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Comment on "*Impact of Routine Clinic Measurement of Random Serum C-peptide in People with a Clinician Diagnosis of Type 1 Diabetes*"

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We commend Foteinopoulou and colleagues on their efforts to determine the impact of random serum C-peptide measurements on diagnosis and treatment in clinically diagnosed

type 1 diabetes (T1D) individuals. We agree that there is a role for the incorporation of C-peptide in the diagnostic algorithm of T1D.

Strikingly, whilst few, those individuals with dual pathogenic monogenic diabetes mutations and GAD positivity raise interest, as they fail (unlike individuals with a monogenic diabetes mutation only) to respond to gliclazide therapy. The authors propose that patient number 1's detectable GAD autoantibody was falsely positive based on their Type 1 diabetes Genetic Risk Score (T1GRS) and titre, yet they failed to respond to gliclazide and remained on insulin. The other two patients are thought to have a combination of both monogenic diabetes and T1D. Clinically, we are unlikely to perform monogenic diabetes testing in the setting of detectable autoantibodies; hence management is unlikely to be changed. However this may explain those few patients who fail to respond to gliclazide therapy. Nevertheless, could this be explained by a 'two-hit hypothesis'? Perhaps in cases of monogenic diabetes where this a lack of an initial response to sulphonylureas, alternative additional mechanisms for diabetes should be considered.

The second group of interest are autoantibody-negative individuals with C-peptide between 200 and 600 pmol/L and/or ketoacidosis at diagnosis with a BMI < 25 kg/m^2. Whilst T1GRS was used to guide diagnosis, we hypothesise that some of these patients may in fact have autoantibody-negative T1D, rather than type 2 diabetes (T2D). Scarce literature to date suggests that C-peptide levels tend to be higher in autoantibody-negative compared to positive individuals, implying slower rates of beta-cell decline[1, 2]. Cautious use of oral diabetes medications may be effective in this group, akin to individuals with Latent Autoimmune Diabetes in Adulthood (LADA), with the aim of slowing the rate of insulin deficiency. The other arguments for trialling T2D medications as adjunct therapies include targeting possible type 2 mediated mechanisms such as insulin resistance, in addition to their metabolic and cardiovascular benefits[3, 4].

Autoantibody-negative T1D is recognised in clinical practice, but this entity is under-reported in the research literature. This cohort is excluded from T1D trials and deemed 'idiopathic' as their aetiopathogenesis is yet to be explored[5]. Perhaps these individuals have undergone autoantibody reversion and share common mechanistic pathways with

classic autoantibody positive T1D. So *et al*, recently analysed multi-autoantibody positive individuals in TrialNet's Pathway to Prevention Study and found that reversion occurred in 134/3284 (4.1%) and was associated with reduced development of T1D [6]. Whilst C-peptide values were not collected in this study, it would be of interest to compare rates of decline and disease progression between autoantibody 'reverters' and 'maintainers'. On the other hand, reversion many years after diagnosis is well recognised and believed to relate to a loss of autoantigenic stimulus related to loss of beta cell mass. Theoretically, those with detectable C-peptide should maintain autoantibody positivity; however, large observational studies have shown otherwise[7, 8]. In the Bart's Oxford Study, autoantibodies declined from 100% at diagnosis to 65% at a disease duration of 23 years. C-peptide was detectable in 35% of individuals and was related to age at diagnosis, but independent of autoantibody status or disease duration[8]. Similarly, in the Joslin Medalist cohort, C-peptide was detectable in 32% whilst 44% of individuals maintained autoantibody positivity with a median disease duration of 53 years[7]. We are yet to unravel which factors affect timing and likelihood of reversion.

In summary, there is a need to revise our diagnostic algorithm with the incorporation of additional testing such as C-peptide, particularly in autoantibody-negative individuals. Further clinical and immune-pathological characterisation of this cohort is required in order to achieve a more precision diagnosis and to be able to predict the most effective therapeutics with fewest adverse effects.

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