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Research article

Increased incidence of type 1 diabetes in children and no change in the age of diagnosis and BMI-SDS at the onset - is the *accelerator hypothesis* not working?

Short title: Age, BMI and Type 1 Diabetes in Children

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What is already known on this topic?

The association between increase of BMI-SDS and younger age of type 1 diabetes manifestation has been postulated by some authors.

What this study adds?

The increase of type 1 incidence in paediatric population is not associated with younger age of diagnosis and higher BMI-SDS.

Abstract

Background: One of the speculated reasons for the observed increase of type 1 diabetes incidence in children is weight gain causing accelerated disease development in predisposed individuals. This so-called *accelerator hypothesis* is, however, controversial. **The aim of the study** was to analyze whether in the ethnically homogeneous population of Lesser Poland an increase in the number of cases of diabetes among children was associated with younger age and higher BMI-SDS at the moment of diagnosis.

Subjects and Methods: Retrospective data analysis from medical records of all patients under the age of 14 (n=559; 50.6% male), with newly diagnosed type 1 diabetes in Lesser Poland between 1st of January 2006 and 31st of December 2017 (11 years).

Results: The incidence ratio ranged significantly ($P < 0.001$) from the lowest in 2006 (11.2/100,000/year) to the highest in 2012 (21.9/100,000/year). The mean age of diagnosis was 8.2 ± 3.5 years; there was no trend of decreasing age ($P = 0.43$). The mean body mass index expressed as the standard deviation score was -0.4 ± 1.2 . Almost all children (99%) at the time of diagnosis presented BMI-SDS within the normal range, with only 2.7% cases of obesity at the moment of diagnosis.

Conclusion: The results of the present study do not confirm that increase of type 1 incidence in paediatric population is associated with younger age of diagnosis and higher BMI-SDS. Therefore are insufficient to prove the *accelerator hypothesis*.

Keywords: Accelerator hypothesis, body mass index, children, type 1 diabetes

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Introduction

Type 1 diabetes is one of the most common chronic diseases in children and adolescents worldwide [1]. Its increasing incidence, especially in industrially developed countries, makes it necessary to look for and define potential risk factors. Some recent studies point to a possible contribution of childhood overweight and obesity to the development of type 1 diabetes in younger age. Obesity is a well-documented risk factor for type 2 diabetes, but there are some studies indicating an association between the increase of body weight in children and adolescents and the increase of the incidence rate of type 1 diabetes in these age groups [2-3]. That postulated association has been called the *accelerator hypothesis* [3-5]. One of the arguments for the existence of such a relationship is the fact that in countries where the incidence of type 1 diabetes is increasing in the younger age groups, a simultaneous increase in the incidence of obesity in the general pediatric population

was found. The number of obese children and adolescents worldwide has increased tenfold in the last 40 years, and childhood obesity defined as the 95th percentile of body mass index (BMI), has been recognized as an epidemic by the World Health Organization [6-7]. The *accelerator hypothesis* identifies three processes which may accelerate the apoptosis of the beta cells: constitution, insulin resistance and autoimmunity. According to that hypothesis, weight gain causing an increase in insulin resistance leads to a deterioration of blood glucose level control. The rising blood glucose level accelerates beta-cell apoptosis directly via glucotoxicity, and indirectly by inducing immunogenicity [3-8]. The authors of the *accelerator hypothesis* postulate that the pathogenesis of type 1 and type 2 diabetes may be to some extent similar, and that overweight and insulin insufficiency are associated with both types of diabetes [4,5]. According to the hypothesis, excessive body weight in a child who is predisposed genetically to the development of type 1 diabetes accelerates the process of beta cells destruction leading to an earlier occurrence of an overt deficit of insulin [3,6,8]. This theory has been confirmed by some studies strongly supporting the association between BMI and earlier diagnosis of type 1 diabetes [6,9,10,11]. Nevertheless, it is not universally accepted, as there is an ample scientific evidence, which does not support such a relationship [12,13,14,15]. The starting point for the current study was a significant increase in the incidence of type 1 diabetes in the young age groups in the Lesser Poland region (from 5.2/100,000/year in 1987 to 21.9/100,000/year in 2012), which was demonstrated in our previous paper [16]. Simultaneously, some studies pointed to an increase of obesity incidence in the general paediatric population in the same time period and in the same geographic area [17].

