in children, insight into the epidemiology of the pre-diabetic state IR seems important. In **Chapter 2**, a systematic review was presented to give an overview of all population-based studies reporting on the prevalence and incidence rates of IR in childhood [18]. Eighteen population-based studies were identified, describing prevalence rates varying between 3.1 and 44 %. This variation could be explained partly by different definitions for IR. The results show that overweight and obese children had higher prevalence rates than normal weight children. In seven out of thirteen studies reporting sex-specific results, girls seemed to be more affected than boys. Since different definitions were used in most studies, comparison of prevalence rates between studies was impeded. It was concluded that consensus on the definition for IR in children is needed to allow for comparisons between different studies.

This variation in definitions for IR was further investigated in **Chapter 3**. Published definitions (methods and cut-off values) to define IR in pediatric populations were applied to a population of patients with obesity from a pediatric outpatient clinic. In 103 identified articles, 146 IR definitions were reported based on 14 different methods. Definitions based on fasted blood samples were used 137 times, whereas oral/intra-

venous glucose tolerance test derived methods were used 9 times. The homeostasis model for the assessment of insulin resistance (HOMA-IR) and fasted plasma insulin (FPI) were the most frequently used fasted methods (83 and 37 times, respectively). A wide range in cut-off values to define IR was observed, resulting in prevalence rates in the predefined obese pediatric population between 5.5% (FPI > 30 mU/l) and 72.3% (Insulin sensitivity index$_{Matsuda}$ ≤ 7.2). The findings of this study underlined the need for a uniform definition for IR.

Currently, the recommended screening to identify children at risk for diabetes and its precursors impaired glucose tolerance (IGT) and IR is fasted plasma glucose (FPG). In **Chapter 4,** the value of FPI to calculate the HOMA-IR in addition to screening with FPG to detect children with IR, impaired glucose tolerance or T2DM, was evaluated [19]. For this, routinely collected data of an oral glucose tolerance test (OGTT) of 311 obese children (10.8±3.2 years) were evaluated. Screening according to the guidelines, using FPG with a cut-off ≥ 5.6 mmol/l was compared to screening with FPG ≥ 5.6 mmol/l combined with HOMA-IR (cut-off value ≥ 3.4). Diabetes and IGT were defined according to the American Diabetes Association (ADA) criteria [20]. Cases of IR, IGT or T2DM identified on the basis of screening with FPG ≥ 5.6 mmol/l, compared to screening with FPG ≥ 5.6 mmol/l or HOMA-IR ≥ 3.4, were respectively four (80%) vs five (100%) for T2DM, 7 (28%) vs 16 (64%) for IGT and 0 (0%) vs 93 (100%) for IR. In conclusion, screening with FPG and FPI to calculate HOMA-IR has equal burden compared to screening with FPG alone, and identifies all patients with diabetes, and more patients with precursors of diabetes.

To date, the recommended screening interval for children at risk for T2DM, i.e. for example children with overweight or obesity and IR, is 3 years. In **Chapter 5,** a follow up study was performed in children at risk for T2DM, to evaluate weight, insulin sensitivity, and progression to T2DM approximately 3 years after being diagnosed with overweight/obesity and IR (measured by HOMA-IR) [21]. Out of 86 invited children, 44 (mean age 15.4 ± 3.6 years) participated. Medical history, physical examination, and laboratory workup were performed. While the mean BMI-SDS significantly increased from 2.9 to 3.4, the mean HOMA-IR significantly decreased from 5.5 to 4.6 (baseline vs follow up visit). Change in HOMA-IR was due to a decrease in mean FPI (24.1 vs 21.1, p=0.073). Although the increase in BMI-SDS in these children is worrisome, none of the children at risk for T2DM developed T2DM during the screening interval of three years proposed by the American Diabetes Association.

