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Beta cell function in type 1 diabetes determined from clinical and fasting biochemical parameters.

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Abstract

Background—Beta cell function in type 1 diabetes is commonly assessed as the average plasma C-peptide concentration (CP_{AVE}) following a mixed meal. Monitoring of disease progression and response to disease-modifying therapy would benefit from a simpler, more convenient and less

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Data availability

Data used for this study can be accessed by application through the TrialNet (www.trialnet.org) and Immune Tolerance Network (www.immunetolerance.org) websites.

Duality of interest

Dr Gitelman received funding from the Immune Tolerance Network (in turn funded by NIAID) for his role as principal investigator of the START trial (ITN-28). Dr Geyer received a grant from NIDDK for unrelated work. No other author has a duality of interest associated with this manuscript.

Contribution statement

JMW devised the study, and analysed the data and prepared the manuscript with NGB, LCG and LCH. All named authors contributed to collection, collation, analysis and interpretation of the data and helped revise the manuscript and approved it for publication. Authors listed in Acknowledgements contributed by performing the TrialNet and ITN clinical trials.

Guarantor statement

JMW takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Suggested Tweet

Measure beta cell function in type 1 diabetes without a meal test. A simpler method was published today @WEHI_research@TheRMH

costly measure. Therefore, we determined if CP_{AVE} could be reliably estimated from routine clinical parameters.

Method—Clinical and fasting biochemical data from eight randomised therapy trials involving participants with recently-diagnosed type 1 diabetes were used to develop and validate linear models to estimate CP_{AVE} and to test their accuracy in estimating loss of beta cell function and response to immune therapy.

Results—A model based on disease duration, body mass index, insulin dose, HbA_{1c}, fasting plasma C-peptide and fasting plasma glucose most accurately estimated loss of beta cell function (area under ROC 0.89; 95% CI 0.87, 0.92) and was superior to the commonly used insulin dose-adjusted HbA_{1c} (IDAA1C) measure (area under ROC 0.72; 95% CI 0.68, 0.76). Model-estimated CP_{AVE} (CP_{EST}) reliably identified treatment effects in randomised trials. CP_{EST}, compared to CP_{AVE}, required only a modest (up to 17%) increase in sample size for equivalent statistical power.

Conclusion—CP_{EST}, approximated from six parameters at a single time-point, accurately identifies loss of beta cell function in type 1 diabetes and is comparable to CP_{AVE} for identifying treatment effects. CP_{EST} could serve as a convenient and economical measure of beta cell function in the clinic and as a primary outcome measure in trials of disease-modifying therapy in type 1 diabetes.

Keywords

Adult; Beta cell function; Children; Clinical trial; Linear model; Immune therapy; Immune Tolerance Network; TrialNet; Type 1 diabetes

Introduction

Therapies targeting pancreatic islet autoimmunity are being tested for their ability to preserve insulin-secreting beta cells and modify the natural history of type 1 diabetes after diagnosis [1]. The widely accepted measure of their efficacy is the average plasma C-peptide concentration during the first two hours of a mixed meal test (CP_{AVE}) [2]. However, the measurement of CP_{AVE} requires ingestion of a liquid meal and at least seven venous blood samples. A more convenient measure would streamline the assessment of beta cell function, particularly when disease-modifying therapies enter routine clinical practice.

In clinical trials, the biologic agents rituximab, teplizumab and abatacept have been shown to improve beta cell function for at least one year in people with recently-diagnosed type 1 diabetes [3–5]. Improved CP_{AVE} in these trials was associated with a decrease in insulin requirement and in HbA_{1c}, suggesting these routine clinical measures may be useful surrogates of beta cell function. Indeed, insulin dosage and HbA_{1c} are used to calculate ‘insulin dose-adjusted HbA_{1c}’ (IDAA1C), which identifies type 1 diabetes children with residual beta cell function [6, 7]. Other studies in children and adults at high risk of developing type 1 diabetes have shown that HbA_{1c}, age and body mass index (BMI) correlate with the C-peptide response to oral glucose [8–10], again suggesting that these routine measures could also serve as useful surrogates of beta cell function in the clinic.

We aimed to develop a simple and reliable model that could accurately estimate CP_{AVE}, based on a combination of routine clinical measures and fasting plasma C-peptide (FCP). Data from eight trials involving people with recently-diagnosed type 1 diabetes [3, 4, 11–16] were used to build predictive models to approximate CP_{AVE} and derive estimates of variability for use in future trial design.

