Non- stimulated c-peptide is independently associated with requirement at 1 year for insulin therapy in patients with diabetes.
A retrospective cohort study of 872 patients.

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Introduction

Diabetes Mellitus is a significant cause of morbidity and mortality. In recent years, c-peptide has emerged as a useful measure of endogenous beta cell function. (1) This 31 amino-acid peptide is cleaved from pro-insulin prior to co-secretion with insulin from pancreatic beta cells. A practical application of c-peptide measurement may be in determining beta cell reserve, and hence likely insulin requirement in future.

Our aim was to explore the association between non-stimulated c-peptide and progression to insulin therapy in patients with diabetes. A secondary outcome was to determine the association between c-peptide and mortality in patients with diabetes.

Methods

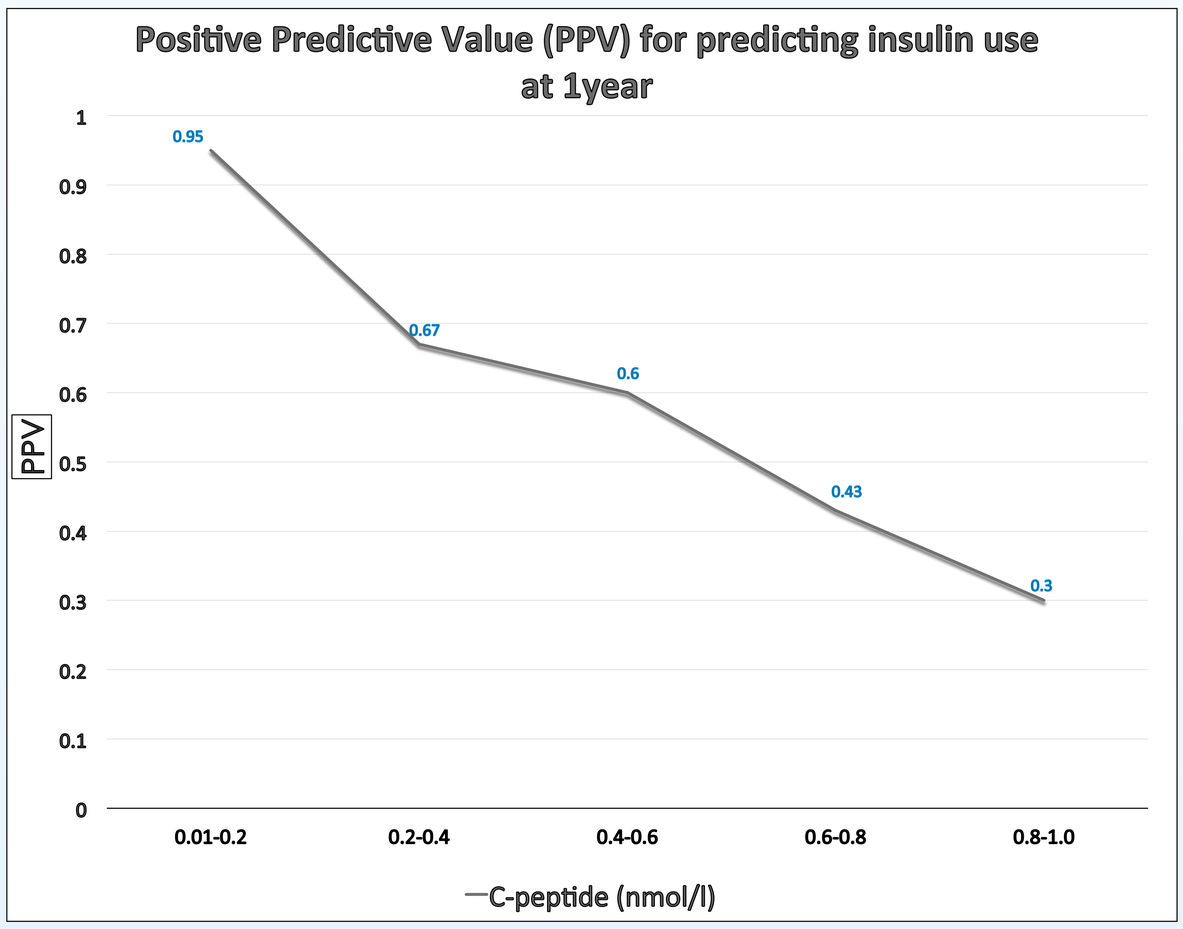
1971 patients with unstimulated c-peptide measurements, taken between February 2007 and December 2016, were identified within Greater Glasgow and Clyde. 872 individuals appeared on national diabetes database SCI-diabetes and were included in analysis.

All data was analysed with first c-peptide in dataset, age and BMI as co-variables. Insulin-free survival (time to first insulin prescription or end of follow-up) was investigated using survival analysis (Cox proportional hazard model). Mortality at 3 years was additionally investigated using logistic regression.