Objective

The aim of the study was to analyze whether in the ethnically homogeneous population of Lesser Poland an increase in the number of cases of diabetes among children was associated with younger age and higher BMI-SDS at the moment of diagnosis.

Material and Methods

Retrospective data analysis from medical records of all patients under the age of 14 (n=559; 50.6 percent male), with newly diagnosed type 1 diabetes in Krakow region (former *województwo krakowskie*) between 1st of January 2006 and 31st of December 2012 and in whole Lesser Poland between 1st of January 2013 and 31st of December 2017. The analysis included children with type 1 diabetes only; patients with other types of diabetes were excluded. Type 1 diabetes was defined as acute-onset diabetes presenting with ketoacidosis and/or symptoms of polyuria, polydipsia and weight loss, complete insulin dependence within < 1 year from diagnosis, or positive anti-GAD or anti-IA2 test on diabetes diagnosis. All data were collected in one reference centre for the region – the Department of Pediatric and Adolescents Endocrinology, Chair of Pediatrics, Jagiellonian University Medical College, which is the reference centre for the region.

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a stadiometer (Harpender, UK) and a balanced scale (Seca, Germany). All measurements were done during the hospitalization at the moment of diabetes diagnosis, after the normalization of the general condition and rehydration. As the standard of reference for calculating BMI-SDS, normal values from the local population were used [18]. Incidence rate was evaluated based on the data from the Central Statistical Office (Polish: *Główny Urząd Statystyczny, GUS*) for the population of the region which was subject to analysis [19].

Statistical Analysis

Statistics data are presented as means with standard deviations or medians and quartiles for continuous variables, or counts and percentages for categorical variables. Univariate and multiple regression models were used to test the association between BMI, age of diagnosis and calendar year of diagnosis. P-values < 0.05 were considered significant.

Ethics

The study was conducted in accordance with the requirements of ethics, with particular regard to the protection of sensitive data. No additional consent from the bioethics committee was required due to the retrospective nature of the studies. Parents (legal guardians) and study participants gave informed consent.

Results

There were 559 cases of type 1 diabetes diagnosed before age 14. The incidence ratio ranged significantly ($P < 0.001$) from the lowest in 2006 (11.2/100,000/year) to the highest in 2012 (21.9/100,000/year) (Figure 1). The median age of diagnosis was 8.4 years (1st and 3rd quartile 5.4 and 11.1 years), mean 8.2 ± 3.5 years. The mean BMI expressed as the standard deviation score (SDS) was -0.4 ± 1.2 , indicating type 1 diabetes onset in individuals somewhat leaner than the reference population. This reflects the weight loss characterizing the onset of diabetes. During the observation period, there was no trend of decreasing age at the moment of diagnosis (Figure 2, $P = 0.43$). Almost all children (99%) at the time of diagnosis presented BMI-SDS within the normal range, with only 15 [2.7%] cases of obesity at the moment of diagnosis (Table 1). There was no association between calendar year of diabetes diagnosis and BMI-SDS ($P = 0.87$, see Figure 3). A significant relationship was observed between the age of diabetes diagnosis and BMI-SDS. An increase in BMI-SDS by 1 unit was associated with the development of the disease 0.54 years later (Figure 4) and this association remained unchanged after adjusting for sex and calendar year of diabetes diagnosis ($P < 0.001$). This association had the opposite direction that expected from the *accelerator hypothesis*.

Discussion

The incidence of type 1 diabetes, as well as overweight and obesity in children are increasing in Poland [13,17]. The present study is an attempt to determine whether these phenomena are interrelated or only co-exist in the same time and place. This continuous and longitudinal study is the first such study conducted in our country. According to the current definitions, type 1 diabetes mellitus is an autoimmune chronic disease in children and adolescents determined by insulin insufficiency, while type 2 diabetes mellitus is a metabolic disorder in adults and elderly population associated with obesity and insulin resistance [13]. The *accelerator hypothesis* attempts to unify both types of diabetes as the same insulin secretion disorder, but with a different background [3, 6, 8]. The rate of beta cell damage and insulin loss in type 1 diabetes seems to be associated with