Methods

Study participants gave informed consent if adult and assent if aged under 18 years. All studies were approved by the responsible ethics committee and were carried out in accordance with the Declaration of Helsinki as revised in 2008. Clinical and biochemical data from the TrialNet (TN)-02, −05, −08, −09 and −14 clinical trials (Table 1) [3, 11–13] were extracted from the TrialNet data repository in April 2014. In all of these trials, predominantly white participants were assessed at 0, 3, 6 and 12 months after enrolment and, for TN-08 and TN-14, also at 9 months. Additional data from the Immune Tolerance Network (ITN)-27, −28 and −45 trials [14–16] were extracted in February 2016 and comprised clinical and biochemical measures obtained at the 0-, 6- and 12-month time points. Data from Australian adults with recently-diagnosed type 1 diabetes participating in an ongoing clinical trial of empagliflozin in recently-diagnosed type 1 diabetes (ACTRN12617000016336) were obtained April 2018. Plasma C-peptide concentrations in TrialNet and ITN trials were determined to sensitivities of 0.017 and 0.05nmol/L with TOSOH 2000 and TOSOH 1800 autoanalysers (TOSOH, South San Francisco, CA), respectively. In Australia, C-peptide and HbA_{1c} were measured by Melbourne Health Pathology (Parkville, Australia) using ARCHITECT (Abbott, Wiesbaden, Germany) and Ultra^2 (Primus Diagnostics, Kansas City, MO) kits respectively.

After receipt of the archived data, missing weight, height, insulin dose and HbA_{1c} values were imputed where possible by filling backward or forward from the nearest time point (if within 1 month) or by averaging values either side of the missing value. Undetectable C-peptide concentrations observed in TrialNet and ITN datasets were assigned values of half of the lower limit of detection. Because daily insulin requirements are ~20% lower with insulin pump compared to injection therapy [17], the daily insulin dose of TrialNet participants who reported using insulin pumps was multiplied by 1.25.

Correlation and receiver-operator curve (ROC) analyses were performed using Prism software (v6.0g for Mac; GraphPad, CA). Data modelling was performed using R software v3.3.2 (www.r-project.org). Half of the participants aged<21 years at baseline were randomly assigned to train the Linear Mixed Models to determine the estimated CP_{AVE} (CP_{EST}) and a Validation Dataset, comprising data from the remaining participants aged<21 years at baseline, was used to identify the best models. CP_{AVE} was log-transformed after adding 1 [18] and eight covariates were chosen for inclusion in the prediction model: age, sex, body mass index (BMI), diabetes duration, insulin dose per kilogram body weight, fasting plasma C-peptide (FCP), fasting plasma glucose (FG) and HbA_{1c}. Participant ID was added as a random effect to account for the repeated measurements from the same individual. The ‘dredge’ function in the MuMIn library (v1.15.6) was used to construct 256 models from all possible combinations of variables and these models were ranked by Akaike

Information Criterion (AIC), corrected for a finite sample size. To validate the rankings of the models, the *lmer* function in the lme4 library (v1.1–13) was used to rebuild the models in the Validation Dataset based on the relevant inputs, thereby enabling their AIC values to be determined. To compare treatment arms of clinical trials, mixed models were fitted using *lmer* with a random intercept per participant and adjusted for sex, age and baseline $\log_e(CP_{AVE}+1)$ or $\log_e(CP_{EST}+1)$. The *lmer-Test* package was used to *calculate p* values based on F statistics for treatment comparisons.

Power calculations for the comparison of two groups with equal variance were performed using placebo-group data from the Validation Dataset and Stata (v14.2) software (StataCorp LLC, TX). They were based on the mean and standard deviation (SD) of the $\log_e(CP_{AVE}+1)$ values and a conservative approximation of the SD of $\log_e(CP_{EST}+1)$ values, calculated by combining the variance of $\log_e(CP_{AVE}+1)$ values with an estimated variance of the difference between the $\log_e(CP_{AVE}+1)$ and $\log_e(CP_{EST}+1)$ values according to the formula:

$$SD_{APPROX} = \sqrt{\sigma^2_{[\log_e(CP_{AVE}+1)]} + \sigma^2_{[\log_e(CP_{AVE}+1)]} - [\log_e(CP_{EST}+1)]}$$

A standard trial design that assumed a treatment effect of 50% increase in $\log_e(CP_{AVE}+1)$ at 12 months, two-tailed $\alpha = 0.05$, power = 0.8 and 2:1 (active:placebo) randomisation was used to estimate the required number of participants.

