Title: Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes

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Research in context

What is already known about this subject?

- Differentiating type 1 from type 2 diabetes when diagnosed over 30 years of age is difficult. There is a lack of robust clinical criteria and many patients in this age group with positive islet autoantibodies have a clinical phenotype of type 2 diabetes without rapid insulin requirement.

- Recent research using novel genomic methods has suggested that over 42% of type 1 diabetes occurs after age 30 and the phenotype remains severe with 89% insulin treated within 1 year of diagnosis.

- Severe (near absolute) insulin deficiency is a hall mark of type 1 diabetes and defines treatment and education requirements. However the prevalence and characteristics of diabetes leading to severe insulin deficiency in older adults has not been previously reported.

What is the key question?

- What is the prevalence and characteristics of type 1 diabetes defined by severe endogenous insulin deficiency diagnosed after age 30, and in clinical practice are these patients identified and managed as having type 1 diabetes?

What are the new findings?

- 21% of participants with insulin treated diabetes diagnosed after 30 had severe insulin deficiency. These participants had similar clinical, islet autoantibody and genetic characteristics to a comparison cohort with young onset type 1 diabetes.

- 38% of those with absolute insulin deficiency did not receive insulin treatment at diagnosis.

- Rapid insulin requirement was highly predictive of severe endogenous insulin deficiency: 85% required insulin within 1 year of diagnosis, and 57% of those progressing to insulin within 3 years of diagnosis had type 1 diabetes.

How might this impact on clinical practice in the foreseeable future?

- This study provides clear evidence that type 1 diabetes leading to severe, near absolute, insulin deficiency is common in later life but is often not recognised in clinical practice. We show that clinicians should strongly consider type 1 diabetes where a person previously classified as having type 2 requires insulin within 3 years of diabetes diagnosis.

Abstract

Aims/ hypothesis

Late onset type 1 diabetes can be difficult to identify. Measurement of endogenous insulin secretion, using C-peptide, provides a gold standard classification in longstanding diabetes that closely relates to treatment requirements. We aimed to determine the prevalence and characteristics of type 1 diabetes defined by severe endogenous insulin deficiency after age 30 and assess whether these patients are identified and managed as having type 1 diabetes in clinical practice.

Methods

We assessed the characteristics of type 1 diabetes defined by rapid insulin requirement (within 3 years of diagnosis) and severe endogenous insulin deficiency (non-fasting C-peptide <200pmol/l) within 583 participants with insulin treated diabetes diagnosed after age 30 from the DARE population cohort. We compared characteristics with participants with retained endogenous insulin secretion (>600pmol/L) and 220 participants with severe insulin deficiency diagnosed under age 30.

Results

Twenty one percent of participants with insulin treated diabetes diagnosed after age 30 met study criteria for type 1 diabetes. Of these participants, 38% did not receive insulin at diagnosis, of whom 47% self-reported type 2 diabetes. Rapid insulin requirement was highly predictive of severe endogenous insulin deficiency: 85% required insulin within 1 year of diagnosis, and 57% of those progressing to insulin within 3 years of diagnosis had type 1 diabetes. Participants with late onset type 1 diabetes defined by development of severe insulin deficiency had similar clinical characteristics to those with young onset type 1 diabetes. However those with later onset type 1 diabetes had modestly lower type 1 diabetes genetic risk score (0.268 vs 0.279, $p<0.001$, expected type 2 diabetes population median 0.231), higher islet autoantibody prevalence (GAD, IA2 or ZnT8 positive 78 vs 62% at 13 vs 26 years diabetes duration, $p=0.02$), and were less likely to identify as having type 1 diabetes (79 vs 100%, $p<0.001$).

Conclusion

Type 1 diabetes diagnosed over 30 years of age, defined by severe insulin deficiency has similar clinical and biological characteristics to when occurring at younger ages, but is frequently not identified. Clinicians should be aware that patients progressing to insulin within 3 years of diagnosis have a high likelihood of type 1 diabetes, regardless of initial diagnosis.