more susceptible genotypes and the influence of undefined environmental factors. To date there are more than 60 genomic loci identified, but HLA 6p21 has the strongest association with type 1 diabetes development, and islet autoimmunity develops in about 5% people with that genetic predisposition [19,20]. Contrary to the well-defined genetic background, most of the environmental factors contributing to betacell loss remain unidentified [21]. One of the investigated problems is the possible impact of overweight on the acceleration of insulin insufficiency. Over the past years, many trials have been conducted to prove this theory. Studies conducted in different ethnic settings worldwide reported conflicting results (inverse, positive or lack of correlation between body weight and the development of type 1 diabetes). A Norwegian cohort study pointed to an increased risk of autoimmunity in individuals with high-risk genotype with a weight gain of over 15 kg within the first year of life and/or maternal BMI during pregnancy over 30 kg/m² [19]. Even stronger evidence supporting the *accelerator hypothesis* was provided by the Southeastern Wisconsin study that revealed a significant inverse correlation between BMI and age of diagnosis [9]. In a European study, Knerr et al. also proved that elevated BMI has an impact on younger age of diabetes onset [10]. Slightly more cautious conclusions were drawn from the study by Dabelea et al., that indicated an inverse correlation only in children with an already reduced beta cell function (fasting C-peptide level below the median) [11]. In our study, we did not confirm an association between BMI-SDS and age at the moment of diagnosis. In fact, in younger children we observed a small association in an opposite direction. Similar observations were also made by authors investigating this phenomenon in various parts of the world. Over 20 years of observation of Australian children under 16 years of age with type 1 diabetes, Islam et al. noticed that the number of overweight and obese children has remained on a similar level, despite an increase in the incidence rate of type 1 diabetes [13]. Moreover, Derraik et al. showed that the mean BMI-SDS of newly diagnosed type 1 diabetes over the period 1990-2009 in New Zealand did not alter in comparison to the general population [12]. Also in our group the incidence of obesity at the moment of type 1 diabetes diagnosis was comparable to the general population living in the same geographic area [17]. The prevalence of overweight and obesity is not regularly screened among Polish children. There is no national registry, therefore the precise, reliable data is not available. Nevertheless, in recent years several publications have been published on the prevalence of overweight and obesity in children and adolescents living in different regions of Poland. However, mainly due to differences in research methodology, their results are quite divergent. For example, in Gdańsk (North of Poland) obesity was found in 1.5-7.5 subjects, depending on sex and age at the time of the study [22]. In a study conducted among seven-year-olds in a city of Wrocław (Lower Silesia, South-Western Poland), obesity was found in as many as 10.7%-26.6% of children, depending on the place of living [23]. In a In South-Eastern in 2012, the prevalence of obesity in preschool children was 10.8%. [24] In the region covered by our study, the prevalence of obesity in adolescents (14-18 y.o.) is 4.2% [17]. To some extent the prevalence of excess weight may be obscured by the fact that anthropometric measurement were taken at diabetes diagnosis. The effect of dehydration may be ruled out, but some degree of loss of body mass has persisted at that time. That is an undoubted limitation of this study, as well as other similar papers. All the weight measurement took place after the diagnosis of the disease on the basis of clinical symptoms. Although the body weight values analyzed came from measurements made after rehydration, resolution of acidosis and improvement of general condition, they cannot take into account the full weight loss associated with lypolysis of adipose tissue before the onset of diabetes. In fact, such an analysis is not possible, because in the first phase type 1 diabetes occurs without clinically overt symptoms and it is not possible to accurately determine its onset, and thus accurate determination of BMI-SDS at the time of actual onset of the disease is also not possible. We were unable to use body weight from before diabetes onset, as regular and standardized measurement were never taken on regular basis in healthy children. Since weight loss would affect all study subjects, we do not expect that this issue has altered the relationships between age of diabetes diagnosis and BMI-SDS. Recently published data from over 360,000 British children and young adults (< 25 y.o.) observed during 1994-2013 did not show any significant correlation between BMI and type 1 diabetes incidence. Interestingly, the authors pointed to a slightly higher incidence rate in overweight, but not in obese children [14]. Attempts to include additional ethnic factors showed that the *accelerator hypothesis* is not universal [15]. Interestingly, we found that BMI-SDS was significantly higher in the older age groups. An increase in BMI-SDS by 1 unit was associated with the development of the disease 0.54 years later. This novel observation seems to be particularly important if we take into consideration the possible impact of puberty on insulin secretion. The relationship between obesity, puberty and type 2 diabetes incidence is clear and well documented [25]. During puberty, growth hormone and cortisol secretion increases, causing physiological insulin resistance [2]. Therefore type 2 diabetes almost never occurs in children before puberty. Our results point to a potential contribution of increased body weight during puberty on the age of type 1 diabetes manifestation. Perhaps, the *accelerator hypothesis* may therefore partly explain the incidence of type 1 diabetes in the period of puberty. This is very difficult to be proven and needs further investigation.