Results

Developing and validating equations to interpolate beta cell function

The baseline characteristics of participants whose data were used to develop the models are presented according to clinical trial and treatment assignment in Table 1. Initially, we used data from participants aged less than 21 years to fit and test linear models for three reasons: i) this age group accounts for over 75% of classic type 1 diabetes presentations [19]; ii) beta cell function declines more slowly in older people [20, 21]; and iii) preservation of beta cell function is more characteristic of younger participants in trials of biologic agents [22]. Half of the participants were randomly assigned to train linear models to estimate CP_{AVE} using one or more of the eight input variables of age, sex, body mass index (BMI), diabetes duration, insulin dose per kilogram, fasting C-peptide (FCP), fasting glucose (FG) and HbA_{1c}. Based on one to eight predictor variables, the Akaike Information Criterion (AIC) was used to identify the most accurate models, hereafter referred to as M1 to M8. The coefficients and associated standard errors of the variables included in the eight models are provided in ESM Table 1. Data from the remaining half of the participants were used to validate the models. Model 6 (M6), which is based on BMI, diabetes duration, insulin dose per kilogram, FCP, FG and HbA_{1c}, was chosen for subsequent testing because its AIC was lowest in the Validation Dataset (Figure 1). Within the Validation Dataset, M6-modelled CP_{AVE} (hereafter called CP_{EST}) and observed CP_{AVE} were strongly correlated (r^2=0.816, p<0.001). The equation for M6 is $\log_e(CP_{EST}+1) = 0.317 + 0.00956\times BMI_{(kg/m2)} - 0.000159\times duration_{(days)} + 0.710\times FCP_{(nmol/l)} - 0.0117\times FG_{(mmol/l)} - 0.0186\times HbA_{1c(\%)} - 0.0665\times insulin_{(U/kg)}$ (ESM Method file).

Because M6 did not require age as an input, we determined if it might also be accurate in the 150 trial participants aged over 21 years whose data were not included in either the Training or Validation datasets (baseline characteristics presented in ESM Table 2). Correlation analysis of data from 554 meal tests performed during the first trial year again demonstrated a strong correlation between CP_{AVE} and CP_{EST} (r^2=0.729, p<0.001). Strong agreement between CP_{AVE} and CP_{EST} (r^2=0.869, p<0.001) was also observed when M6 was applied to data from 31 meal tests from 10 participants (3 females, 7 males, aged 18 to 37 years at diagnosis; ESM Table 3) in an ongoing Australian trial of empagliflozin in recently-diagnosed type 1 diabetes.

Applying CP_{EST} to clinical practice

Receiver-operator curve (ROC) analysis of the Validation Dataset was performed to determine how accurately CP_{EST} identified significant loss of beta cell function at 3, 6 and 12 months after clinical trial entry, defined as a decrease of 7.5% or more of the baseline CP_{AVE} [20, 23]. The ROC curves (Figure 2) show areas under the curve ranging from 0.86 (95% CI 0.81, 0.91) to 0.91 (95% CI 0.87, 0.95). When tested for the ability to identify significant loss of beta cell function at 3, 6 and 12 months compared to baseline, CP_{EST} furnished an area under the ROC (AUROC) of 0.89 (95% CI 0.87, 0.92). The corresponding AUROC for trial participants aged over 21 years was 0.88 (95% CI 0.84, 0.91). We also determined how accurately insulin dose-adjusted HbA_{1c} (IDAA1C), an extant clinical measure of beta cell function [6], identified trial participants who had lost significant beta cell function. The AUROC of the ratio of baseline to 3-, 6- and 12-month IDAA1C was markedly lower at 0.72 (95% CI 0.68, 0.76).

Implications for clinical trial design

The potential suitability of CP_{EST} as an alternative primary outcome measure for clinical trials was then assessed. All available data from participants (children and adults) in the TN-05 rituximab [4], TN-09 abatacept [3] and ITN-27 teplizumab [15] trials were analysed. The major conclusion from each trial, that the active therapy preserved beta cell function over the first year after diagnosis, held regardless of whether CP_{AVE} or CP_{EST} was used to compare treatment groups (Figure 3). We also applied CP_{EST} to data from the other five negative trials and observed similar treatment effects (ESM Figure).

To examine implications for clinical trial design, the standard deviation (SD) of $\log_e(CP_{EST}+1)$ values was conservatively estimated by combining the variance of $\log_e(CP_{AVE}+1)$ values with the variance of the difference between the $\log_e(CP_{AVE}+1)$ and $\log_e(CP_{EST}+1)$ values, as outlined in Methods. Using 12-month placebo-group data from the Validation Dataset from participants aged<21 years, the mean±SDs of $\log_e(CP_{AVE}+1)$ and $\log_e(CP_{EST}+1)$ were 0.320±0.218 and 0.331±0.166, respectively. The variance of the difference between these values was 0.0087, resulting in an estimated SD for $\log_e(CP_{EST}+1)$ of 0.237. When the $\log_e(CP_{AVE}+1)$ mean±SD and the estimated SD for $\log_e(CP_{EST}+1)$ were applied to a standard trial design that assumed a treatment effect of 50% increase in $\log_e(CP_{AVE}+1)$ at 12 months (i.e. Δ=0.160), two-tailed α=0.05 and 2:1 (active:placebo) randomisation, the number of participants required to achieve 80% power was 69 for $\log_e(CP_{AVE}+1)$ and 81, i.e. 17% higher, for $\log_e(CP_{EST}+1)$. When the validation data were combined with placebo-

