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Title Page

The Metabolic Syndrome is frequent in Children and Adolescents with Type 1 Diabetes Compared to Healthy Controls

Running Title: Type 1 Diabetes and the Metabolic Syndrome

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Abstract

Context. There is a rise in overweight and obesity among children and adolescents with type 1 diabetes (T1D) in parallel with the rise in the metabolic syndrome (MetS) among children and adolescents.

Objective. The aim of the study was to describe the prevalence and characteristics of MetS in children and adolescents with T1D compared to their healthy counterparts.

Design and Setting. The study includes two Danish cohorts; (i) the Copenhagen cross sectional cohort 2016 of 277 children and adolescents with T1D that attend the pediatric outpatient clinic at a large hospital in greater Copenhagen and (ii) the CHAMPS-study DK which is a population-based cohort study of Danish children and adolescents (control cohort). Participants were categorized to have MetS if at least two of the following criteria were met: (i)systolic and/or diastolic blood pressure ≥ 90th percentile, (ii)waist circumference ≥ 90th percentile, and (iii)triglyceride ≥ 90th percentile and/or HDL ≤ 10th percentile.

Results. The prevalence of children with Mets in the T1D cohort was higher than in the control cohort (p=0.002). Moreover, participants with T1D had MetS at a lower level of BMI (p<0.001) and waist circumference (p<0.001) than participants with MetS from the control cohort (z-scores=0.90 and 1.51). Participants with MetS were younger than the other T1D participants (median 12.8 [9.9,14.8] vs median 14.6 [11.2,16.9] years, p=0.006).

Conclusions. Children and adolescents with T1D have an increased risk of MetS compared to healthy controls and clinicians and caretakers should consider early prevention and health promotion strategies.

Introduction

For the past 30-40 years there has been a global rise in overweight and obesity among children and adolescents, as well as a rise in the metabolic syndrome (MetS)[1,2]. The definition of the MetS has not been uniform and thus having an impact on the absolute prevalence numbers of the various study. As a result the MetS prevalence in children and adolescents has been estimated between 6 to 39% depending on the criteria used[3].

Most definitions include: Dyslipidemia, disturbed glucose metabolism, arterial hypertension and abdominal obesity[4]. Unfortunately, most definitions have limited potential in the pediatric population since they refer to children after the onset of puberty[4]. In a large cross national European study of a prepubertal cohort from Ahrens et.al. suggested a new definition based exclusively on percentiles of the risk factors allowing for age adjusted evaluation[5].

Frequency of overweight and obesity has also increased in children and adolescents with type 1 diabetes (T1D) challenging the traditional understanding that people living with T1D are characterized by a BMI below that of the general population[6]. The prevalence of overweight and obesity among people with T1D ranges between 13-50% depending on definition and country of origin[6–10]. Youths with T1D have now been found to have the same or higher prevalence of overweight and obesity as their healthy peers[11]. In adults with T1D the rise in obesity has shown to be at a faster rate than in the general population[12], increasing the risk of MetS, and in a large cross-sectional study of children and adolescents with T1D it was found that duration of T1D adjusted for age associated significantly with higher BMI-SDS[10]

In addition, MetS risk factors are frequent in people living with type 1 diabetes and associate with increased risk of chronic complications and mortality[6]. In a study of adolescents and young adults, it was found that female adolescents with type 1 diabetes had higher rates of overweight and MetS compared with healthy peers[13]. However, knowledge about MetS in prepubertal children with T1D is limited including the association with glycosylated hemoglobin A1c (HbA1c) and endogenous insulin production.

It is a challenge to compare the appearance of the MetS in children and adolescents with T1D to already existing pediatric cohorts, since disturbed glucose tolerance is an inherent circumstance in people living with T1D due to the lack of insulin production characterizing the disease. This means that the definition of MetS must be adjusted to fit this group. There seems to be agreement in the literature to consider the criteria of disturbed glucose tolerance to be fulfilled per se in participants with T1D[8,9,13]. The adjusted definition challenges the comparison with studies of the general population. To address this problem, we compare our T1D cohort to a community based cohort of healthy children and adolescents[14] applying the same definition of the MetS in both cohorts.

The most widely used definition for insulin sensitivity (IS) in people who do not have T1D is the homeostatic model assessment (HOMA)-insulin resistance (IR) model[15]. Unfortunately, it is not suitable for a person with T1D, since fasting insulin merely reflects the amount of exogenous insulin. Instead, we use a model developed in young adults to define insulin sensitivity (IS)[16].

Therefore, this study aims to describe the prevalence of MetS in children and adolescents with T1D and compare them with data from a large reference cohort of children from the general

population. In addition, we examined if MetS presents differently in children and adolescents with T1D cohort compared with children from the general population.

Methods

Participants

Participants with T1D are from the Danish CPH cross sectional cohort 2016 (T1D cohort) previously described in details[17]. In short, all children and adolescents with T1D >1 year attending the pediatric outpatient clinic at Herlev and Gentofte University Hospital between July 2016 and March 2018 were eligible for inclusion. All children and adolescents that attend the clinic have had their diagnosis confirmed by autoantibodies. 478 were invited, 51 did not meet inclusion criteria, 61 were transferred to adult clinics prior to inclusion and 94 declined participation, leaving 277 to be included. All children were testet for coeliac disease and thyroiditiswith autoantibodies. 16 individuals were diagnosed with thyroiditis and 2 with coeliac disease. This did not lead to exclusion from the cohort.

