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Short Communication

Brakes on the accelerator: the journey of accelerator hypothesis from "the missing link" to "an evolving concept"

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ABSTRACT

The incidence of Type 1 diabetes (T1D) has increased significantly over the past few decades but the causes for this increase are poorly understood and hence the strategies for preventing T1D are difficult to design. T1D is characterised by autoimmune destruction of pancreatic β-cells resulting in insulin deficiency as opposed to Type 2 diabetes (T2D) characterised by weight driven insulin resistance (IR). The accelerator hypothesis (AH), proposed by the late Prof Terence Wilkin in 2001 offers an alternative mechanism for T1D and a different approach to prevention of T1D. This hypothesis considers both T1D and T2D as one and proposes that obesity driven IR is the key factor that may lead to either type of diabetes. It thus offers an easy explanation for the increasing worldwide incidence of childhood diabetes which is paralleled by the increase in childhood obesity rates. However, one of the key predictions of AH that the obesity related IR accelerates the onset of diabetes and hence heavier children should develop diabetes at a younger age, has remained a matter of debate since the hypothesis was first proposed. Since the inception of AH, the results of a number of studies which aimed at testing the hypothesis in diverse patient populations have shown support or opposed this key prediction. This article discusses the relevance of AH in the context of data from these studies.

Keywords: Accelerator hypothesis, Childhood diabetes, Type 1 diabetes, Type 2 diabetes, BMI, Obesity, Insulin resistance, Children

CONTEXT

The accelerator hypothesis (AH) proposed by the late Prof Terence Wilkin attempts to unite the type 1 (T1D) and type 2 diabetes (T2D) by obesity driven insulin resistance (IR) and tends, in part, to explain the rising incidence of T1D by a parallel increase in the incidence of obesity.[1] Since its inception in 2001, several studies have been conducted across the world to test the validity of AH. The results of these studies have shown considerable variability with some studies confirming and others refuting or showing neutrality to the key proposals of AH. This brief communication discusses the journey of AH over the last 16 years in the light of data accumulated from studies that aimed to test relevance and applicability of AH in diverse patient populations.

KEY PREDICTIONS AND CONTROVERSIES

The AH proposes that all the three processes or accelerators i.e. IR, autoimmunity and genetic predisposition that result in presentation of diabetes (either type 1 or 2) are driven by excess weight gain, which is thought to be "the missing link" between the two types of diabetes.[1] In particular, IR associated with recent weight gain is considered the main accelerator of pancreatic β-cell apoptosis that leads to earlier onset of T1D in individuals at genetic risk. The acceleration of diabetes and its presentation at a younger age will,

therefore, occur in populations with increasing prevalence of obesity. In relation to childhood diabetes, the two key predictions of AH are that children who develop T1D should be heavier before onset than their peers who do not, and the heavier children should develop diabetes at a younger age.[1] The first prediction has a firm basis in several reports that linked heavier weight in infancy and early childhood to development of T1D.[2,3] However, the second prediction has always remained a matter of debate since the hypothesis was originally proposed in 2001. In the first few years following the hypothesis proposal, 4 studies (Table 1, nos. 1-4) where age at onset of T1D was shown to be inversely related to BMI, supported this prediction. However the support has been dwindling with only three studies over the past decade supporting the AH (Table 1, nos. 10, 11, 17). Simultaneously, the emergence of new data from several independent cohorts during the past decade (Table 1, nos. 5-9, 12-16) has shown no support for AH. The UK study that included Asian children who are generally considered to have greater IR than white children and hence expected to present earlier with T1D, as the hypothesis would predict, was the first one that refuted the hypothesis.[4] Our own study conducted in an ethnically different patient population and aimed at testing the AH in a developing country setup, demonstrated no association between BMI and age at diagnosis.[5] This was despite the fact that the prevalence of overweight and obesity in children has shown a significant average increase of 3% in our country during the time frame of our study.[6,7] Furthermore, the incidence of T1D at our hospital has also shown a significant increase over a similar time span.[8] Similar observations have been made in other studies that refute one of the key predictions of AH (Table 1, nos. 5-9, 12-16).

Table 1: Main findings of studies that aimed to test the accelerator hypothesis since it was first proposed.