Treatment of obese children with insulin resistance

In the second part of this thesis, the effect of long-term treatment with metformin in obese children with IR was presented. With the rising prevalence of childhood obesity, and thereby of IR, the risk of complications in childhood rises as well. To prevent

these complications, lifestyle intervention is the cornerstone in treatment. However, long-term efficacy of lifestyle intervention is questionable [22]. As adolescents with obesity and IR may be refractory to lifestyle intervention therapy alone [23], additional off-label metformin therapy is often applied [24, 25]. Metformin has been shown to be moderately effective to reduce BMI in adolescents with obesity and hyperinsulinemia [26-32]. However, data on long-term efficacy and safety are lacking. In **Chapter 6a,** the study protocol of the Metformin study was presented [33]. The primary objective of the Metformin study was to determine the effect of adding metformin treatment to lifestyle-intervention in reducing BMI in adolescents with obesity and IR. The Metformin study is a multi-centre prospective study, that consists of two parts of each 18 months: a double-blind randomized placebo-controlled trial (part 1) and an open-label follow up study (part 2). During part 1 the participants were given Metformin 1000 mg or placebo twice daily and were offered a lifestyle intervention program over 18 months. During part 2, no structured lifestyle intervention program was offered. All participants who still met the criteria for the use of metformin were free to choose whether they would use metformin in part 2. Primary endpoints were change in BMI and IR measured by the HOMA-IR. Secondary endpoints were safety and tolerability of metformin. Other endpoints were body fat percentage and HbA1c. In **Chapter 6b,** the results of part 1 of the Metformin study were presented [34]. Forty-two participants completed the 18 month-study (66% girls, median age 13 (12-15) years, BMI 30.0 (28.3-35.0) kg/m^2 and HOMA-IR 4.08 (2.40-5.88)). Median ΔBMI at 18 months was +0.2 (-2.9-1.3) kg/m^2 (metformin) versus +1.2 (-0.3-2.4) kg/m^2 (placebo) (p=0.015). No significant difference was observed for HOMA-IR. No serious adverse events were reported. Median change in fat percentage was -3.1 (-4.8-0.3) vs -0.8 (-3.2-1.6)% (p=0.150), in fat mass -0.2 (-5.2-2.1) vs +2.0 (1.2-6.4) kg (p=0.007), in fat free mass +2.0 (-0.1-4.0) vs +4.5 (1.3-11.6) kg (p=0.047), and in ΔHbA1c +1.0 (-1.0-2.3) vs +3.0 (0.0-5.0) mmol/mol (p=0.020) (metformin vs placebo). To conclude, long-term treatment with metformin in adolescents with obesity and IR results in stabilisation of BMI and improved body composition compared to placebo. Its seems therefore that metformin may be useful as additional therapy next to lifestyle intervention in adolescents with obesity and IR.

Because treatment effects reported in clinical trials may differ from the effects in daily clinical practice, the aim of **Chapter 7** is to compare the effects of metformin (in addition to a lifestyle intervention program) on change in BMI between adolescents with obesity treated with metformin in daily clinical practice and adolescents who participated in the RCT (Chapter 6). For this study, all adolescents with obesity treated off-label with metformin in our pediatric obesity outpatient clinic, with clinical follow up of at least 18 months from start of treatment were identified. Anthropometric data (age, height, weight, body mass index) and laboratory parameters (FPG, FPI and HbA1c) were collected at baseline and at t=18 months. Change in BMI after 18 months was

compared between the two groups. Nineteen patients (median age 14.3 (interquartile range 11.7-15.7) years, BMI 31.3 (28.8-33.8) kg/m^2, BMI-SDS 3.23 (3.05-3.64)) in the daily clinical practice group were compared to 23 patients receiving metformin during the RCT (age 13.6 (12.6-15.3) years, BMI 29.8 (28.1-34.5) kg/m^2, BMI-SDS 3.10 (2.72-3.52). Change in BMI after 18 months was -0.36 (-2.10-1.58) vs +0.22 (-2.87-1.27) kg/m^2 for the two groups, respectively. In the multivariable model, the changes in BMI were not statistically significantly different (p=0.61). In these populations, treatment with metformin in adolescents with obesity in daily clinical practice is associated with a change in BMI similar to the change observed during metformin treatment in obese adolescents in a RCT. This finding further supports considering metformin as an add-on therapy next to lifestyle intervention.