The control group in this study is derived from the CHAMPS-study DK (control cohort), which is a school-based study of ostensibly healthy Danish school children from the municipality of Svendborg, Denmark. Inclusion criteria are previously described, only criteria for participation was to attend a school in the area [14]. Since the original study included an intervention arm, only data from baseline visit (year=2008) prior to the intervention as well as all data from follow-up visits for the control group (year=2010 and 2015) is included in the present study. In the control group we

excluded a visit if the participant did not have full data on variables included in the definition of the MetS.

Clinical measurements and blood analyses

Information about duration of T1D was obtained from participants. Waist circumference was measured at the midpoint between the base of the rib case and the top of the hips. All participants from the T1D cohort were tested by the same investigator. In the control cohort, there were different investigators. All investigators received a two days standardized training program in the protocol in order to reduce inter- and intra-investigator variability. Blood pressure was measured by trained personal using a size-adjusted arm cuff. Insulin sensitivity in the T1D cohort was calculated with a surrogate marker: logeIS =4.64725-0.02032 *(waist circumference; cm)- 0.09779*(HbA1c; %) -0.00235*(triglycerids (TG); mg/dL). TG values are converted from mmol/L to mg/dL by dividing with 0.0113), developed by Dabelea et.al.[16]

All participants in the T1D cohort provided information on their weekly hours of exercise in a questionnaire. If the child was <12 years, a parent or guardian answered the questionnaire. Fasting c-peptide was used to determine endogenous insulin production. It was analyzed with Immulite® 2000, chemiluminescent immunometric assay. The reportable range was 33-6.620 pmol/L, hence results below the detection limit were reported as 0.

Measurements and analyses of BMI, current insulin and HbA1c in the T1D cohort is described in a previous publication[17]. Height was measured by trained personnel in both cohorts. In the control cohort with a stadiometer to the nearest cm, in the T1D cohort to the nearest mm. In both

cohorts, weight was measured in light clothes and without shoes on an electronic scale to the nearest 0.1 kg. The reference material for the BMI z-score comes from a large national reference material[18]. Glucose metabolic outcome was evaluated using HbA1c and presented in mmol/mol.

Pubertal stage was assessed by a physician in the T1D cohort and self-assessed in the control cohort according to the Tanner criteria[19,20]. Due to this we decided to distinguish only between prepubertal and pubertal participants, since self-assed Tanner criterium is most accurate in the distinguishing between prepubertal and pubertal[21].

Definition of the MetS

The cut-off values of the MetS are based on the criteria presented by Ahrens et.al.[5]. We used waist circumference (>90th percentile), blood pressure (≥90th percentile systolic or diastolic), triglycerides (>90th percentile and/or HDL ≤ 10th percentile). Disturbed glucose metabolism was not included in the criteria applied for neither groups. Waist circumference z-scores were obtained from a large Danish age-sex specific material[18], blood pressure z-scores were from a large American material[22]. The distribution in the control study was used to generate reference values for TGs and HDL. If participants had an abnormal height (>99th percentile for age) the blood pressure percentile could not be calculated according to the reference material[22], and was therefore not included. The same reference values were used in both cohorts.

For individuals with T1D, MetS is defined as meeting two or more of the criteria since disturbed glucose homeostasis is defined by the condition. We used the same definition to define MetS in the control cohort.

DXA scan

The T1D cohort had their body composition evaluated by a DXA scan (GE lunar iDXA, GE Healthcare Technologies, Madison, Wisconsin, US: software version 16). Scans were performed in the morning in light clothes, more details about scanning procedures for this cohort is published previously[17].

Total body fat percentage (fat%) was defined as weight of body fat/total weight measured by the DXA scanner. Regional body fat % was defined weight of body fat/total weight in area of interest.

Statistics

All statistical analyses were performed with Rstudio, R version 3.6.1[23]. Summary statistics are presented as median and the 25th to 75th percentile (Q1-Q3). Binary outcomes were compared with x^2-test. For small frequencies, Fisher's exact test was used. Continuous variables were compared with Student's t-test for symmetrically distributed data and Mann Whitney U test for non-symmetrically distributed data. Associations and cross-sectional data were evaluated with multiple linear regression models. To account for correlated observations in the longitudinal measurements in the control cohort, we used a cluster robust estimate of the standard errors. Reference values based on the control cohort were calculated by the LMS method[24] implemented as a generalized additive models using the gamlss R package[25].

For all analyses, a p-value < 0.05 was considered significant.

We repeated all analyses on a subgroup of the T1D cohort (T1D 5-15 years cohort). This cohort was selected to be within the age span of the control cohort. The purpose of this sub analysis was to investigate whether findings in the T1D full cohort and the control cohort could be confirmed in this group.

Results

Participant characteristics

The T1D full cohort consisted of 277 participants (median age 14.4 years, age range 3.4-20.2 years). The T1D 5-15 years cohort consisted of 149 participants (median age 11.9 years, age range 6.2-14.9 years).

The control study consisted of 1273 observations of 967 individuals. The median age was 9.23 years with the age range 5.4-15.0 years. Eighteen observations were excluded due to lack of complete data for the MetS defining variables (blood pressure, waist, TG and HDL).

The participants in the T1D full cohort were on average 4.4 years older than in the control cohort ($p<0.001$) and were more likely to be at pubertal stage 2 or above ($p<0.001$). There was no difference in the distribution of males and females ($p=0.090$). The participants in the T1D 5-15 years cohort were on average 2.2 years older than the control cohort ($p<0.001$). There was a higher proportion of boys in the T1D 5-15 years cohort compared to the control cohort ($p=0.004$) but no difference if their tanner pubertal stage were 1 or above tanner stage 1($p=0.500$).