Limitation of the study

The main limitation of our study is the inclusion of a relatively small group of participants. However, taking into consideration that we analyzed all new cases of type 1 diabetes under the age of 14 in the homogeneous Lesser Poland population, the results can be considered valuable. To obtain more reliable data, it would be advisable to perform a similar analysis for the whole country, and even Europe.

Conclusion

The results of the present study do not confirm that increase of type 1 incidence in paediatric population is associated with younger age of diagnosis and higher BMI-SDS. Therefore are insufficient to prove the *accelerator hypothesis*.

Authorship Contributions

Concept: Barbara Wasyl-Nawrot, Małgorzata Wójcik

Design: Barbara Wasyl-Nawrot, Małgorzata Wójcik

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Analysis or Interpretation: Jan Skupień, Małgorzata Wójcik,

Literature Search: Barbara Wasyl-Nawrot, Małgorzata Wójcik

Writing: Barbara Wasyl-Nawrot, Małgorzata Wójcik, Jan Skupień, Joanna Nazim, Jerzy B. Starzyk

Conflict of Interest: No conflict of interest

Financial Disclosure: No financial disclosure

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Table 1. The occurrence of obesity (BMI- SDS > 2.0 SDS) a in patients with newly diagnosed type 1 diabetes in the subsequent years of observation

Year	Number of patients with obesity (BMI-SDS >2.0) [number of all newly diagnosed type 1 diabetes cases]
2006	0 [21]
2007	1 [20]
2008	2 [21]
2009	0 [22]
2010	0 [23]
2011	0 [27]
2012	0 [22]
2013	5 [97]
2014	1 [75]
2015	2 [92]
2016	1 [61]
2017	4 [78]

Figure 1. Incidence rates (per 100,000) for type 1 diabetes in Krakow and Lesser Poland region

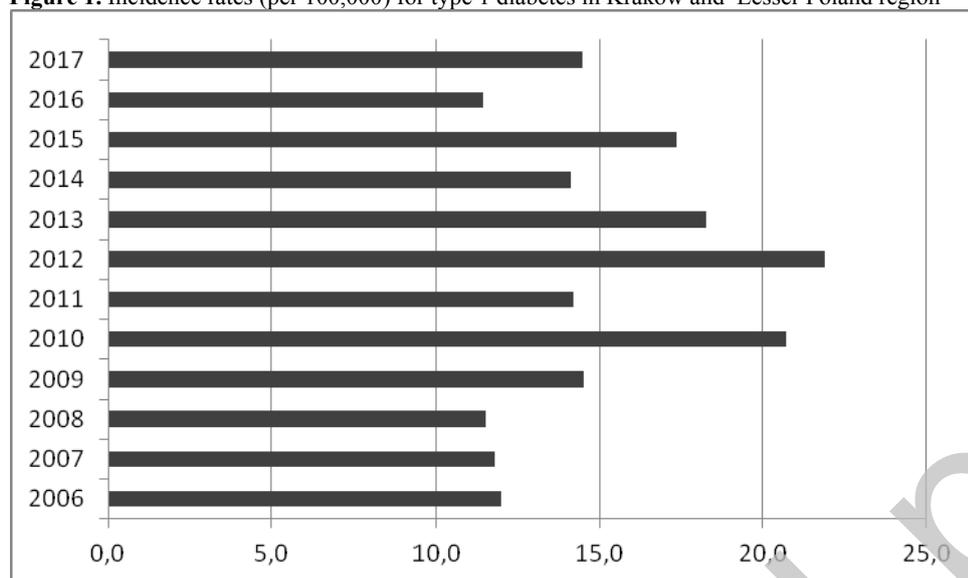


Figure 2. Mean age at the moment of type 1 diabetes diagnosis in subsequent analyzed calendar years. The upper and lower box boundaries indicate quartiles and the line across the centre of the graph joins the medians. The whiskers indicate the range of age in each year