Perspectives

The importance of a uniform definition for IR and how to get to a uniform definition

In this thesis, the lack of a uniform definition for IR in children and adolescents has become clear. As a result of this lack of uniform definition for IR, the incidence and prevalence of IR in pediatric populations remains unclear [18]. Differences in prevalence rates between populations can in part be explained by the use of different definitions. With a uniform definition for IR, it will be possible to compare prevalence and incidence rates between populations and trends over time. In clinical practice, a clear definition and cut-off value will help clinicians to identify children at risk for T2DM and other cardiometabolic complications. For the follow up of children with IR, the factors resulting in a physiological increase or decrease of insulin concentration, such as age and pubertal stage, have to be taken into account in the definition and cut-off value for use in the follow up in clinical practice.

Although IR is an important risk factor for T2DM and cardiometabolic complications [11, 14]., other risk factors should not be ignored. In most patients a combination of risk factors results in the development of T2DM or other complications. These risk factors are combined in the metabolic syndrome, also called insulin resistance syndrome or syndrome X. For the metabolic syndrome however, there is no consensus on the best definition for the use in pediatric populations either [35, 36]. At least six definitions for the metabolic syndrome in pediatric patients have been reported [36-41]. These definitions all include criteria for overweight, blood pressure and blood lipids, with various cut-off values. The criterion on blood glucose and/or insulin varies: four definitions include impaired fasted glucose (with different cut-off points in each definition) [37, 38, 40, 41]; the other two definitions include impaired fasted glucose (with different cut-off

points in each definition), hyperinsulinemia or increased HOMA-IR as criterion [36, 39]. A uniform definition for IR could be applied in these definitions combining the most important risk factors for cardiometabolic complications.

Towards a uniform definition for IR in children

A uniform definition for IR in children should meet certain criteria to be of use in daily clinical practice. First, it should be accurate. The gold standard is the euglycemic-hyperinsulinemic clamp study [42]. However, this clamp study is not suitable for daily clinical practice because of the invasive, time consuming character and high burden for the patients. Many surrogate measures have been developed and compared to the euglycemic-hyperinsulinemic clamp study [43-45]. The correlations of measures based on the OGTT are comparable to the measures based on fasted samples [43, 46, 47]. However, the surrogate measures based on fasted samples have lower burden than OGTT-based measures, which is preferable for use in daily clinical practice. The most frequently studied fasted measures in pediatric populations, i.e. HOMA-IR, QUICKI and FPI, have moderate to strong correlations with IR assessed with the euglycemic-hyperinsulinemic clamp, respectively 0.51-0.81, 0.43-0.91 and 0.48-0.92 [46-51]. Therefore, this criterion does not distinguish in which method would be the best to use. To minimize the burden for the patients as much as possible, preferably fingertip capillary blood testing should be used. However, the accordance between insulin measured from capillary blood and blood from an antecubital venous puncture was poor (coefficient of variation 36.0%) [52].

A second criterion is the reproducibility of the test. Data available from adult studies showed a coefficient of variation (CV) for HOMA-IR of 11.8% (7.8-11.9), for QUICKI 1.8% (1.1 – 2.9) and for FPI 13.4% (8.8 – 21.9) [53]. The low CV reported for the QUICKI was however debated by Antuna et al. because this measure is composed of log transformed values of FPG and FPI [54]. When the CV of log transformed HOMA-IR values are compared to the CV of the QUICKI, similar, low CV's were found for both measures. Since all of these formulas are based on the same measurements of glucose and insulin, the CV is not discriminating between HOMA-IR and QUICKI either.

