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Original Article

Increased insulin requirement may contribute to risk of obesity in children and young people with Type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Type 1 diabetes mellitus (T1DM) is an autoimmune disorder that interferes with the function of the beta cells in the pancreas. Reports show that the incidence of T1DM is increasing throughout England and Wales, along with the Body Mass Index (BMI) of this patient group. The association between type 2 diabetes mellitus (T2DM) and obesity is recognised, but literature describing the association between T1DM and high BMI is more limited.

The aim of this paper is to identify factors affecting BMI and the impact that this increasing trend has on children and young people with T1DM.

Methods: Information was obtained from the medical records of patients with T1DM at the local paediatric centre. BMI standard deviation scores (SDS) were calculated and compared to other factors, which include insulin requirement, HbA1c, pubertal status and age at diagnosis.

Results: This study involved 102 patients (43 male and 59 female). The mean age at diagnosis was 7.79 years (range from 0.16 to 16.91 years). Our results showed a significant association between insulin requirement and BMI SDS ($r = 0.23$, $p = 0.02$) and a significant association between insulin requirement and mean HbA1c ($r = 0.59$, $p = <0.01$). A multivariable regression analysis of factors affecting BMI SDS showed that insulin requirement was an independent factor affecting BMI SDS.

Conclusion: There were significant associations between increased insulin requirement, high BMI SDS and poorer glycaemic control. Further research is required to fully understand the risk factors that may contribute to obesity in T1DM.

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder that progresses by focusing on and destroying the beta cells within the pancreas [1,2]. The function of beta cells is the production of insulin and therefore destruction results in hyperglycaemia and eventually diabetic ketoacidosis (DKA) if left untreated [1,2].

The National Paediatric Diabetes Audit (NPDA) is completed every year and investigates the care received by patients with diabetes under eighteen years of age and whether standards have been met [3]. In 2016/2017, the cohort had a total sample size of 29,153 patients. It reports that the incidence of T1DM in England and Wales for Children and Young People (CYP) is 25.4 per 100,000 general population in 0–15 year old age group [3]. This is reduced from the previous year, which had an incidence 25.9 per 100,000 general population, but still higher than 2013/2014 figures. The 2016/2017 report also shows an increasing incidence trend amongst 5–9 year old [3]. These figures are worrying for both the population and health service. In 2012, Hex et al. reported that diabetes (both type 1 and type 2) cost the National Health Service (NHS) 10% of its total expenditure [4]. It also predicted that if there was no change, this would increase to 17% by 2035 [4]. It is promising to see a slight reduction in the number of patients diagnosed this last year, but this trend would need to be maintained to avoid continuing strain on the NHS and its funds.

Therefore, it is important for the risk factors of T1DM to be recognised so that preventive measures can be put into place if possible. Obesity is a known factor for diabetes in the adult population, but there is little information available in the paediatric population [5]. In people below the age of eighteen years, BMI is standardised for age and sex and then divided into four categories:

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Abbreviations

BMI	Body Mass Index
CYP	Children and Young People
DKA	Diabetic Ketoacidosis
HbA1c	Haemoglobin A1c or Glycated Haemoglobin
HDL	High- Density Lipoproteins
LDL	Low- Density Lipoproteins
NHS	National Health Service
NPDA	National Paediatric Diabetes Audit
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
SDS	Standard Deviation Scores
SPSS	Statistical Package for the Social Sciences

underweight (<5th centile), healthy weight (5–85th centile), overweight (85–95th centile) and obese (>95th centile) [3]. The NPDA compared the BMIs of children with T1DM to their peers. Unfortunately, in England and Wales, there is limited BMI data on non-diabetic populations so the report focuses on four to five year olds and ten to eleven year olds [3]. In children with diabetes, results from the NPDA showed that in 2016/17, 33.4% of 4–5 years old with T1DM in England are overweight or obese, compared to their peers (22.6%) [3]. This figure has decreased by 0.3% when compared to 2015/16 data. In Wales for the same age group, 39.4% of T1DM patients were above the 85th centile compared to 26.2% of those in the Measurement Programme [3]. This shows a large improvement from 45.4% in 2015/16. Interestingly, for children aged ten to eleven years old, of those who had T1DM, 35.3% were overweight or obese. This is an increase from 33.7% in 2015/16 and higher than the Programme population which was 34.3% [3].