group data from adult participants aged over 21 years (Combined Dataset), the mean±SD for $\log_e(CP_{AVE}+1)$ and $\log_e(CP_{EST}+1)$ increased to 0.370±0.227 and 0.377±0.174, respectively, and the estimated SD for $\log_e(CP_{EST}+1)$ to 0.247, yielding Δ=0.185 and a requirement for 57 participants if $\log_e(CP_{AVE}+1)$ was the primary outcome measure, and 66, i.e. 16% higher, if $\log_e(CP_{EST}+1)$ was used. If geometric means for $\log_e(CP_{AVE}+1)$ were instead used as the basis for power calculations, the use of $\log_e(CP_{EST}+1)$ as the primary outcome measure required 17% and 13% more participants, respectively, in the context of the Validation Dataset and Combined Dataset.

Discussion

Using six, single time point measures, we describe a model (CP_{EST}) for estimating CP_{AVE} that reliably identifies loss of beta cell function in children and adults with recently-diagnosed type 1 diabetes. The accuracy of CP_{EST} was comparable to that of CP_{AVE} and was superior to that of IDAA1C. When applied to data from the active and placebo arms of three trials of immune modulators that preserved beta cell function, CP_{EST} identified differences in beta cell function over the first year that were similar to those identified using CP_{AVE}. These findings reinforce the strong correlation between FCP and CP_{AVE} in people with recently-diagnosed type 1 diabetes [8, 20] and suggest that the relatively simple biochemical measurement of HbA_{1c}, FCP and FG combined with BMI, insulin dose and disease duration may be sufficient to assess an individual's response to disease-modifying therapy.

CP_{EST} did not require age as an input despite the known strong association of age with beta cell function and with its rate of decline following diagnosis [20, 24]. Whereas age was an input for Model 4, it was not used in the optimal models that incorporated 5 or 6 inputs, which instead used HbA_{1c}, BMI and insulin dose. Clearly these other clinical measures accounted for the effect of age on beta cell function. During model development with the Training Dataset, using age as an input did not always increase accuracy. For example, of the eight models based on four inputs that were more accurate than Model 3, only two (including Model 4) included age as an input. Similarly, of the six models based on five inputs that were more accurate than Model 4, only three used age.

Power calculations, based on a conservative estimate of the SD of $\log_e(CP_{EST}+1)$, indicated that sample size would need to increase by up to 17% if CP_{EST} was used as a primary outcome measure. However, because the SD of $\log_e(CP_{EST}+1)$ was lower than the SD of $\log_e(CP_{AVE}+1)$, it is possible that modelled values are inherently less variable and therefore more accurate measures of beta cell function. This may be explained by the fact that a single fasting test eliminates variation attributable to meal ingestion and multiple sampling. Alternatively, incorporation of fasting glucose in the model may account for day-to-day variation in insulin sensitivity [25], which in turn could alter beta cell function [26] and increase CP_{AVE} variability between meal tests. It will be important to establish the power of CP_{EST} relative to CP_{AVE} in future trials because CP_{EST} is simpler and much more convenient. Even if subsequent testing shows that using CP_{EST} would require a modest increase in sample size, this would need to be balanced against its potential to improve participant recruitment and satisfaction. CP_{EST} also enables more frequent assessment of

beta cell function during a trial and obviates the need to admit participants to a clinical trials unit for a meal test, thereby reducing trial costs.

In the clinical setting, the ability of CP_{EST} to identify individuals who lose beta cell function commends it for routine use in monitoring an individual's beta cell function over time and determine their response to disease-modifying therapy. CP_{EST} is also likely to be useful for larger Phase 3 and 4 trials, and for studies of type 1 diabetes cohorts that aim to identify factors associated with disease progression and the relationship between C-peptide preservation and long-term complications such as hypoglycaemia unawareness and rates of micro- and macro-vascular disease.