In summary, the three surrogate measures for IR based on fasted samples are comparable to each other, with equal burden for the patients.

Factors influencing the insulin concentration, such as age, pubertal stage [55-57], ethnicity [58, 59], and gender [60] have to be considered when defining cut-off values for IR in children. The available (population based) studies present percentiles for FPI and HOMA-IR levels for gender and age [36, 61-66]; and percentiles for HOMA-IR and QUICKI by Tanner stage and by Tanner stage and gender [67]. None of these studies differentiated between ethnic groups, and most studies included participants of only

one ethnicity. In a study by Chiu et al, it was found that ethnicity was an independent factor influencing the insulin sensitivity indices [58].

To produce age, pubertal stage, ethnicity and gender specific reference values for FPI, HOMA-IR and QUICKI the data of the performed studies could be used, complemented with data from additional new studies. The available large populations based studies are predominantly performed in Caucasian children. These studies provide data for HOMA-IR and FPI in European, mainly Caucasian children aged 3-10.9 years (n=7074 children) [36, 66]; for FPI in European children aged 7-20 years (n=1976) [63]; and for FPI and HOMA-IR in Caucasian children 9-16 years (n=2244) [65]. Two large population based studies in children from different ethnicities have been performed: one study in Mexican-American children aged 6-18 years (n=3701) providing values for HOMA-IR [61]; and a study by Yi et al. performed in Asian children aged 10-20 years (n=2716), providing data for FPI and HOMA-IR [64]. Additional data for Tanner stage and other ethnicities are required, as well as values for Asian children under the age of 10. Based on the values for FPI, HOMA-IR and QUICKI from these large studies, cut-off values could be defined. As cut-off values, the 95th percentile or a SD-score of 2 for gender, age or pubertal stage and ethnicity could be used.

Since there seems to be no advantage for the use of FPI above HOMA-IR or QUICKI, the clinician could use the measure he or she prefers, in combination with age, gender, pubertal stage and ethnicity specific cut-off values. For the comparison of prevalence rates and incidence rates, the use of one measurement is preferred. In our studies we used the HOMA-IR, since this was to our opinion the most frequently used, well-known measure in pediatrics. Furthermore, the calculation for HOMA-IR is easier than QUICKI to perform.

Preventive interventions in children with obesity at risk for cardiometabolic complications

Screening and follow up of obese children at risk for T2DM was discussed in chapter 4 and 5. The current ADA recommendations apply to children with overweight or obesity and additional risk factors for T2DM [20]. No specific recommendations are available for children with overweight or obesity without additional risk factors [20, 68]. On the basis of screening for risk factors and complications, children with obesity are classified with mild, moderate, high or very high risk of complications. The Dutch guideline 'Diagnosis and treatment of obesity in adults and children' differentiates in their treatment recommendations based on this 'weight-related health risk' ('Gewichtsgerelateerd Gezondheidsrisico') [68]. Children at higher risk, should receive a more intensive lifestyle intervention program.

There have been many studies assessing the effect of lifestyle intervention programs in overweight and obese children [22, 69-73]. Only a few studies compared the effects

of these programs between children with different degrees of overweight or obesity. A study by Rijks et al. showed that the effects of a lifestyle intervention program, with a follow up of 24 months, were similar in overweight, obese and morbidly obese children with respect to change in BMI z-score. After 12 months, cardiovascular risk factors such as blood pressure, cholesterol, FPG and HbA1c improved equally in all groups [74]. In contrast to this, Knop et al. described more effects in extremely obese children (<10 years) compared to obese children. For adolescents (≥ 10 years), the obese group had a better result of lifestyle intervention than extremely obese group [75]. In large prospective studies, the risk of T2DM and cardiovascular risk factors in adulthood was similar for both normal weight adults who were overweight or obese during childhood, and adults who had normal weight during childhood [76].