The comparison between the T1D participants and the control cohort is presented for both the T1D full cohort and the T1D 5-15 years cohort in **table 1**.

The Metabolic syndrome in the T1D full Cohort

Thirty-six of the 277 (13.0%) participants in the T1D full cohort presented with MetS **(table 2**).

The participants from the T1D full cohort with MetS were on average younger than the participants without MetS from the same cohort (p=0.006). There was no significant difference in pubertal stage. Median age was 12.8 vs. 14.6 years. The participants with T1D and MetS had higher BMI z-score adjusted for puberty (p=0.004) (**figure 1**), a higher total % body fat evaluated by DXA scans and adjusted for puberty (p=0.036), but no significant difference in detectable c-peptide levels (p=0.857).

Individuals with T1D and MetS had higher HbA1c, adjusted for sex and age (p=0.003) compared to individuals with T1D without MetS. There was no difference in reported hours of exercise during the last week (p=0.598), in the summer (p=0.436), or in the winter (p=0.498).

The metabolic syndrome in the T1D 5-15 years cohort

In the T1D 5-15 years cohort, 25 (20.2%) of the 149 participants presented with MetS. They had similar age as those with T1D without MetS (p=0.604). They had higher BMI z-score (p<0.001) and higher total % body fat evaluated by DXA-scans (p=0.006), both adjusted for puberty. There was no difference in detectable c-peptide levels (p=0.913) to those without Mets. The difference in age and sex adjusted HbA1c (p=0.055) and simulated c-peptide was non-significant (p=0.055),

however borderline higher and the participants with MetS. There was no difference between reported hours of exercise during the last week (p=0.109), in the summer (p=0.062), or in the winter (p=0.217).

The metabolic syndrome in the control cohort compared to the T1D cohort

The MetS was present in 93 of 1273 (7.3%) observations in the control cohort from 84 different participants. It was significantly less than the 13.0% in the T1D full cohort (p=0.001).

The participants with MetS from the T1D full cohort had lower BMI z-score (p<0.001) (**figure 1**), lower waist z-score (p<0.001) (**figure 2)**, lower systolic blood pressure z-score (p<0.001), lower diastolic blood pressure z-score (p<0.001) compared to the participants with MetS from the control cohort. There was no significant difference in TG z-score (p=0.541) or HDL z-score (p=0.124). All comparisons were adjusted for tanner stage (prepubertal/pubertal).

In the T1D 5-15 years the prevalence of MetS was 20.2%. There was a significantly lower HDL-score (p=0.007)and higher TG-score z-score (p<0.001) between the participants with MetS from the T1D 5-15 years cohort and the control cohort. All other findings were similar to those found for the T1D full cohort. The analyses were adjusted for pubertal stage.

Table 3 shows the differences in selected variables between participants with MetS from the T1D full cohort, the T1D 5-15 years cohort, and the control cohort, respectively.

Discussion

The major findings of the present investigation are that: 1) An almost twice as high prevalence of MetS exists in participants from the T1D full cohort compared to participants from the control cohort; 2) Participants with MetS and T1D had a lower waist circumference- and BMI-z-score than the participants with MetS from the control cohort. 3) HbA1c was higher for T1D participants with MetS compared to T1D participants without MetS; 4) Moreover, these findings are similar when the T1D cohort is reduced to only include participants from 5-15 years. 5) In the T1D full cohort the participants with MetS were younger than the participants without MetS, in the T1D 5-15 years cohort there was no significant age difference between the two groups.

Apart from the higher prevalence of MetS in T1D as compared to the controls, an important observation of the present study is that the age of participants with T1D and MetS was lower than the age of participants with T1D without MetS. An explanation for the age difference between participants with and without MetS in the T1D group could be that the young children with T1D are more likely to have a phenotype often described as double diabetes. It describes a situation, where people with T1D also present with characteristics that are normally associated with type 2 diabetes, e.g. obesity, a family history of type 2 diabetes and signs of insulin resistance[26]. Obesity increases the risk of developing T1D[11], a meta-analysis found a significant association between high BMI prior to onset of T1D[27], and increased BMI has also been described to increase the risk of developing T1D at a younger age[28–30].

However, increased BMI and double diabetes is not the only explanations why these children and adolescents with T1D have developed MetS. In this study we show that the children with T1D have MetS at a lower waist circumference - and BMI z-score than the participants from the school-based study, but without any difference in the amount of prepubertal versus pubertal children. Taking MetS as a surrogate for IS, this is very well in line with a study from Nadeau et.al from 2010, which showed that adolescents with T1D had significant lower IS than healthy peers when using the euglyceamic hyperinsulinemic clamp[31]. Hence, the children and adolescents with T1D might be more vulnerable to weight gain since they already have impaired IS due to their condition, and this leads them to develop MetS at lower BMI and waist circumference compared to healthy children and adolescents

Another hypothesis of the higher prevalence of MetS in children and adolescents with T1D could be that it is the other way around, that T1D and T2D in childhood is the same disorder of insulin resistance set against different genetic backgrounds with obesity and overweight as the trigger of diabetes. This theory is known as the accelerator hypothesis, presented by Wilkin in 2001[32]. Thus, it could be that the MetS may accelerate the development of T1D. In our study we do not have data about the BMI z-score prior to diagnosis of T1D, hence any causal relationship cannot be established from this study.