IDAA1C is a measure of beta cell function that has gained acceptance in clinical practice because it reliably identifies children with type 1 diabetes who have substantial beta cell reserve, defined as a peak plasma C-peptide response to a mixed meal of greater than 0.3nmol/l (0.9ng/ml) [6, 7]. However, our analysis shows that IDAA1C has relatively poor accuracy for diagnosing significant loss of beta cell function, in accord with an earlier study that showed IDAA1C was not a reliable surrogate of CP_{AVE} during the first 4 years following the diagnosis of type 1 diabetes [21]. Therefore, compared to modelled CP_{EST}, IDAA1C is not suitable for assessing disease-modifying therapy.

Lastly, several caveats are in order. Our cohort comprised participants who were mostly of European descent and had type 1 diabetes for no more than 100 days when CP_{AVE} was first measured. Therefore, the accuracy of our model in other ethnic groups or those with longer-standing type 1 diabetes is uncertain. In addition, despite the model's accuracy in the two adult populations tested, caution should be exercised in applying it to other adult populations until its accuracy is further confirmed. Finally, because FCP and HbA_{1c} were measured at only three laboratories, the generalisability of CP_{EST} should be determined in the context of other laboratories and assay platforms.

In summary, CP_{EST} modelled from six routine clinical and biochemical parameters is an accurate measure of beta cell function in children and young adults with recently-diagnosed type 1 diabetes. The simplicity and convenience of CP_{EST} combined with its superior accuracy when compared to IDAA1C argues for its implementation and further validation in assessing beta cell function in clinical trials and during the course of routine clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AIC	Akaike information criterion
AUROC	area under the receiver operator curve
BMI	body mass index
CI	confidence interval
CP_{AVE}	average C-peptide over two hours following mixed meal challenge
CP_{EST}	estimated CP_{AVE}
FG	fasting glucose
FCP	fasting C-peptide
IDAA1C	insulin dose-adjusted HbA_{1c}

ITN	Immune Tolerance Network
M6	model 6
ROC	receiver operator curve
SD	standard deviation

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Research in context

What is already known about this subject?

- Measuring average C-peptide after a mixed meal, the gold standard measure of beta cell function in type 1 diabetes, is laborious and inconvenient.
- Insulin dose-adjusted HbA_{1c} (IDAA1C), based on HbA1c and insulin dose, is widely used as a simple measure of beta cell function in routine care but this measure is not accurate and is not ideal for assessing responses to disease-modifying therapy.

What is the key question?

- Can a more accurate measure of beta cell function in type 1 diabetes be developed from routine clinical measures?

What are the new findings?

- Estimated C-peptide (CP_{EST}), based on six routine measures, accurately identifies significant loss of beta cell function and reliably identifies treatment effects in randomised trials of immune therapy for type 1 diabetes.
- CP_{EST} is more accurate than IDAA1C

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

- CP_{EST} could serve as a simple measure of beta cell function in routine practice and as a more economical and acceptable primary outcome measure in future trials of disease-modifying therapy.