Introduction

Type 1 diabetes is classically defined by autoimmune or idiopathic B-cell destruction leading to severe insulin deficiency[1] but this **aetiopathalogical** definition is difficult to apply in clinical practice. Definitions based on clinical criteria have been little investigated in adults and are poorly defined, with many features commonly thought of as discriminatory having no evidence base[2]. As a result there is no robust evidence based guidance on identifying type 1 diabetes in later life. Recent novel population based genetic stratification analysis has suggested at least 42% of type 1 diabetes occurs after age 30[3]. This research suggests late type 1 diabetes has similar characteristics to young onset disease and in contrast to classification defined by autoantibody status alone, continues to have a severe phenotype: 89% were treated with insulin within one year, and 11% developed ketoacidosis[4]. However this technique does not allow classification of type 1 diabetes at an individual level, and neither islet autoantibodies or measures of endogenous insulin secretion were available.

Measurement of C-peptide, a surrogate marker of insulin secretion, allows robust diagnosis of type 1 diabetes in longstanding diabetes (>3 years duration) that closely relates to treatment requirements[5]. The development of severe (near absolute) insulin deficiency (commonly defined by stimulated C-peptide <200pmol/L) results in high glucose variability, marked hypoglycaemia risk, absolute insulin requirement and poor glycaemic response to non-insulin therapies[5, 6]. Therefore those with severe insulin deficiency will require glycaemic management according to type 1 diabetes guidelines regardless of disease aetiology. The prevalence and characteristics of diabetes leading to severe insulin deficiency in older adults is not known.

We aimed to determine the prevalence and characteristics of type 1 diabetes defined by severe endogenous insulin deficiency after age 30 in patients with insulin treated diabetes, and assess whether these patients are identified and managed as having type 1 diabetes in clinical practice.

Methods

We assessed the prevalence and characteristics of type 1 diabetes defined by early insulin requirement and severe endogenous insulin deficiency in an insulin treated population cohort.

Participants: 583 participants from the population based Exeter DARE (Diabetes Alliance for Research in England) cohort (http://exeter.crf.nihr.ac.uk/node/87) met the following inclusion criteria: diagnosed with diabetes after age 30, insulin treated and measured C-peptide. Participants with previous pancreatic pathology (n=2) were excluded from analysis. To allow comparison with young onset type 1 diabetes we assessed a further cohort of 220 DARE participants diagnosed before age 30, meeting study criteria for type 1 diabetes (see below).

Non-fasting (random) C-peptide, islet autoantibodies (GAD, ZNT8, IA2) and a type 1 diabetes genetic risk score (T1DGRS) were assessed in all included participants at mean 16 years duration, as previously described (see ESM methods)[6, 7]. Where multiple C-peptide measurements were available (70% of participants, median 3 values per participant) the median value was used.

The DARE study was approved by the South West ethics committee (UK). Participants gave informed consent.

Definition of diabetes type

Type 1 diabetes was defined as continuous insulin treatment commenced within 3 years of diagnosis and severe insulin deficiency defined by a non-fasting C-peptide <200pmol/L. Insulin treated type 2 diabetes was defined as participants currently insulin treated with a C-peptide ≥600pmol/L and a duration of diabetes at C-peptide measurement of over 3 years. Participants insulin treated and with a C-peptide level ≥200-<600pmol/l (n=115, median 48 months to insulin therapy) were considered indeterminate and were not included in analysis (ESM figure 1).[5]

Statistical analysis

Data were assessed visually for distribution. All continuous variables except age were not normally distributed data therefore is presented as median and IQR. We compared the clinical characteristics, islet autoantibody status and T1DGRS of participant groups defined

by C-peptide, initial insulin treatment and age of diagnosis using the Wilcoxon rank-sum test for continuous variables and χ2 analysis for comparison of categorical characteristics. All analyses were performed using Stata 15 (StataCorp LP, Texas).