MetS in people with T1D might be associated with increased risk of diabetes related complications[33] which makes the onset of MetS early in life particularly concerning. From an adult T1D study we know that the presence of the MetS is associated with an increased risk of both

micro- and macrovascular complications[34] Since cardiovascular disease remains the primary cause of death in people with T1D[35], it is important to gain a better understanding of the topic.

We also found higher HbA1c in the MetS group in the full T1D cohort compared to the group without MetS. We found the same tendency, however non-significant, in the 5-15 years cohort. Our findings confirm some previous studies of MetS in T1D[36,37], but other studies have not found the same association[8,9]. The explanation for this is not clear, but since reducing HbA1c is associated with a strong reduction in microvascular disease[38], the association is interesting and reinforces that an effort to reduce MetS in children and adolescents with T1D could reduce complications.

We observe significantly more children with MetS in the T1D population compared to healthy controls. In light of the rise in obesity and overweight in children and adolescents with T1D we suggest more awareness of these complication and an active intervention of clinicians together with caretakers to reduce the risk of MetS in children and adolescents with T1D. There is good evidence that diet intervention[33,39] alone or in particular in combination with exercise[40,41] can reduce the prevalence of MetS in children, and there is reason to assume that this also would be true for children with both MetS and T1D.

Strengths and limitations

To define the MetS we use age and sex adjusted percentiles which reduces a potential impact of the different age distributions in the two cohorts. Despite this, the age difference between the

T1D group and the control group is a limitation since the difference we see between the T1D full cohort and the control cohort could be partly explained by the difference in age. However, when we reduce the T1D cohort and only include participants within the age span of the control cohort, we find the same associations as in the full T1D cohort, and in addition an even higher prevalence of MetS in the T1D cohort. We also do not find a difference of in the distribution between prepubertal and pubertal children.

We do not know if there is a difference between the blood pressure monitors used in the two cohorts, and this could influence the prevalence of MetS cases in the cohorts. However, the consistent direction of unfavorable risk markers in the T1D cohort suggests this is not a measurement artefact.

It is a strength in the study that the control cohort has a BMI z-score and a waist circumference-score that are close to 0 (the median). Since these two z-scores are based on national reference material, this suggests that the control cohort in these parameters is similar to the general population, which makes it a suitable reference cohort for the T1D cohort.

The T1D full cohort has a median HbA1c of 60 mmol/mol. Even though it is higher than the recommended HbA1c at 53 mmol/mol[42], it is comparable to other T1D cohorts, i.e. a big cross national Nordic cohort of 11.025 children where the median HbA1c was 63 mmol/mol[43]. This supports that the participants in this study are representative for children and adolescents with T1D.

Conclusion and Perspectives

The prevalence of MetS syndrome was higher among participants with T1D than in the control cohort. Participants with T1D present with MetS at lower BMI- and waist-z-score than individuals with Mets in the control cohort. The findings suggest that clinicians should pay attention to the increased risk of MetS in this population and consider early prevention and health promotion with diet and physical activity. The relatively small sample size and wide age range should be taken into account as limitations to the study.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Bussler S, Penke M, Flemming G, et al. Novel Insights in the Metabolic Syndrome in Childhood and Adolescence. *HRP*. 2017;88(3-4):181-193. doi:10.1159/000479510

2. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. 2017;390(10113):2627-2642. doi:10.1016/S0140-6736(17)32129-3

3. Reinehr T, de Sousa G, Toschke AM, Andler W. Comparison of metabolic syndrome prevalence using eight different definitions: a critical approach. *Arch Dis Child*. 2007;92(12):1067-1072. doi:10.1136/adc.2006.104588

4. Weihe P, Weihrauch-Blüher S. Metabolic Syndrome in Children and Adolescents: Diagnostic Criteria, Therapeutic Options and Perspectives. *Curr Obes Rep*. 2019;8(4):472-479. doi:10.1007/s13679-019-00357-x

5. Ahrens W, Moreno LA, Mårild S, et al. Metabolic syndrome in young children: definitions and results of the IDEFICS study. *International Journal of Obesity*. 2014;38(2):S4-S14. doi:10.1038/ijo.2014.130

6. Chillarón JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism*. 2014;63(2):181-187. doi:10.1016/j.metabol.2013.10.002

7. Sevaliev N, Strich D, Avnon-Ziv C, Levy-Khademi F. The metabolic consequences of overweight in a cohort of children with type 1 diabetes. *J Pediatr Endocrinol Metab*. 2019;32(7):715-719. doi:10.1515/jpem-2018-0483

8. Yayıcı Köken Ö, Kara C, Can Yılmaz G, Aydın HM. Prevalence of Obesity and Metabolic Syndrome in Children with Type 1 Diabetes: A Comparative Assessment Based on Criteria Established by the International Diabetes Federation, World Health Organisation and National Cholesterol Education Program. *J Clin Res Pediatr Endocrinol*. 2020;12(1):55-62. doi:10.4274/jcrpe.galenos.2019.2019.0048

9. Soliman HM, Mosaad YO, Ibrahim A. The prevalence and the clinical profile of metabolic syndrome in children and adolescents with Type 1 diabetes. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019;13(3):1723-1726. doi:10.1016/j.dsx.2019.03.036

10. Maffeis C, Birkebaek NH, Konstantinova M, et al. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: Data from the international SWEET registry. *Pediatric Diabetes*. 2018;19(7):1211-1220. doi:10.1111/pedi.12730