In view of this, the question is, whether we should focus on obese children with additional risk factors only, or consider overweight and obese children without risk factors as well, with respect to screening, follow up and preventive lifestyle interventions. In our study on screening obese children for T2DM, described in chapter 4, we excluded children with overweight [19]. In chapter 5, where the follow up of children at risk for T2DM was described, overweight and obese children were included [21]. Children with overweight had lower levels of HOMA-IR, compared to children with obesity (HOMA-IR 3.3 vs 4.8, respectively). However, the mean HOMA-IR of 3.3 was only slightly below the threshold of 3.4 used as cut-off value. Since the consequences of childhood overweight and obesity seem reversible provided normal weight is achieved in adulthood [76], lifestyle intervention should in our opinion be offered to all overweight and obese children. Children with overweight have risk factors for complications as described in different studies [77-80]. An economic evaluation of interventions for childhood obesity showed that for both overweight and obese children, lifestyle interventions are potentially cost effective on the long-term [81]. To improve the (long-term) effects of lifestyle intervention, use of e-health, web-based interventions and the use of smartphones should be further investigated. The currently available studies on the use of these technologies showed improved compliance and response, and lower dropout rates [82-84]. As mentioned in the general introduction, parental motivation is important as well. A combination of parent-only interventions and web-based or smartphone support could be an interesting field for future research to improve the effect of lifestyle interventions.

To conclude, both children with overweight and obesity have risk factors for cardiometabolic complications. Current guidelines apply to children with obesity only. Since the long-term risk of complications for both overweight and obese children is reversible provided they become normal weight adults, screening and preventive treatment of overweight children should be considered. Consequently, lifestyle interventions should be offered to both overweight and obese children.

The use of metformin in addition to lifestyle intervention in children with obesity

In the chapters 6 and 7 of this thesis, the effects of metformin in the treatment of children with obesity were described. It was found that metformin over 18 months resulted in a stabilization of BMI, whereas the participants receiving placebo continued gaining weight. Moreover, children with obesity treated in daily practice with metformin had similar results regarding the stabilization of BMI. The effects of metformin on change in BMI has been studied in many short-term trials, which have been analyzed in two meta-analyses, reporting a reduction in mean BMI of -1.42 ((95%CI -2.02 - -0.83) kg/m^2 (based on 5 studies) [26] and -1.38 (95%CI -1.93- -0.82) kg/m^2 (based on 8 studies) [85]. Long-term data are limited to a study of 48 weeks (mean ΔBMI -0.9(±0.5) kg/m^2 (metformin) versus +0.2(±0.5) kg/m^2 (placebo), p=0.03) [86], and our RCT of 18 months (median ΔBMI +0.2 (-2.9-1.3) kg/m^2 (metformin) versus +1.2 (-0.3-2.4) kg/m^2 (placebo) p=0.015) [34]. Regarding side-effects, especially gastro-intestinal side-effects are common, with up to 74% of the participants reporting nausea and 61% reporting diarrhoea in our study. Vitamin B12 deficiency occurred in 13%. In most cases, the gastro-intestinal side-effects are self-limiting; in 6% of cases, side effects resulted in treatment cessation [34]. Based on this evidence, globally there are three scenarios for the future use of metformin in the treatment of children of obesity. These scenarios will be discussed here, and the arguments are listed in table 1.

Table 1. Scenarios for future use of metformin in children with obesity

	Pro	Contra
Scenario 1:		
No use of metformin in obese children	- No risk of side effects, vitamin B12 deficiency or ketoacidosis - No exposure to a therapy of which the mechanism is partially unknown - No overtreatment / unnecessary use of medication	- No opportunity to benefit from effects of metformin on BMI [27-32, 88-90)
Scenario 2:		
Metformin to be used in all obese children if 1 year lifestyle intervention fails	- Equal treatment for obese children who do not benefit from lifestyle intervention alone - Potential benefit against limited burden of side effects	- Evidence for effectivity of metformin mainly in children with obesity and IR or other risk factors [27-32, 88-90) - Side effects and vitamin B12 deficiency, ketoacidosis
Scenario 3:		
Metformin in a select population of children with obesity and IR, hyperinsulinemia or other risk factors	- Available evidence applicable on this population - Effect on BMI (short-term and long-term) and IR (short-term)	- Side effects and vitamin B12 deficiency, ketoacidosis - Mechanism unknown - Effects of prolonged use (>18 months) unknown