Results

Severe insulin deficiency occurs in 21% of insulin treated patients diagnosed after age 30, and has similar clinical characteristics to young onset type 1 diabetes

Twenty one percent (123/583) of insulin treated participants diagnosed with diabetes after 30 years of age met the study criteria for type 1 diabetes with severe endogenous insulin deficiency (insulin treatment within 3 years and C-peptide<200pmol/L) (ESM figure 1).

The characteristics of participants with late onset (>age 30) type 1 diabetes, in comparison to young onset (≤age 30) disease, and late onset type 2 diabetes (retained endogenous insulin secretion) are shown in table 1. Participants with late onset type 1 diabetes defined by development of severe insulin deficiency had broadly similar characteristics to those with young onset type 1 diabetes: BMI, insulin dose and HbA1c did not differ. However those with later onset type 1 diabetes had modestly lower T1DGRS (0.268vs0.279, expected type 2 diabetes population median 0.231[8]), higher islet autoantibody prevalence (78vs62%, at 13vs26 years duration), **and were more likely to be treated (Oral hypoglycaemic agent use 15vs5%, initial insulin 62vs96%) and identify as having T2D (79vs100%).**

Classical clinical criteria cannot reliably identify patients with late onset type 1 diabetes leading to severe insulin deficiency

Despite similar clinical features to young onset type 1 diabetes, classical clinical criteria could not robustly identify late onset type 1 diabetes. Only 41% had a BMI <25, and 28% of participants with BMI <25 had type 2 diabetes. UK National Institute of Clinical Excellence guidance for type 1 diabetes identification (age of diagnosis <50 or BMI <25 kg/m^2) identified 81% of type 1 diabetes but had very low specificity (41%). The specificity of these criteria would be far lower had non-insulin treated individuals been included in this cohort.

Thirty eight percent of participants with late onset type 1 diabetes do not receive insulin at diagnosis

These participants commenced insulin a median of 12 months from diagnosis, and had similar characteristics to those commencing insulin at diagnosis (ESM table 1). However only 51% reported a diagnosis of type 1 diabetes, and 30% received co-treatment with oral glucose lowering therapy, in marked contrast to the 7% in those receiving insulin from diagnosis $p<0.01$.

Early progression to insulin is a strong predictor of future severe insulin deficiency

Eighty five percent (104/123) of all participants meeting criteria for T1D in this cohort were treated with insulin within 1 year of diagnosis versus 18% (55/306) of those meeting criteria for type 2 diabetes, and 77% (36/47) with an intermediate C-peptide. 57% of those progressing to insulin within 3 years of diagnosis met study criteria for type 1 diabetes (figure 1). Severe insulin deficiency was rare in those progressing to insulin after 3 years, occurring in only 10 of 231 participants (4%).

30% of those starting insulin at diagnosis after age 30 have type 2 diabetes by C-peptide criteria

Despite clear clinical, biochemical and genetic characteristics of type 2 diabetes, 25% of these patients reported a diagnosis of type 1 diabetes and only 59% received concurrent oral glucose lowering therapy at a median 10 years diabetes duration (ESM table 2).

Discussion

To our knowledge, this is the first population analysis evaluating the prevalence of type 1 diabetes defined by low endogenous insulin secretion. **Our study shows that late onset type 1 diabetes with severe endogenous insulin deficiency is relatively common (21% of insulin treated patients), has very similar characteristics to young onset type 1 diabetes, but is frequently initially treated as type 2 diabetes. The majority of participants progressing to insulin within 3 years had type 1 diabetes and severe endogenous insulin deficiency, but this was often unrecognised**

Our finding that the clinical features of those with late onset type 1 diabetes are similar to young onset type 1 diabetes is consistent with recent research using a novel genetic stratification methodology[3]. This showed that 89% of those with genetically defined type 1 diabetes occurring after age 30 required insulin within a year, strikingly similar to the 85% we report using a C-peptide based definition. This is in contrast to diabetes defined solely by islet autoantibody status where the phenotype appears intermediate between classical type 1 diabetes and type 2 diabetes in this age group[4].