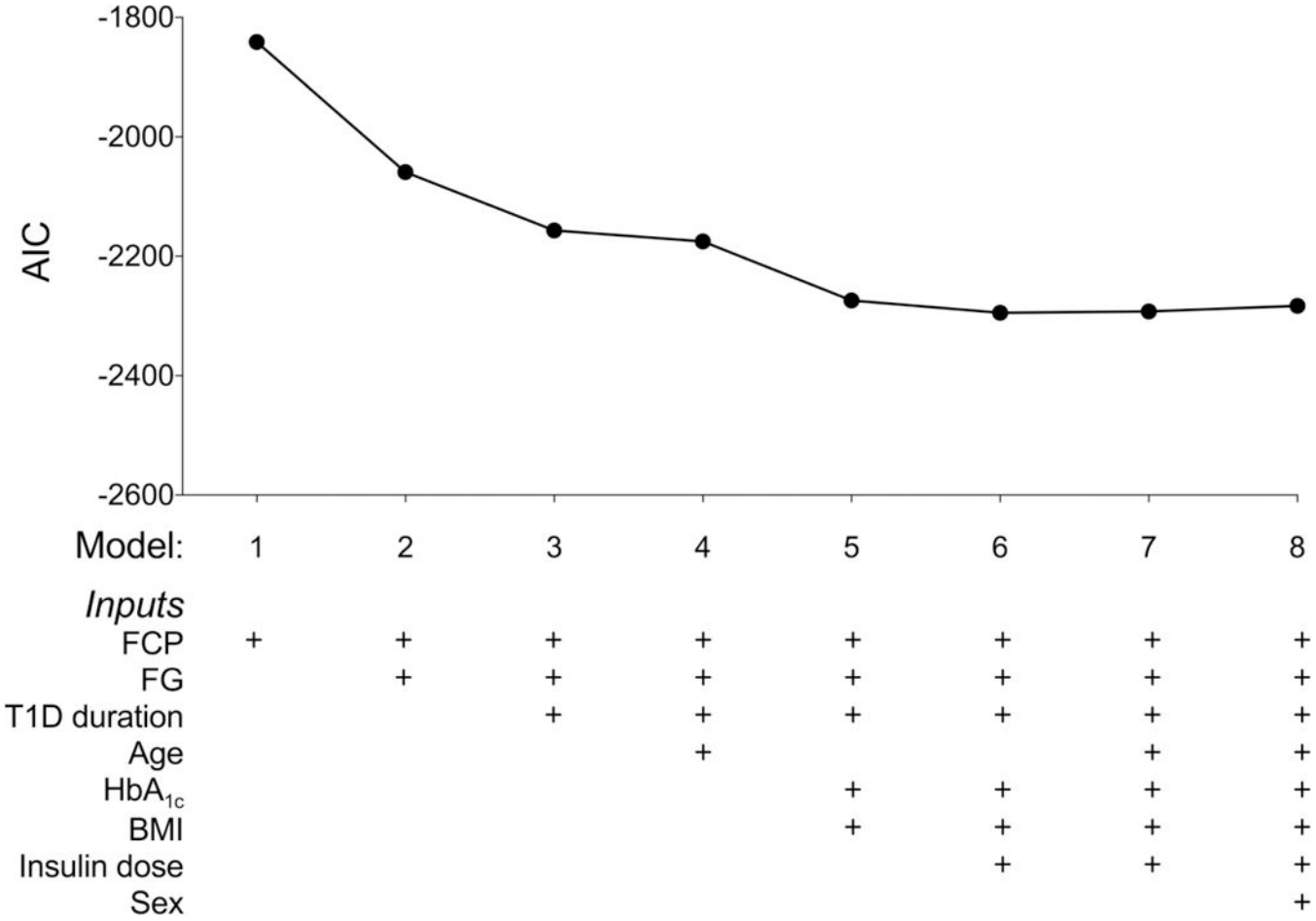

Figure 1. Performance characteristics of eight models to estimate $\log_e(CP_{AVE+1})$ from single-time point data

The components of each model are indicated below the graph of the Akaike Information Criterion (AIC) against the number of model variables in the context of the Validation Dataset. Model 6 was used to calculate CP_{EST} values. FCP: fasting C-peptide; FG: fasting glucose; BMI: body mass index.