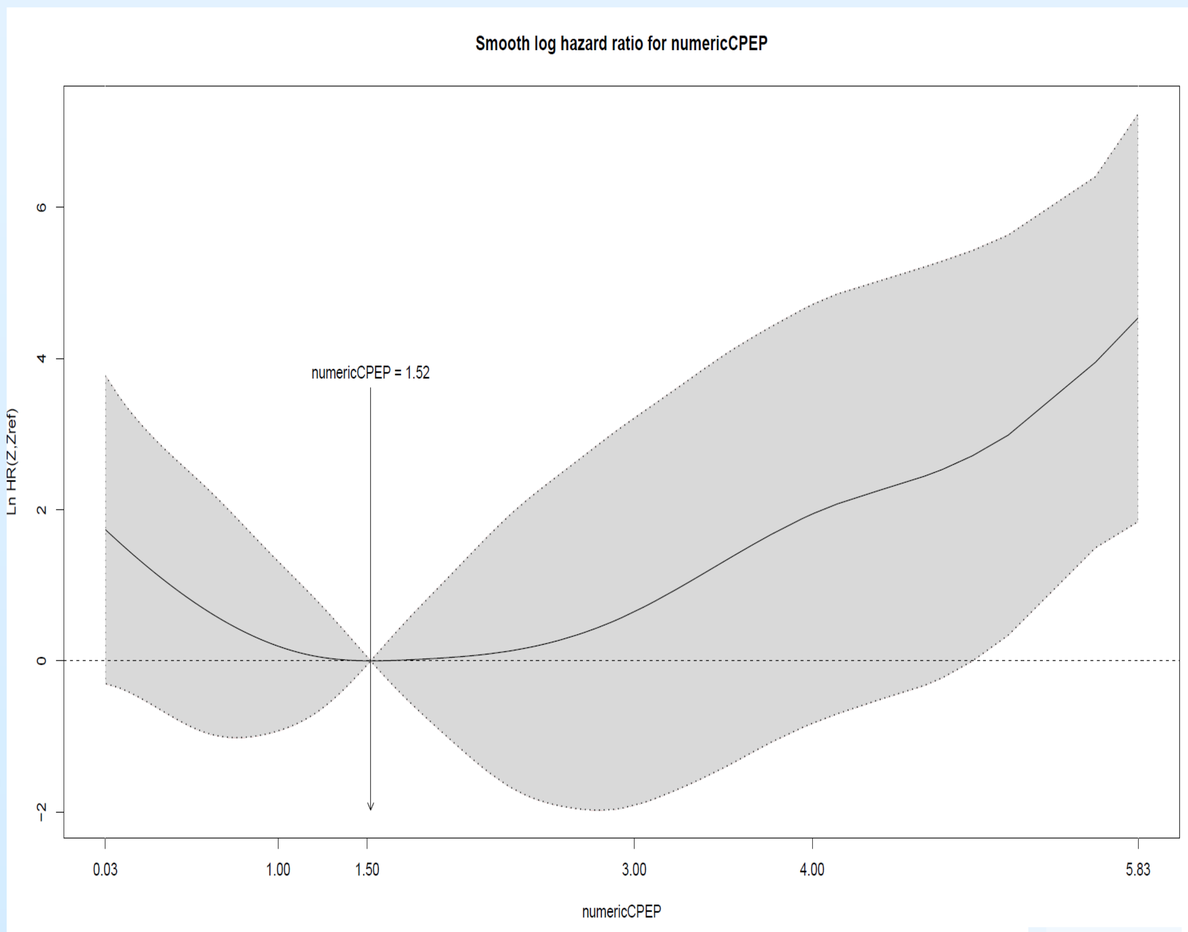
Results

458 individuals had BMI data available, and were insulin-naive at the time of c-peptide measurement. In this cohort a c-peptide in the lower half of the range of observed values (<0.76nmol/l) is associated with a significantly decreased insulin-free survival time (p<0.001, HR 3.0). PPV for initial c-peptide (nmol/l) increments were: c-peptide 0.01-0.2 PPV=0.95, 0.2-0.4 PPV=0.67, 0.4-0.6 PPV=0.6, 0.6-0.8 PPV=0.43, 0.8-1.0 PPV=0.3, as demonstrated in figure 1.

C-peptide showed a U shaped relationship with mortality at 3 years with a nadir of 1.52nmol/l as demonstrated by figure 2. Above 1.52nmol/l increasing c-peptide concentration is associated with increased mortality independent of age and BMI (n = 464, p=0.02, estimate 0.42). At concentrations below 1.52nmol/l c-peptide appears to be negatively associated with risk of mortality.



PPV for Insulin prescription (%) at 1 year



Mortality hazard ratios at 3 years: logistic regression with age and BMI as covariables

Conclusions

C-peptide below the median value for the cohort was associated with a reduced time to insulin prescription and an increased probability of requiring insulin at 1 year. C-peptide may therefore be a useful guide to predict future insulin requirement. However, these findings are likely to be partly explained by c-peptide already being used by clinicians of patients included in this study to decide if insulin therapy is necessary.
Increasing c-peptide above 1.52nmol/l is associated with mortality at 3 years independent of BMI. In this cohort c-peptide may be a marker of insulin resistance and adverse metabolic profile. The negative association seen below 1.52nmol/l may be reflective of a different group of patients more likely to have early type 1 diabetes or diabetes with a predominantly insulinopenic aetiology. In this group low c-peptide may confer poor outcome by making stable glycaemia more difficult.
These findings may be helpful in guiding treatment and discussing risk in patients with diabetes where the diagnostic category of diabetes and optimal therapy is unclear.

References

1. The clinical utility of C-peptide measurement in the care of patients with diabetes Jones AG, Hattersley AT. *Diabet. Med.*, 2013