A limitation of this study is the cross-sectional design within a relatively homogenous, geographically restricted population. Time to insulin and age of diagnosis were self-reported, and participants assessed a median 13 years after diagnosis, meaning islet autoantibody positivity will be lower than that found at diagnosis [9] **Negative autoantibody tests in this context therefore do not exclude autoimmune diabetes, and we consider it likely that the aetiology of antibody negative participants with low C-peptide will be autoimmune, as suggested by the high T1DGRS of these participants (median 0.262).** The longer duration at islet autoantibody measurement in our young onset cohort is likely to explain the higher rate of islet autoantibody positivity observed in late onset diabetes in this cohort. **A further limitation of this study is the lack of availability of a concurrent glucose when C-peptide was measured: this test may be reduced in the presence of hypoglycaemia [10]. A final limitation is that we included those within 3 years of diagnosis and C-peptide <200pmol/L in our type 1 definition. As C-peptide may be preserved in early type 1 diabetes a duration over 3 years was required where C-peptide was retained, potentially biasing prevalence estimates. Had we excluded the 19 patients meeting type 1 criteria with duration <3 years our prevalence would be modestly lower at 18%.**

These results have clear implications for clinical practice. Our results show type 1 diabetes leading to endogenous insulin deficiency is common in later life but is difficult to identify. Consistent with this many participants with type 1 diabetes in our cohort were diagnosed and treated as type 2 diabetes. Without a diagnosis of type 1 diabetes a patient will not receive appropriate education and will not be eligible for interventions that are often restricted to type 1 diabetes, such as carbohydrate counting, continuous glucose monitoring and insulin pump therapy. They will be at risk of ketoacidosis if insulin is withdrawn. Our results suggest that where patients are treated as type 2 diabetes but progress to insulin within 3 years of diagnosis, clinicians should reassess the underlying diagnosis, and strongly consider biomarker testing [5, 8, 11].

Conclusion

Type 1 diabetes defined by severe insulin deficiency has similar clinical and biological characteristics to type 1 diabetes occurring at younger ages, however patients are frequently diagnosed and treated as type 2 diabetes. Clinicians should be aware that patients progressing to insulin within 3 years of diagnosis have a high likelihood of type 1 diabetes, regardless of initial diagnosis.

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Duality of Interest

The authors declare that there is no duality of interest associated with this manuscript.

Author Contributions

NJT, ATH and AGJ conceived the idea and designed the study. NJT, ALG, TJM, ATH, RAO, AVH, BMS, and AGJ researched the data. NJT analysed the data with assistance from BMS and AGJ. NJT drafted the manuscript with assistance from AGJ. All authors critically revised the manuscript and approved the final version. AGJ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability

The datasets analysed during the current study are available through application to the Peninsula Research Bank, which is managed by the NIHR Exeter Clinical Research Facility. Information on application or data is available on http://exeter.crf.nihr.ac.uk/content/tissue-banks

Figure Legends

Figure 1: Comparison of time to insulin therapy up to 10 years post diagnosis in participants with severe endogenous insulin deficiency (C-peptide <200pmol/L) in black and retained endogenous insulin secretion (C-peptide≥600pmol/L) in grey. * 5^{th} centile of a young T1D population corresponding to the 50th centile of a T2D population.

Table 1: Comparison of the characteristics of those with insulin treated diabetes diagnosed over 30 years of age, between participants with severe endogenous insulin deficiency (C-peptide <200 pmol/l) versus those with preserved insulin secretion (C-peptide >=600 pmol/l) and those diagnosed 30 years and younger with severe endogenous insulin deficiency (C-peptide<200 pmol/l).

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