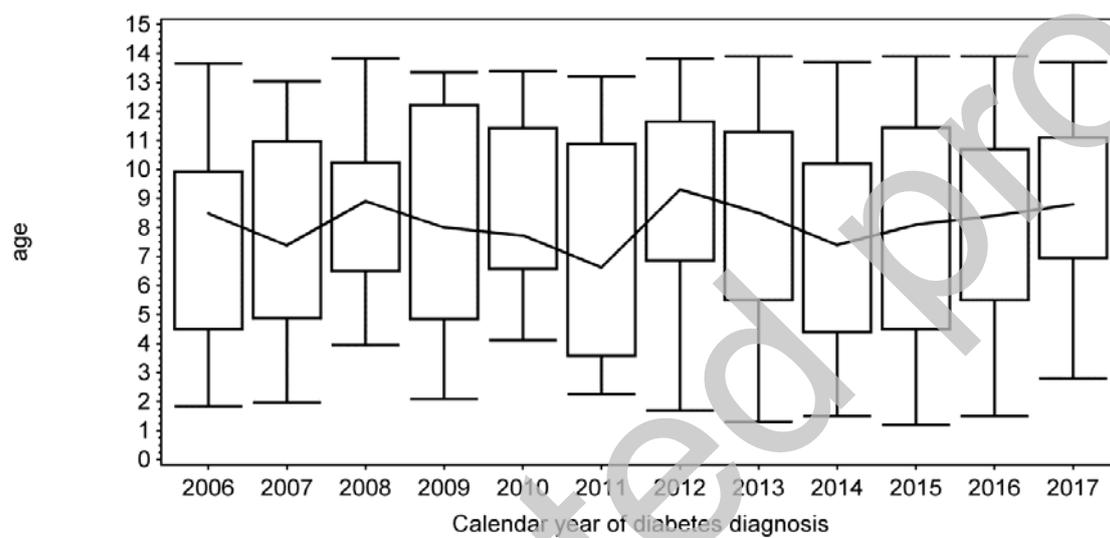


Figure 3. Mean BMI-SDS at the moment of type 1 diabetes diagnosis in subsequent analyzed calendar years. The upper and lower box boundaries indicate quartiles and the line across the centre of the graph joins the medians. The whiskers indicate the range of BMI-SDS in each year

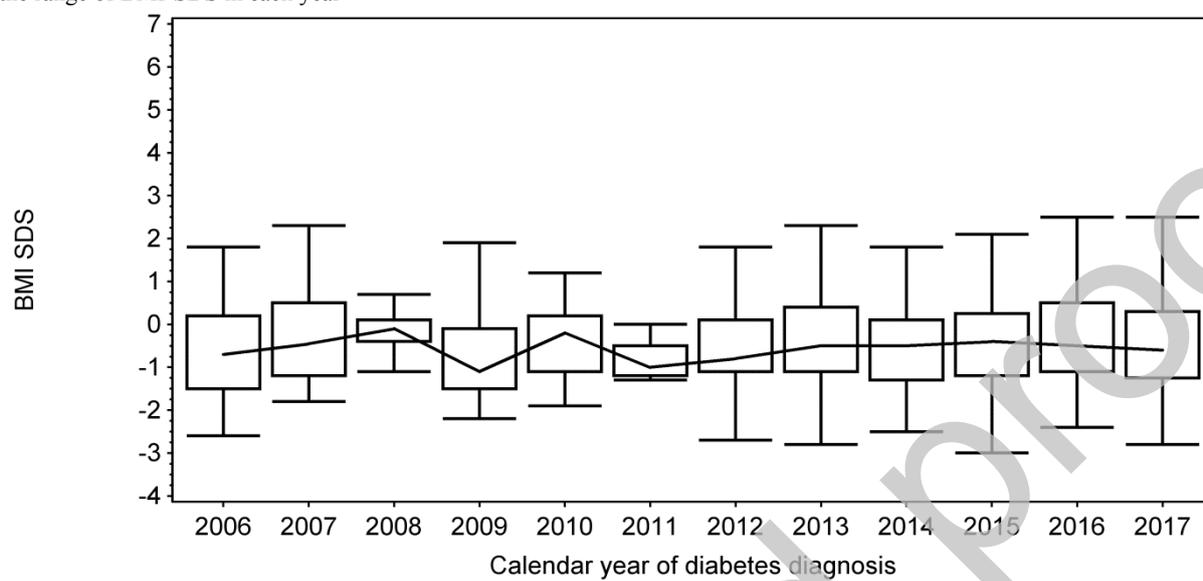


Figure 4. Correlation between the age of type 1 diabetes diagnosis and BMI-SDS