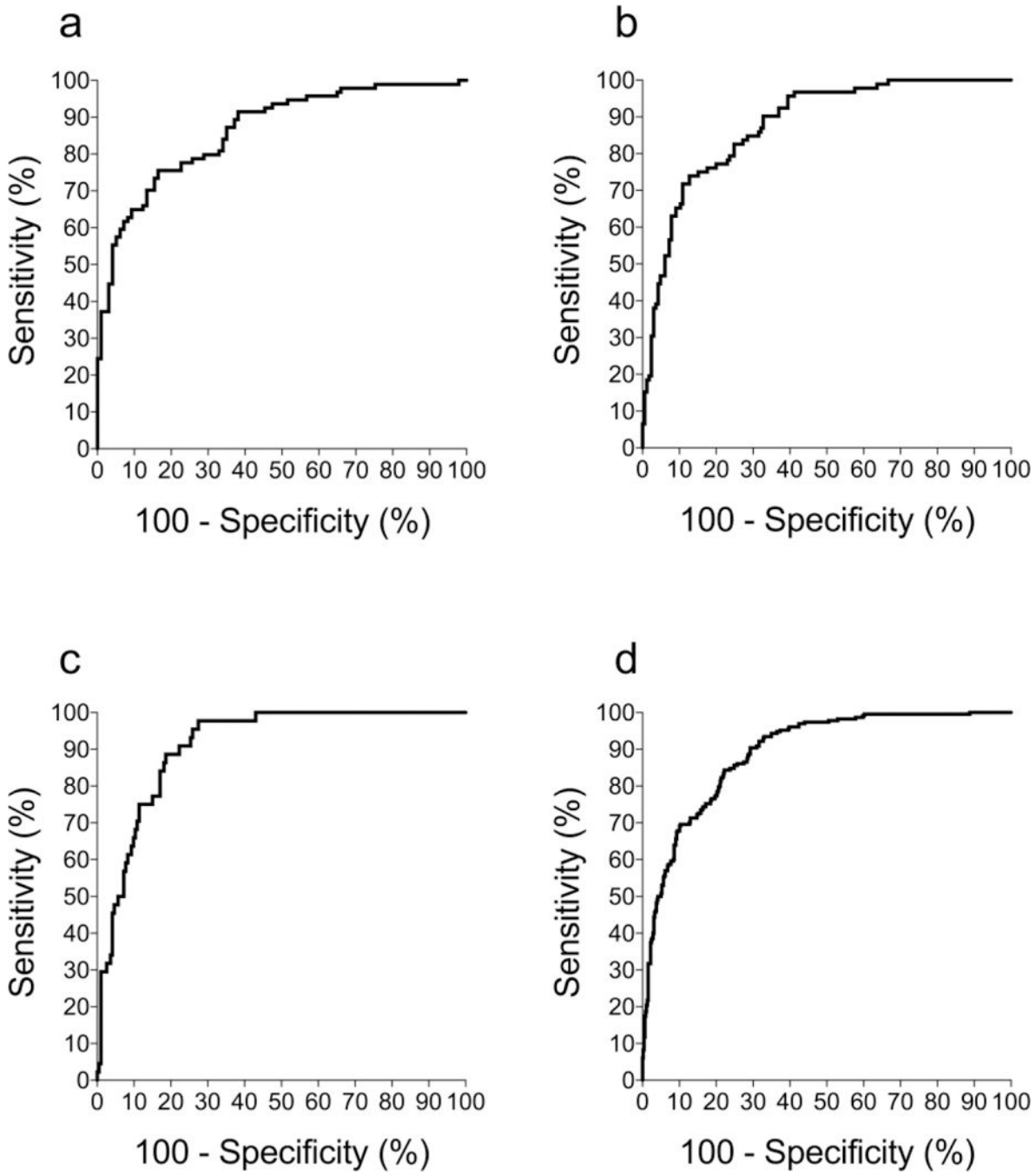

Figure 2. CP_{EST} accuracy

ROC analysis to determine how accurately CPEST identified participants whose CP_{AVE} decreased by more than 7.5% of the baseline value at 3 (a), 6 (b), 12 (c) months after clinical trial entry. The ROC analysis for 7.5% decrease of CP_{AVE} at 3, 6 or 12 months is shown at d. The respective AUROCs (95% CIs) for a-d were 0.86 (0.81, 0.91), 0.88 (0.84, 0.92), 0.91 (0.87, 0.95) and 0.89 (0.87, 0.92). These analyses used the Validation Dataset, which was derived from half of the participant population and was fully independent of the dataset used to develop the CP_{EST} model.