11. Polsky S, Ellis SL. Obesity, insulin resistance, and type 1 diabetes mellitus. *Current Opinion in Endocrinology, Diabetes and Obesity*. 2015;22(4):277-282. doi:10.1097/MED.0000000000000170

12. Mottalib A, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, Hamdy O. Weight Management in Patients with Type 1 Diabetes and Obesity. *Curr Diab Rep*. 2017;17(10):92. doi:10.1007/s11892-017-0918-8

13. Pinhas-Hamiel O, Levek-Motola N, Kaidar K, et al. Prevalence of overweight, obesity and metabolic syndrome components in children, adolescents and young adults with type 1 diabetes mellitus. *Diabetes/Metabolism Research and Reviews*. 2015;31(1):76-84. doi:https://doi.org/10.1002/dmrr.2565

14. Wedderkopp N, Jespersen E, Franz C, et al. Study protocol. The Childhood Health, Activity, and Motor Performance School Study Denmark (The CHAMPS-study DK). *BMC Pediatr*. 2012;12(1):1-8. doi:10.1186/1471-2431-12-128

15. Wallace TM, Levy JC, Matthews DR. Use and Abuse of HOMA Modeling. *Diabetes Care*. 2004;27(6):1487-1495. doi:10.2337/diacare.27.6.1487

16. Dabelea D, D'Agostino RB, Mason CC, et al. Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for Diabetes in Youth study. *Diabetologia*. 2011;54(1):78-86. doi:10.1007/s00125-010-1911-9

17. Madsen JOB, Herskin CW, Zerahn B, et al. Unaffected bone mineral density in Danish children and adolescents with type 1 diabetes. *J Bone Miner Metab*. 2020;38(3):328-337. doi:10.1007/s00774-019-01058-0

18. Wohlfahrt-Veje C, Tinggaard J, Winther K, et al. Body fat throughout childhood in 2647 healthy Danish children: agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. *European Journal of Clinical Nutrition*. 2014;68(6):664-670. doi:10.1038/ejcn.2013.282

19. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44(235):291-303. doi:10.1136/adc.44.235.291

20. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45(239):13-23. doi:10.1136/adc.45.239.13

21. Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, et al. Validity of Self-Assessment of Pubertal Maturation. *Pediatrics*. 2015;135(1):86-93. doi:10.1542/peds.2014-0793

22. *Shypailo RJ (2018) Age-Based Pediatric Blood Pressure Reference Charts. Retrieved 8/26/2021 from the Baylor College of Medicine, Children's Nutrition Research Center, Body Composition Laboratory Web Site: Http://Www.Bcm.Edu/Bodycomplab/BPappZjs/BPvAgeAPPz.Htm*.

23. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL Https://Www.R-Project.Org/*.

24. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med*. 1992;11(10):1305-1319. doi:10.1002/sim.4780111005

25. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. 2005;54(3):507-554. doi:10.1111/j.1467-9876.2005.00510.x

26. Pozzilli P, Guglielmi C, Pronina E, Petraikina E. Double or hybrid diabetes associated with an increase in type 1 and type 2 diabetes in children and youths. *Pediatric Diabetes*. 2007;8(s9):88-95. doi:10.1111/j.1399-5448.2007.00338.x

27. Verbeeten KC, Elks CE, Daneman D, Ong KK. Association between childhood obesity and subsequent Type 1 diabetes: a systematic review and meta-analysis. *Diabetic Medicine*. 2011;28(1):10-18. doi:10.1111/j.1464-5491.2010.03160.x

28. Dabelea D, D'Agostino RB, Mayer-Davis EJ, et al. Testing the Accelerator Hypothesis: Body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes. *Diabetes Care*. 2006;29(2):290-294. doi:10.2337/diacare.29.02.06.dc05-1339

29. Kibirige M, Metcalf B, Renuka R, Wilkin TJ. Testing the Accelerator Hypothesis: The relationship between body mass and age at diagnosis of type 1 diabetes. *Diabetes Care*. 2003;26(10):2865-2870. doi:10.2337/diacare.26.10.2865

30. Knerr I, Wolf J, Reinehr T, et al. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. *Diabetologia*. 2005;48(12):2501-2504. doi:10.1007/s00125-005-0033-2

31. Nadeau KJ, Regensteiner JG, Bauer TA, et al. Insulin Resistance in Adolescents with Type 1 Diabetes and Its Relationship to Cardiovascular Function. *J Clin Endocrinol Metab*. 2010;95(2):513-521. doi:10.1210/jc.2009-1756

32. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia*. 2001;44(7):914-922. doi:10.1007/s001250100548

33. Grabia M, Markiewicz-Żukowska R, Socha K. Prevalence of Metabolic Syndrome in Children and Adolescents with Type 1 Diabetes Mellitus and Possibilities of Prevention and Treatment: A Systematic Review. *Nutrients*. 2021;13(6):1782. doi:10.3390/nu13061782

34. Gingras V, Leroux C, Fortin A, Legault L, Rabasa-Lhoret R. Predictors of cardiovascular risk among patients with type 1 diabetes: A critical analysis of the metabolic syndrome and its components. *Diabetes & Metabolism*. 2017;43(3):217-222. doi:10.1016/j.diabet.2016.10.007

35. Haas AV, McDonnell ME. Pathogenesis of Cardiovascular Disease in Diabetes. *Endocrinol Metab Clin North Am*. 2018;47(1):51-63. doi:10.1016/j.ecl.2017.10.010

36. Valerio G, Iafusco D, Zucchini S, Maffeis C. Abdominal adiposity and cardiovascular risk factors in adolescents with type 1 diabetes. *Diabetes Research and Clinical Practice*. 2012;97(1):99-104. doi:10.1016/j.diabres.2012.01.022