In the first scenario, metformin is not used for the treatment of children with obesity. As a benefit of this scenario there is no risk of adverse events, such as gastro-intestinal complaints, vitamin B12 deficiency and (the scarcely occurring complication) keto-acidosis. Furthermore, children and adolescents are not exposed to a therapy with possible side-effects. It is suggested that metformin results in weight loss because of multilevel influence on the neuropeptides regulating appetite, and thereby reducing food intake [87]. However, weight loss during metformin therapy might also be due to side-effects, since patients with nausea and/or diarrhea have reduced caloric intake because of these side-effects. As such, it is debatable whether the use of metformin is justified given the relatively small reduction in BMI that is obtained.

On the other hand, in view of the broad spectrum of complications due to childhood obesity every small improvement in BMI could be helpful in reducing the risk of complications. Compared to invasive surgical options the complications of metformin are mild and mostly self-limiting and the burden of treatment is relatively low.

As a second scenario, metformin therapy can be initiated in all obese children, for instance in case lifestyle intervention during 1 year does not result in an improvement in BMI. Metformin would be offered to all children with obesity, with or without additional risk factors. It is unknown how motivation for lifestyle intervention is influenced by the availability of pharmacological interventions. In this scenario, all children with obesity have equal chances to benefit from the effect of metformin, against the burden of possible mild side-effects of metformin. Since most studies on the efficacy of metformin to achieve weight loss included patients with obesity and insulin resistance or other additional risk factors, the evidence use of metformin in children with obesity without any other risk factor is scarce [27-32, 88-90]. In the only study that did not require insulin resistance or other additional risk factors, mean baseline levels for HOMA-IR were 3.8±2.8 in the metformin group and 5.0±3.5 in the placebo group [86]. Based on these values the majority of the participants in this study can be thought to suffer from insulin resistance, and the results of this study cannot be interpreted as if the participants have obesity without any additional risk factor.

In the third scenario, metformin is prescribed to a select population of children with obesity and IR, hyperinsulinemia or other risk factors. These risk factors could be ethnicity, a family history of T2DM, or a family history of premature cardiovascular events. As described in the second scenario, most studies regarding the effect of metformin in obesity included children with obesity and IR or hyperinsulinemia. The before mentioned evidence on the (long term) use of metformin with respect to change in BMI is applicable to this population. For this group, the additional risk factors for the development of T2DM or other complications could justify the risk of gastro-intestinal side effects, vitamin B12 deficiency or ketoacidosis. Moreover, besides the effect on BMI, short-term studies on the use of metformin show an improvement in insulin resistance

as well [27, 28, 32, 42, 88]. This finding was however not confirmed in the 48-weeks study by Wilson et al. nor in our 18 months study [34, 86].

The question is whether metformin should also be given to children under the age of 10 years with obesity and IR, hyperinsulinemia or other risk factors. For these younger children the evidence is limited. Three studies included children < 10 years [27, 29, 32], but in 2 of them the mean age was comparable to studies including children aged 10 years and above. Only the study by Yanovski et al. included relatively young participants (6-12 years) with a mean age of 10.1 (±1.6) years for the metformin group and 10.4 (±1.4) years for the placebo group. Changes in BMI over 6 months were -0.78 (95%CI -1.54 - -0.01)kg/m^2 vs +0.32 (-0.54 – 1.18) and in BMI-SDS (-0.11 (-0.16 - -0.05) vs -0.04 (-0.1 – 0.02) for the metformin and placebo groups, respectively [32]. These results are comparable to other studies with 6 months follow up in older children. No studies with longer treatment duration in children under the age of ten years are available. Future research could focus on these younger children with obesity and IR, hyperinsulinemia or other risk factors.