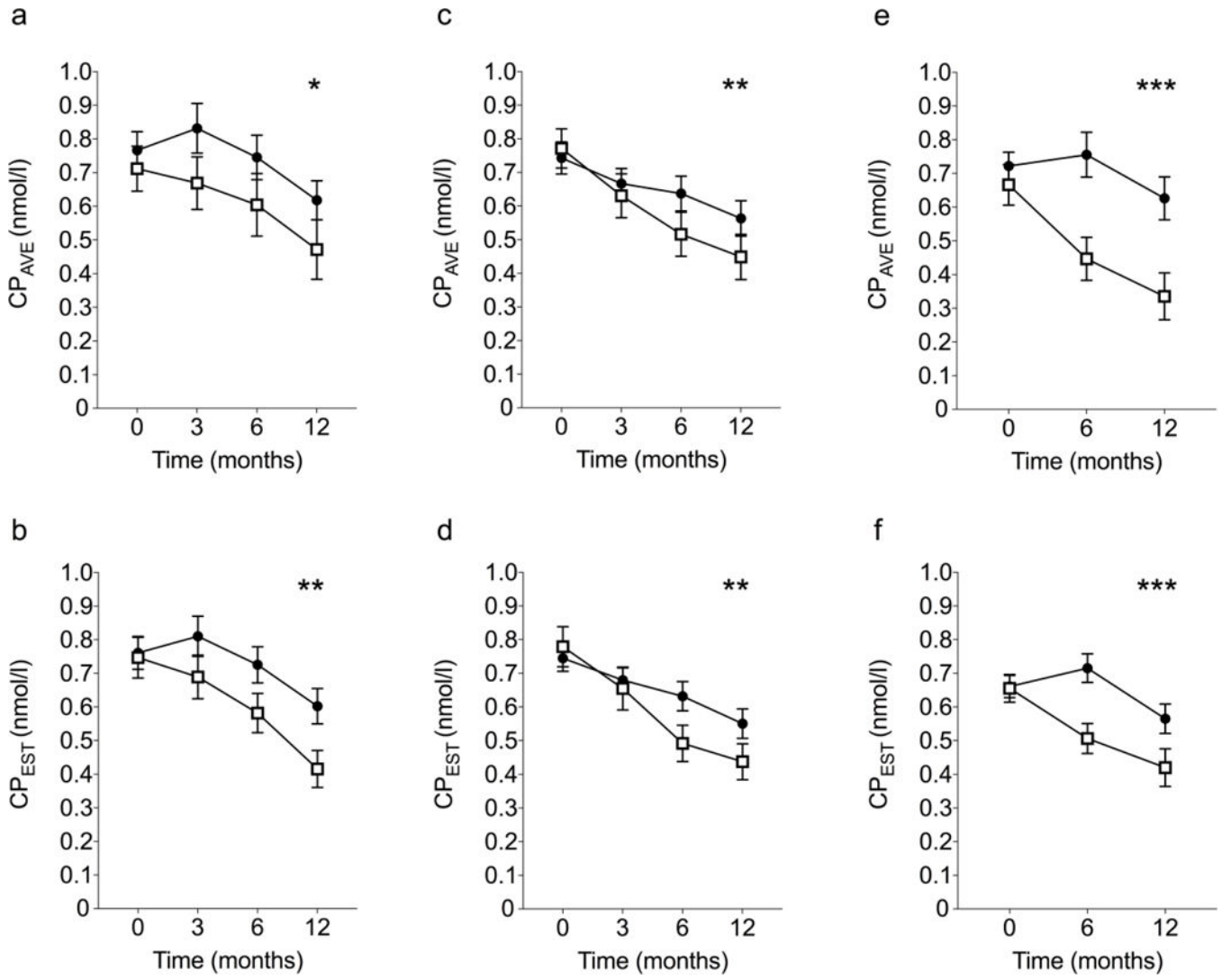

Figure 3. Outcomes of TN-05 (rituximab), TN-09 (abatacept) and ITN-27 (teplizumab) trials according to CP_{AVE} and CP_{EST}

Outcomes for active (filled circles) and placebo (open squares) participants in TN-05 (a,b; 51 active and 29 placebo participants), TN-09 (c,d; 74 active and 31 placebo participants) and ITN-27 (e,f; 54 active and 25 placebo participants) are shown as mean ± SEM. CP_{AVE} measured by meal test is presented in the top panels (a,c,e) and CP_{EST} measured from single time point measures is presented in the bottom panels (b,d,f). Differences between treatment groups were determined using a mixed model that corrects for baseline CP_{AVE} (or CP_{EST}), age and sex, with significance between treatment groups indicated as *, ** and *** for $p<0.05$, <0.01 and <0.001 respectively.

Table 1.

Baseline characteristics of participants aged less than 21 years according to trial and treatment group

Trial	**TN-02**	**TN-05**	**TN-08**	**TN-09**	**TN-14**	**ITN-27**	**ITN-28**	**ITN-45**
Registration number	NCT00100178	NCT00279305	NCT00529399	NCT00505375	NCT00947427	NCT00129259	NCT00515099	NCT00965458
Treatment(s)	Mycophenolate and daclizumab	Rituxumab	GAD s.c. immunisation	Abatacept	Cankinumab	Teplizumab	Anti-thymocyte globulin	Alefacept
Main Trial Outcome	No preservation of CP_{AVE}	Preserved CP_{AVE} at 12 months	No preservation of CP_{AVE}	Preserved CP_{AVE} at 12 months	No preservation of CP_{AVE}	Preserved CP_{AVE} at 12 months	No preservation of CP_{AVE}	No preservation of CP_{AVE}
N	75	58	105	95	66	73	38	29
Percent males	60	64	52	57	53	59	63	59
Percent Hispanic or Latino	4	5	8	6	6	3	6	4
Age (years)	13.5±3.0	13.8±2.7	12.7±4.3	12.6±3.7	11.8±3.6	12.1±2.7	15.9±2.5	16.1±2.1
Body mass index (kg/m^2)	20.6±3.4	21.4±4.2	20.0±3.5	20.5±4.4	20.3±5.0	19.5±4.0	22.4±2.9	22.5±5.7
Diabetes duration (days)	54±21	63±22	63±18	60±18	49±21	49±7	50±20	51±23
HbA_{1c} (mmol/mol)	61±15	56±12	49±11	48±9	53±12	58±12	51±12	55±16
HbA_{1c} (percentage units)	7.7±1.4	7.3±1.1	6.6±1.0	6.5±0.8	7.0±1.1	7.5±1.1	6.8±1.1	7.2±1.5
Insulin dose (U/kg)	0.27±0.26	0.42±0.21	0.40±0.24	0.40±0.26	0.38±0.25	0.42±0.27	0.41±0.26	0.38±0.19
CP_{AVE} (nmol/L)	0.68±0.29	0.75±0.39	0.71±0.30	0.75±0.40	0.64±0.33	0.70±0.31	0.98±0.45	0.83±0.41

Continuous data are mean±SD