37. Saki F. Prevalence of Metabolic Syndrome in Children With Type 1 Diabetes in South of Iran. *J Compr Ped*. 2016;7(3). doi:10.17795/compreped-37703

38. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391(10138):2449-2462. doi:10.1016/S0140-6736(18)31320-5

39. DeBoer MD. Assessing and Managing the Metabolic Syndrome in Children and Adolescents. *Nutrients*. 2019;11(8):1788. doi:10.3390/nu11081788

40. Caranti DA, de Mello MT, Prado WL, et al. Short- and long-term beneficial effects of a multidisciplinary therapy for the control of metabolic syndrome in obese adolescents. *Metabolism*. 2007;56(9):1293-1300. doi:10.1016/j.metabol.2007.05.004

41. Albert Pérez E, Mateu Olivares V, Martínez-Espinosa RM, Molina Vila MD, Reig García-Galbis M. New Insights about How to Make an Intervention in Children and Adolescents with Metabolic Syndrome: Diet, Exercise vs. Changes in Body Composition. A Systematic Review of RCT. *Nutrients*. 2018;10(7):878. doi:10.3390/nu10070878

42. DiMeglio LA, Acerini CL, Codner E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes*. 2018;19:105-114. doi:10.1111/pedi.12737

43. Birkebaek N, Kahlert J, Bjarnason R, et al. Body mass index standard deviation score and obesity in children with type 1 diabetes in the Nordic countries. HbA1c and other predictors of increasing BMISDS. *Pediatric Diabetes*. 2018;19(7):1198-1205. doi:10.1111/pedi.12693

Figure 1. Boxplot of BMI z-score compared between participants with and without type 1 diabetes and the metabolic syndrome

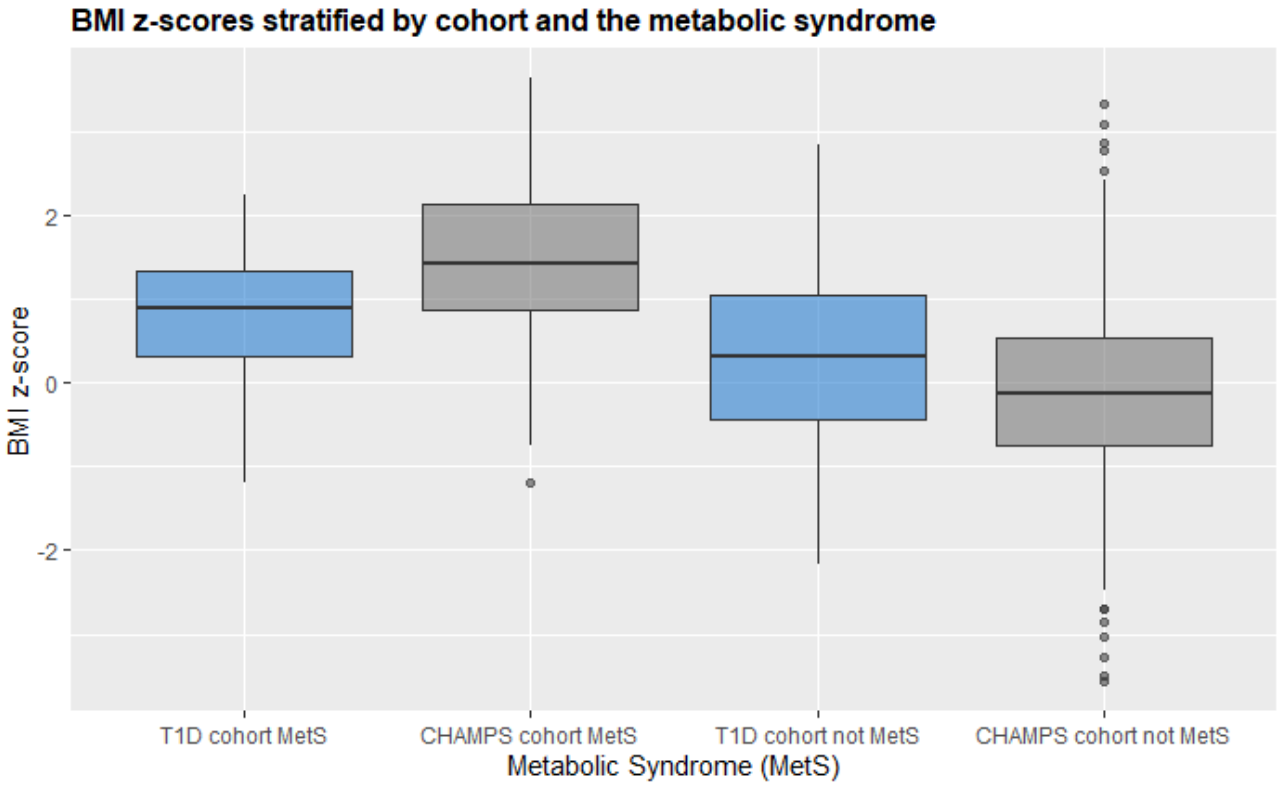

Figure shows the significant differences between body mass index (BMI) z-score in participants with the metabolic syndrome (MetS) from the type 1 diabetes full cohort (T1D) and the control cohort ($p<0.001$), between T1D full with and without the MetS ($p<0.001$) as well as the control cohort with and without the ($p<0.001$)