NPDA also evaluates BMI in children with T1DM, and in 2016/17, 34.1% of children aged 0–11 years old and 40.6% of 12–18 year olds were overweight or obese in England and Wales (in 2015/16, 32.9% and 38.9% respectively) [3].

The aim of this paper was to identify the factors associated with increased body mass index (BMI) and risk of obesity in children and young people with T1DM.

2. Methods

Data was collected from our local paediatric centre between 1st April 2014 and 30th March 2015. Over this time period, the sample size was 102 children and young people with T1DM. For each patient we were able to obtain their insulin requirement (total daily insulin dose per kilogram body weight), BMI standard deviation scores (SDS; adjusted for age and sex), mean HbA1c (four HbA1c determinations taken over twelve months period); age at diagnosis and pubertal status at the time of annual review between 1st April 2014–30th March 2015.

Outcomes were measured as continuous variables. Assumptions of normality were checked using a visual inspection of a histogram. Correlations were analysed using Pearson's correlation. Factors (HbA1c, gender, pubertal status, age at diagnosis, insulin requirement) affecting the BMI SDS were evaluated using multivariable linear regression stepwise model. The data was analysed using statistical software Statistical Package for the Social Sciences (SPSS 21.0, Chicago).

3. Results

Of the 102 patients analysed, 43 were male and 59 were female. All patients were under the age of eighteen years and the mean age at diagnosis was 7.79 years (range from 0.16 to 16.91 years). The mean BMI SDS was 0.89 (−3.7 to +3.32) and height and weight SDS were 0.02 (−2.95 to +2.99) and 0.73 (−3.02 to +4.48), respectively (Table 1).

The mean insulin requirement in our sample size was 1.01 units/kg/day, with a range from 0.38 to 2.43 units/kg/day (Table 2). The insulin requirement was analysed with BMI SDS and the results showed that higher insulin requirement was associated with higher BMI SDS ($r = 0.23$, $p = 0.02$; Fig. 1).

The mean HbA1c over twelve months was 64 mmol/mol (8%) and this data ranged from 34 to 123 mmol/mol (5.3–13.4%; Table 2). Our data also found a significant association between higher insulin requirement and higher mean HbA1c levels ($r = 0.59$, $p = < 0.01$; Fig. 2).

With regards to their pubertal status 24 were pre-pubertal, 28 were pubertal and 50 were post-pubertal. A multivariable regression analysis of factors affecting BMI SDS (factors: HbAc1, gender, pubertal status, age at diagnosis, insulin requirement) showed that insulin requirement was an independent factor affecting BMI SDS (Table 3).

4. Discussion

The results have shown that there is a significant association between increased insulin requirement and high BMI SDS. We were also able to demonstrate an association between poorer glycaemic control and high insulin requirement, but interestingly there was no association between BMI SDS and glycaemic control.

Current literature reports varied views on the association between higher BMIs and T1DM. In 2001, Wilkin et al. discussed the theory regarding the 'Accelerator Hypothesis', which argued that T1DM and Type 2 Diabetes Mellitus (T2DM) were the same condition, but variation in the diseases were secondary to beta cell destruction rate and three 'accelerators'. These accelerators include beta cell apoptosis, insulin resistance and autoimmunity [6,7]. In 2009, Wilkin et al. implied the hypothesis predicted that a child who is heavier at a younger age is at a higher risk of developing T1DM [6,8,9]. This predication was based on the overall rise of obesity in children and incidence of T1DM [9]. Betts et al. backed this theory up by analysing the BMI and age of diagnosis in 168 young people [10]. The results suggested that a child with a higher BMI was more at risk of developing T1DM earlier ($p = < 0.001$) [9,10]. They also found that T1DM patients had a greater waist circumference compared to children without T1DM [10]. Channanath et al. had similar results when focusing on children aged 6–18 years of Arab ethnicity [6]. The results of 474 patients showed that BMI was inversely associated with age of diagnosis [6]. In 2017, Ferrara et al. studied 1117 T1DM patients who had autoantibody positive relatives. The results showed after adjustment to age and gender, a greater BMI was significantly associated with an increased risk of developing T1DM [11]. Gimenz et al. disagreed with the accelerator hypothesis when they studied just over 3000 patients living in the Mediterranean area. Their results showed a positive correlation between the age of diagnosis of T1DM and BMI [8]. Abbasi et al. followed suit with an observational cohort study ($n = 1318$), which