S.no	Authors, country, year	Characteristics of study populations	Results
1.	Kibirige et al, UK 2003	94 children with acute onset T1D	BMI at diagnosis, weight change since birth, and BMI 1 yr after diagnosis inversely related to age at presentation.[a]
2,	Betts et al, UK 2005	168 children (<16 yr) with T1D from 1980-2002	Pre- and post-onset BMI above the population mean and inversely related with age at onset. Waist circumference substantially greater than the population average.[a]
3.	Knerr et al, Germany & Austria 2005	9,248 patients (<20 yr) with T1D from 1990-2003	Weight and BMI significantly higher in patients. Higher BMI in 0-4.9-yr age group than higher age groups. Continuous rise in weight and BMI over 10 yr period.[a]
4.	Clarke et al, Australia 2006	960 children (<15 yr) with T1D from 1976 to 2004	Younger age at diagnosis associated with higher BMI. Youngest age-group had highest weight and BMI as compared to older age groups.[a]
5.	Porter et al, UK 2004	95 children (<16 yr) with T1D	No correlation between BMI and age at diagnosis.[b]
6.	Dabelea et al, USA 2006	449 patients (<20 yr)	Increasing BMI associated with younger age at diagnosis only among subjects with reduced β-cell function.[b]
7.	O'Connell et al, Australia 2007	1030 patients ≤19 yr with new onset T1D from 1992 to 2003	No association between BMI and age at diagnosis, children <5 yr old at diagnosis had the lowest BMI.[b]
8.	Giménez et al, Spain 2007	3,203 patients (<25 yr) with T1D from 1990 to 2004	No increase in BMI at diagnosis over 15 yr period, positive association between BMI and age at diagnosis.[b]
9.	Giménez et al, Spain 2008	93 patients (>18 yr) with new onset T1D from 1994-2003	No relationship between BMI and age at diagnosis, metabolic characteristics particularly IR similar in the patient groups diagnosed at 3 different time periods over a decade.[b]
10.	Knip et al, Finland 2008	T1D incidence determined in children aged <15 yr over 12-yr	Positive correlation between the incidence of T1D and mean BMIs.[a]
11.	Evertsen et al, USA 2009	1618 newly diagnosed T1D patients (<19 years).	Age at diagnosis was inversely correlated with BMI SDS.[a]
12.	Derraik et al, New Zealand 2012	Incidence of T1D determined in children aged <15 yr of age over 20 yr period.	No association between BMI SDS and age at diagnosis. Increase in age at diagnosis observed with the greatest increase in incidence in 10-14 yr group.[b]
13.	Kaminski et al, USA 2013	490 children (2-19 yr) with new onset T1D.	Mean BMI scores for children developing T1D were slightly lower than controls.[b]
14.	Cedillo et al, USA 2015	263 patients (<19 yr) with new onset T1D	No evidence that obesity accelerates the autoimmunity or presentation of T1D, once autoantibodies are present.[b]
15.	Dayal et al, India 2015	467 children (<16 yr) with new onset T1D, 629 controls	Mean BMI in patients significantly lower compared to controls, No correlation between age at diagnosis and BMI.[b]
16.	Antvorskov et al, Denmark 2016	238 children with T1D and 10147 controls	No correlation between age at onset and high BMI, BMI rise contributed only 2.8 % of a 40% increase in incidence of T1D over 10 yr period.[b]
17.	Channanath et al, Kuwait 2017	474 children (6-18 yr) with T1D and 5164 controls.	BMI z-score inversely associated with onset age of T1D.[a]

[a]: results support accelerator hypothesis; [b]: results do not support accelerator hypothesis.

The AH considers that the two types of diabetes lie at different points of the same spectrum and differ only with respect to the tempo of development of IR which is largely determined by obesity.[1] The development of islet autoimmunity is regarded as secondary to the obesity driven IR postulating that increasing BMI may have an association with risk of development of islet autoimmunity in susceptible individuals.[1] However, the recent data in this regard also has shown variable conclusions. The TEDDY Study Group that explored the relationship between childhood growth and development of islet autoimmunity during the first 4 years of life in 7,468 children at genetic risk for T1D suggested that greater weight was associated with an increased risk of islet autoimmunity and progression to T1D.[9] A similar study on 1,117 children in the TrialNet pathway to prevention (PTP) cohort (autoantibody-positive relatives of patients with T1D) also showed a positive association of elevated BMI with risk of diabetes progression in autoantibody-positive relatives, but the effect varied by sex and age.[10] However, another study on the TrialNet PTP cohort could not find any significant relationships between BMI, weight status or HOMA1-IR and progression from one to multiple autoantibodies and progression to diabetes in 1,310 single and 1,897 multiple Aab-positive PTP participants, thus negating a broad influence of metabolic variables on diabetes risk.[11] Studies on the BABYDIAB cohort also did not find any influence of BMI on islet autoantibody seroconversion indicating that obesity driven IR is not a risk factor for islet autoimmunity.[12] Thus the influence of increasing BMI on progression of islet autoimmunity or progression to diabetes in susceptible populations, too, remains controversial. In other words, the prediction of AH that weight gain accelerates the presentation of T1D may not be relevant in diverse patient populations. Overall, the number of "accelerators" (studies supporting AH) have been fewer as compared to "brakes" (studies that do not support AH) in the 16 year long journey of AH.

THE FUTURE OF AH

At the time when the AH was raised, it seemed plausible as it offered an easy explanation for the rising incidence of T1D as secondary to the global increase in rates of childhood obesity. However, in view of the evidence accumulated over the past decade, weight gain reflected in the BMI z-scores at diagnosis of T1D, appears to contribute only a small fraction to the increasing incidence of T1D. In a review article, Prof Terence Wilkin, the proposer of the hypothesis, acknowledged that AH is still "an evolving concept".[13] In his own words, "If the AH is to progress beyond speculation, it will be necessary to demonstrate that β-cell loss is slowed (and the incidence of T1D reduced) by protecting the cell against stress, and that β-cell stress is indeed the mechanism that drives the immune response that we call autoimmunity".[13] In this regard, the currently recruiting adAPT1 (autoimmune diabetes accelerator prevention trial) study in UK in which children at high risk of T1D (double antibody positive) will receive metformin for five years in order to establish whether β-cell protection can reduce the incidence of diabetes, may truly test the AH.[14] Prof Wilkin believed that a successful outcome of adAPT will lead to a safe, cheap and universal approach to the prevention of T1D probably hinting at the strategies for obesity reduction.[13,14] But what if the results of the adAPT are negative or inconclusive? Will the AH lose its relevance? Probably not. The hypothesis may still remain worth consideration in certain ethnic patient populations of T1D. The recent study from Kuwait does indicate that ethnic differences in patient populations may explain the association between BMI and age at diagnosis.[15] In order to truly test the relevance of AH, there is a need to conduct prospective worldwide studies in ethnically diverse patient populations with a focus similar to adAPT. That will be a true tribute to a legend who sought to challenge some of the major doctrines in endocrinology during his lifetime.

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