Title: The challenge of diagnosing type 1 diabetes in older adults

Dear Sir,

We thank Professor Sinclair and colleagues for their helpful position statement addressing the important clinical problem of managing type 1 diabetes in older adults (1). We believe that further considerations about the difficult area of making a diagnosis of type 1 diabetes in older adults would benefit future versions of these guidelines.

The present guidelines do not emphasise how difficult this diagnosis is to make because in the older adult, where type 2 diabetes represents over 98% of all diabetes (2). The rarity of type 1 diabetes in this age group means that it is very hard to separate type 1 diabetes from an unusual presentation of type 2 diabetes. Errors are therefore common with post honeymoon C-peptide studies showing that ~50% of those treated with insulin from diagnosis do not have type 1 diabetes (3) and ~40% of those with definite type 1 diabetes are initially treated with tablets (4). This means the reassessment of diagnosis in older adults treated with insulin is crucial.

A Body Mass Index (BMI) ≤24kg/m^2 is proposed as a reason for considering type 1 diabetes, which is reasonable but it is important to emphasise that most people with a normal BMI diagnosed over 50 years will have type 2 diabetes and not type 1 diabetes. With increasing age of diagnosis type 2 diabetes develops at substantially lower BMI (5). In UK general practice records, a BMI under 25 kg/m^2 is found in 7.2% of people presenting with type 2 diabetes after age 35 years, and 13.0% presenting after age 70 (personal communication Dennis JM – analysis Clinical Practice Research Datalink, n=70,150).

Similarly, it is important to emphasise that the vast majority of older adults with diabetes and the clinical features of atypical presentation (rapid onset or ketosis at diagnosis), or a family history of autoimmune diabetes will not have type 1 diabetes. These factors were not supported as having evidence of diagnostic utility for differentiating between type 1 and type 2 diabetes on systematic review (6). Even if ketosis or family history of autoimmunity are more common in type 1 diabetes this does not mean they are substantially predictive of type 1 diabetes in this age group. Based on data from 1048 participants with adult onset diabetes (7), in a population with diabetes onset after age 30 years and prevalence of type 1 diabetes of 5% the positive predictive value of a personal history of autoimmune disease for type 1 diabetes will be 8.5%, with the positive predictive value for established ketoacidosis 16%. The predictive value of family history of autoimmunity or ketosis (without acidosis) is likely to be far lower. This issue is likely to contribute to the high rates of reported misclassification in older adults.

A clinical feature which is strongly predictive for type 1 diabetes in older adults at diagnosis is rapid insulin requirement (within 3 years of diagnosis) in those who were initially treated as type 2 diabetes (4, 6).This is particularly important as around 40% of those aged over 30 years who have type 1 diabetes and develop absolute insulin deficiency will be initially treated as type 2 diabetes by their clinician (4). Despite rapid progression to insulin half of those with missed type 1 diabetes will still be thought to have type 2 diabetes when assessed decades later, and are therefore ineligible for the education and technology needed to effectively manage their glycaemia. All those who progress to insulin within 3 years of diagnosis of diabetes should therefore be further investigated with biomarker testing (C-peptide and islet autoantibodies) to detect missed late-onset type 1 diabetes.

We think it is vital to consider to consider diabetes duration when referring to potential discriminative biomarker tests that can be used to help define diabetes type. At diagnosis where there is diagnostic uncertainty islet autoantibodies antibodies are most appropriate (8). In

longstanding diabetes C-peptide is the most appropriate test and can define the need for type 1 clinical care with a non-fasting random value of less than 200pmol/L(9). Autoantibodies are less prevalent with time from diagnosis and there is limited evidence for utility of C peptide testing at diagnosis over and above freely available features (8, 9).

Finally we suggest that GADA, IA2A and/or ZnT8A are the islet autoantibodies of choice in adult onset disease as they are robust, inexpensive, and common in adult onset disease (10). In contrast commercially available ICA has persistently very poor historical performance (with only a single UK centre still taking part in the islet autoantibody standardisation program for this assay), and insulin autoantibodies are infrequent in adult onset diabetes, have poor reproducibility between laboratories and are susceptible to false positive results where insulin has been commenced (8, 11).

A major issue for older adult onset type 1 diabetes is getting the correct diagnosis. This is a difficult diagnosis to make and has been little researched making it hard to make evidence based recommendations. We hope that this area receives more attention in future research allowing future guidelines to give this area more emphasis.

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Conflict of Interest Statement

None to declare.

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