Table 1
Shows the mean and range for each demographic factor.

Demographic	Mean (SD)	Range
Age at diagnosis (years)	7.79 (4.0)	0.16 to 16.91
BMI SDS	0.89 (1.1)	−3.7 to +3.32
Height SDS	0.02 (0.8)	−2.95 to +2.99
Weight SDS	0.73 (1.1)	−3.02 to +4.48

Table 2
Shows the mean and range of insulin requirement for patients in sample size, along with HbA1c and diastolic blood pressure.

	Mean (SD)	Range
Insulin Requirement (units/kg/day)	1.01 (0.35)	0.38 to 2.43
HbA1c (mmol/mol) (%)	64 (8) (8.3) (1.5)	34 to 123 (5.3 to 13.4)
Diastolic Blood Pressure (mmHg)	69 (6.9)	51 to 89

Table 3
Shows a multivariable regression analysis of factors affecting BMI SDS.

Variable	B coefficient	P Value
Age at Diagnosis (years)	−0.004	0.883
HbA1c	0.006	0.929
Gender (Female)	0.023	0.921
Pubertal Status	0.01	0.973
Insulin (units/kg/day)	0.744	**0.019**

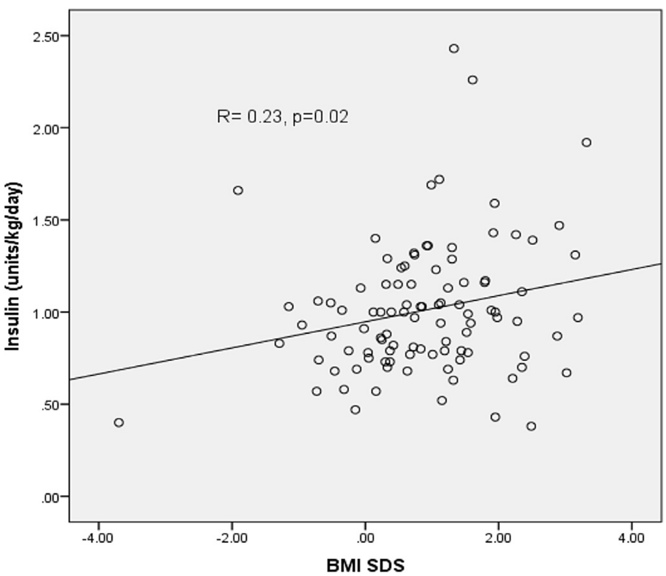

Fig. 1. Shows higher insulin requirement was associated with higher BMI SDS.