Figure 2. Boxplot of waist z-score compared between participants with and without type 1 diabetes and the metabolic syndrome

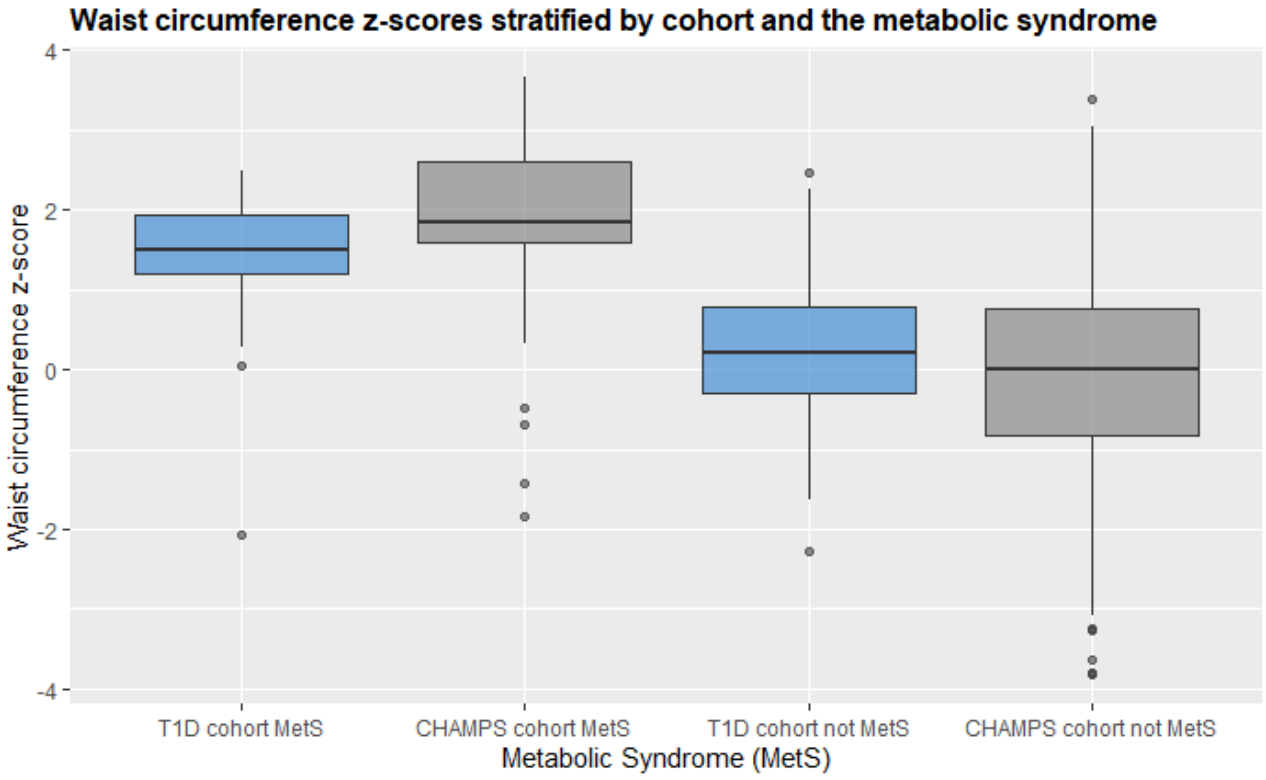

Figure shows the significant differences between waist circumference z-score in participants with the metabolic syndrome (MetS) from the type 1 diabetes full cohort (T1D) and the control cohort ($p<0.001$), between T1D full with and without the MetS ($p<0.001$) as well as the control cohort with and without the ($p<0.001$)

Table 1. Basic Characteristics of the type 1 diabetes cohort full and with the age span 5-15 years compared to the control cohort

	T1D full cohort	T1D 5-15y cohort	Control cohort	p-values#	p-values^
Number of participants	277	149	1273	---	-
Age (years)	14.4 [10.9, 16.6]	11.8 [9.8, 13.3]	9.2 [7.9, 10.4]	**p<0.001**	**p<0.001**
Pubertal stage (1/2+)	79/186	70/67	364/395	p=0.500	**P<0.001**
Sex = male (%)	145 (52%)	88 (59)	595 (46.7)	p=0.090	**p=0.004**
Hba1c (mmol/mol)	60 [53, 71]	58 [52, 65]	---	---	-
Duration of type 1 diabetes (years)	4.0 [2.0, 6.9]	2.5 [1.7, 5.3]	---	---	-
BMI z-score	0.39 [-0.39, 1.15]	0.20 [-0.42, 0.83]	-0.01 [-0.69, 0.72]	**p<0.001***	**p=0.009***
Waist circumference z-score	0.37 [-0.20, 1.16]	0.37 [-0.19, 1.15]	0.11 [-0.77, 0.94]	**p<0.001***	**p<0.001***
Systolic blood pressure z-score	0.64 [-0.10, 1.28]	0.71 [-0.05, 1.34]	0.23 [-0.33, 0.74]	**p<0.001***	**p<0.001***
Diastolic blood pressure z-score	0.64 [0.15, 1.17]	0.58 [0.20, 1.08]	-0.13 [-0.55, 0.31]	**p<0.001***	**p<0.001***
HDL z-score	-0.06 [-0.59, 0.62]	-0.25 [-0.83, 0.38]	-0.03 [1.40, 0.69]	p=0.464*	**p<0.001***
TG z-score	0.38 [-0.30, 0.93]	0.26 [-0.36, 0.87]	0.00 [-0.66, 0.66]	**p<0.001***	**p<0.001***
Insulin sensitivity score'	2.28 [2.04, 2.49]	2.45 [2.26, 2.57]	---	---	-

Data presented as median values and interquartile range [IQR]

p-values in table 1 are adjusted for clustered data measurements in the control cohort using a cluster robust standard error estimate.