Although metformin has beneficial effects there are some disadvantages, for example the above mentioned side-effects. Furthermore, data on the effects of prolonged use of metformin (>18 months) are not yet available, and it is therefore not clear whether treatment with metformin should stop after 18 months or be continued. In the second part of our RCT (chapter 6), follow up data of the participants are collected [33]. In the first 18-month part of our study, the effect seemed to fade out during the treatment (Figure 1). The results of the follow up study are therefore important to provide data on the effect of prolonged treatment with metformin (up to 36 months).

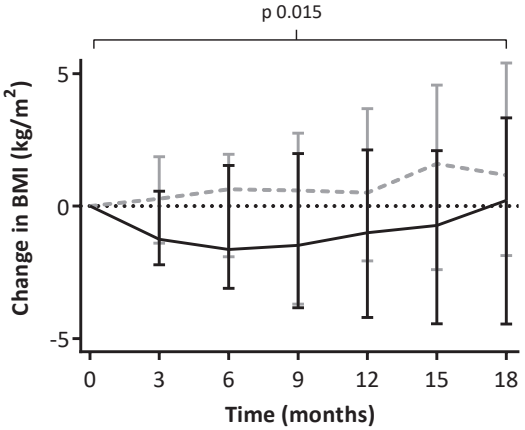

Figure 1. Effect of metformin on ΔBMI over 18 months

In conclusion, whether metformin should be applied in childhood obesity is open for discussion. Since metformin is safe with acceptable burden for the patients, we think it should be considered in pediatric patients with obesity and IR, hyperinsulinemia or other risk factors. It remains debatable whether metformin should be started when lifestyle intervention alone has failed or as a first step combined with lifestyle intervention. Another group of interest are children under the age of 10 years.

In this thesis, we aimed to study the epidemiology of IR, the screening and follow up of obese children at risk for T2DM, and the effect of metformin treatment in children with obesity and IR.

Prevalence rates for IR reported by population-based studies vary from 3.1 up to 44%. A comparison between these studies was not possible, since all studies used different definitions for IR. This difference in definitions was visualized by calculation of the prevalence rate of IR in an outpatient population of obese children using the reported definitions for IR. Depending on the definition, prevalence rates varied between 5.5 and 72.3% in this population. Therefore, a uniform definition for IR is essential to compare prevalence rates in populations. Moreover, since many factors influence the insulin concentration, specific cut-off levels for IR for age, pubertal stage, ethnicity and gender should be defined.

For screening on T2DM in obese children, a comparison was made between calculation of IR based on FPG and FPI with the use of HOMA-IR and on FPG alone. Screening with FPG and HOMA-IR was found to identify more children with IR and IGT, and with T2DM, compared to screening with FPG alone. In addition, as the recommended screening interval for children at risk of T2DM is 3 years, we performed a follow up study of children with obesity and IR. Even though during follow up their BMI-SDS increased, none of the children developed T2DM, leading to the conclusion that for now a screening interval of 3 years can be considered adequate.

Finally, long-term treatment of children with obesity and IR with metformin in addition to lifestyle intervention was studied in a RCT. In children treated with metformin for 18 months, BMI stabilized, whereas BMI increased in children receiving placebo. Based on these results, treatment with metformin in addition to lifestyle intervention in children with obesity and IR could be considered. This is underlined by comparing the results of metformin treatment on BMI in the RCT to the results in adolescent with obesity treated with metformin in daily clinical practice. These results were comparable to each other. In order to further optimize the effects of a combined treatment of metformin with life style intervention, and to obtain data on the optimal treatment duration, long term follow up of these children is needed. For long-term follow up, the results of the second part of our RCT have to be awaited.

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