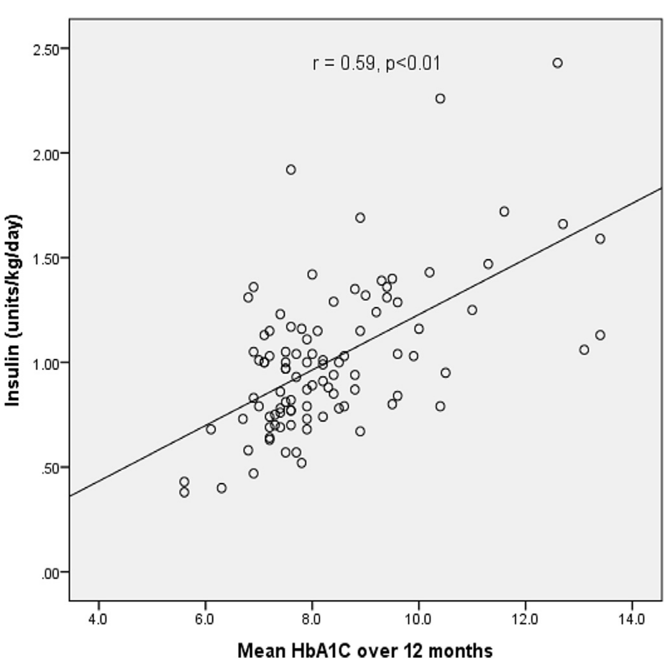

Fig. 2. Shows a significant association between higher insulin requirement and higher mean HbA1c levels (%).

found an association between higher BMI and T2DM, but not with T1DM [5,12].

This study showed a significant correlation between insulin requirement and BMI SDS in children and adolescents with T1DM. This is interesting as previous studies have shown little association. Deed et al. analysed fifty children and twenty-two adults with T1DM [12]. They found no association between BMI and basal insulin requirement in patients with insulin pumps [12]. In 2015, Akesson et al. showed an inverse relationship between BMI and insulin daily dose during follow up [13].

Minges et al. investigated obesity in over five thousand adolescents with T1DM. Interestingly, they supported our finding that higher insulin doses were associated with obesity, but they found that their HbA1c levels were lower in this group [14]. The understanding behind this HbA1c association is unclear and further research is required, as we found glycaemic control was poorer in the obese patients.

It is still not fully understood why insulin requirement may be associated with increased BMI SDS or poor glycaemic control. Lipids were considered to having an effect in the population group [15]. Patients with poor glycaemic control have been shown to have increased triglyceride and LDL levels [15]. This theory was supported by Hassan et al. who found that 65% of children with T1DM had evidence of dyslipidaemia, higher than the comparison group without T1DM [16,17]. The group with T1DM had high levels of LDL and low levels of HDL cholesterol [16,17]. Interestingly, no association was found between HbA1c and insulin requirement between dyslipidemic and normolipidemic groups [16].

Verges et al. investigated over 3000 patients with T1DM and found that BMI was associated with beta cell loss [1]. Patient with higher BMI at diagnosis went on to have a more rapid drop in c-peptide levels over the following one year [1]. The authors thought it was likely to be secondary to 'beta-cell exhaustion' [1], but further research is required to identify the true cause for this. In 2013, Minges et al. reviewed seven manuscripts that showed BMI was rising in the population of patients (under 18 years old) with T1DM [2]. Weight gain was found to be associated with less napping time, increased periods in front of screens and missing breakfast or dinner, but was interestingly not associated with time spent doing exercise [2]. The study size was limited and the other suggests further research would be beneficial. Finally, Bae et al. found a significant association between high BMI patients and suboptimal glycaemic control [18]. The sample size was large with 14,028 T1DM patients involved, but it was limited to over 18 year olds [18].

Another theory suggested between T1DM and weight gain was the difference in insulin delivery. It is thought that the hepatic response to insulin is not as effective with subcutaneous delivery. This results in poor glucagon release and peripheral hyperinsulinaemia, leading to poor glucose control and weight gain [19].

Mottalib et al. enrolled 68 patients with T1DM and obesity on to a twelve weeks weight loss programme which did not involve surgery. The findings of this study were that weight loss was significantly associated with better glycaemic control and reduction in total daily insulin dose [20]. These results support the need to investigate potential factors affecting obesity in patients with T1DM.

Limitation to the study was the difficulty in obtaining accurate dietary history evaluating potential other causes of obesity and the small sample size within this cohort of patients.

In conclusion, this study shows a significant association between increased insulin requirement, high BMI SDS and poorer glycaemic control. It is important to stress that increased insulin requirements do not cause obesity, but rather overeating and lack of exercise in patients with T1DM when not well controlled, leads to hyperglycaemia requiring higher insulin doses that contributes to obesity. Further research is required to fully understand the risk factors that may contribute to obesity in T1DM so that preventive measures and healthy lifestyle advice can be put into place early.

Conflicts of interest

None.

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