T1D full cohort = All participants in the type 1 diabetes cohort

T1D 5-15y cohort = All participants from the type 1 diabetes cohort within the age span of the control cohort (age 5-15 years)

Pubertal stage = Tanner pubertal stage [19,20]

HbA1c = glycosylated hemoglobin type A1c

BMI = body mass index

HDL = high density lipoprotein

TG = triglycerids

'Insulin sensitivity score in T1D cohort calculated with surrogate marker as described in the methods section

*= The analysis was adjusted for pubertal stage (tanner 1 or 2 and above)

#T1D cohort compared to controls

^ T1D 5-15 years cohort compared to controls

Table 2. Participants from the type 1 diabetes full cohort with and without the metabolic syndrome

	T1D Mets n=36	T1D not MetS n=241
Age*	12.8 [9.9-14.8]	14.6 [11.2-16.9] (**p=0.006)**
Sex = male (%)^	19 (53%)	126 (52%) p=1.0
Pubertal stage (1/2+)	15/19	64/127 p=0.232
HbA1c (mmol/mol)	64 [52, 75]	59 [53, 70] **p=0.003**
Total body fat %	31.5 [14.5, 36.3]	26.5 [20.9, 32.8] **p=0.036***
Android fat %	23.7 [14.6, 36.6]	19.8 [13.0, 28.9] **p=0.031***
Gynoid fat %	35.7 [29.6, 41.5]	31.5 [23.8, 38.4] **p=0.049***
Body mass index z-score	0.90 [0.32, 1.35]	0.31 [-0.44, 1.05] **p<0.004***
Waist circumeference z-score	1.51 [1.19, 1.92]	0.21 [-0.29, 0.78] **p<0.001***
HDL z-score	-0.43 [-1.39, 0.29]	0.02 [-0.53, 0.73] **p<0.001***
TG z-score	1.55 [0.82, 1.96]	0.25 [-0.43, 0.79] **p<0.001**
Systolic blood pressure z-score	1.13 [0.69, 1.56]	0.52 [-0.28, 1.23] **p<0.001***
Diastolic blood pressure z-score	1.31 [0.89, 1.58]	0.55 [0.10,1.04] **p<0.001***
Duration of T1D (years)	2.67 [1.62, 7.16]	4.04 [2.12 – 6.90] P=0.370
Insulin sensitivity score[#]	2.15 [1.78, 2.37]	2.31 [2.06, 2.51] **p<0.001**
C-peptid above detectable limit	18 (50%)	104 (43%) (p=0.857)

The table compares participants with and without the metabolic syndrome (MetS) in the type 1 diabetes (T1D) full cohort.

Pubertal stage = Tanner pubertal stage [19,20]

HDL = high density lipoprotein

TG = triglycerids

^=not adjusted for age and sex.

* The analysis was adjusted for pubertal stage (tanner 1 or 2 and above)

#Insulin sensitivity in T1D cohort calculated with surrogate marker as described in the methods section

Table 3. Participants with the metabolic syndrome from the type 1 diabetes full cohort, the type 1 diabetes 5-15 years cohort and the control cohort

	T1D full Mets n=36	T1D 5-15y Mets n=25	Control cohort MetS n= 93	p-values[#]	p-values[^]
Age	12.8 [9.9,14.8]	10.94 [9.76,12.99]	9.6 [8.1-10.7]	**p<0.001**	**p<0.001**
Pubertal stage (1/2+)	15/19	13/10	22/34	p=0.652	p=0.161
Males	19 (53%)	15 (60%)	36 (39%)	P=0.147*	p=0.056
BMI z-score	0.90 [0.32, 1.35]	0.87 [0.33, 1.49]	1.43 [0.87, 2.13]	**p<0.001***	**p=0.009***
Waist z-score	1.51 [1.19,1.92]	1.50 [1.81, 1.83]	2.02 [1.68, 2.73]	**p<0.001***	**p<0.001***
HDL z-score	-0.43 [-1.39, 0.29]	-0.75 [-1.47, -0.07]	-1.33 [-1.62, -0.55]	p=0.124*	**p=0.007***
TG z-score	1.55 [0.82, 1.96]	1.43 [0.52, 1.92]	1.38 [0.68, 1.76]	p=0.541*	**p<0.001***
Systolic blood pressure z-score	1.13 [0.69, 1.56]	1.34 [0.36, 1.56]	0.25 [-0.27, 0.84]	**p<0.001***	**p<0.001***
Diastolic blood pressure z-score	1.31[0.89, 1.58]	1.04 [0.47, 1.34]	0.10 [-0.69, 0.10]	**p<0.001***	**p<0.001***

The table compares variables between the type 1 diabetes full (T1D full) cohort and the control cohort as well as the type 1 diabetes cohort within the age span of the control cohort (T1D 5-15y). To account for correlated observations in the CONTROL cohort, we fitted a linear regression model with cluster robust standard errors to account for clustering of individuals.

*= The analysis was adjusted for pubertal stage (tanner 1 or 2 and above)

Pubertal stage = Tanner pubertal stage [19,20]

HDL = high density lipoprotein

TG = triglycerids

#T1D full cohort compared to the control cohort

^ T1D 5-15 years cohort compared to the control cohort