



Home Urine C-Peptide Creatinine Ratio Can Be Used to Monitor Islet Transplant Function

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OBJECTIVE

Islet graft function is defined by serum C-peptide in a standardized challenge test. We assessed whether urine C-peptide creatinine ratio (UCPCR) sent from home could provide a viable alternative.

RESEARCH DESIGN AND METHODS

Seventeen islet recipients provided 90-min serum C-peptide (sCP90) and 120-min UCPCR (UCPCR120) samples during 68 interval posttransplant mixed-meal tolerance tests, also posting from home a 120-min postbreakfast UCPCR sample every 2 weeks. UCPCR was compared with a clinical score of islet function, derived from HbA_{1c} and insulin dose.

RESULTS

UCPCR120 and mean home postmeal UCPCR were strongly correlated with sCP90 ($r_s = 0.73$, $P < 0.001$; and $r_s = 0.73$, $P < 0.01$, respectively). Mean home UCPCR increased with clinical score ($r_s = 0.75$; $P < 0.001$) and with graft function defined both by sCP90 >200 pmol/L and insulin independence. UCPCR cutoffs to detect insulin independence and poor graft function were sensitive and specific.

CONCLUSIONS

Home UCPCR provides a valid measure of C-peptide production in islet transplant recipients.

Allogeneic islet transplantation is a therapeutic option for people with type 1 diabetes complicated by recurrent severe hypoglycemia (1,2). Measurement of serum C-peptide after stimulation in a carbohydrate or secretagogue challenge test is a core test of graft function (3–6). Frequency of testing is limited by the time and resources needed for repeated blood sampling particularly when patients live far from the assessment center. An alternative is to measure urine C-peptide creatinine ratio (UCPCR) in a spot urine sample that is stable for 3 days and can be posted from home (7). UCPCR correlates well with serum C-peptide in type 1 and type 2 diabetes (8–10).

We aimed to assess if, in islet transplant recipients, UCPCR was a valid measure of C-peptide during a standard mixed-meal tolerance test (MMTT) and whether home postmeal UCPCR could be used to monitor islet transplant function.

RESEARCH DESIGN AND METHODS

We recruited 17 islet allograft recipients (15 islet transplant alone and 2 islet after kidney) from the U.K. program (11) following ethical approval and informed written

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consent. All participants provided serum and urine samples from interval MMTTs, and 16 posted home samples for analysis (Supplementary Fig. 1).

At the latest time point studied, median (interquartile range [IQR], range) age was 53 (49–59, 36–66) years, BMI 22.6 (21.3–25.8, 15.6–27.9) kg/m², transplanted islet mass 11,254 (8,802–13,231, 5,556–16,734) islet equivalents/kg, time posttransplant 23 (16–28, 11–44) months, insulin dose 0.2 (0.1–0.5, 0–0.9) units/kg/24 h, HbA_{1c} 7.1 (6.5–8.0, 5.7–11.8)% [54 (48–64, 39–105) mmol/mol], creatinine 109 (90–119, 55–197) μmol/L, and 90-min serum C-peptide (sCP90) was 377 (282–1,106, <50–1,760) pmol/L.

In MMTTs performed 1 month and then 3 months post-first transplant (Supplementary Table 1), UCPCR (centrally analyzed in Exeter) from a sample taken at 120 min was compared with sCP90 (3).

Participants were asked to mail UCPCR samples every 2 weeks, taken 120 min after their usual breakfast and insulin dose (if on insulin) (8,12). In addition to the standard Beta-score (13), a clinical score that reflected islet function but did not itself include MMTT parameters was calculated (Supplementary Table 1).

Results were collected prospectively and analyzed at the end of the study. Correlations between UCPCR (both single and mean of three consecutive values) taken within the 3 months before clinical score and sCP90 were assessed. To allow for nonindependence of repeated assessments from a single subject, a weighted average Spearman correlation was used (14). Clinical score across tertiles of mean UCPCR and comparison of UCPCR across groups defined by a combination of sCP90 and insulin independence were compared using Jonckhere's trend test.

RESULTS

In 68 MMTTs, 120-min UCPCR was strongly correlated with sCP90 (Fig. 1A). The mean of the most recent three UCPCR values measured on samples taken at 120 min after the participant's usual breakfast correlated with both standard MMTT sCP90 (Fig. 1B) and clinical score in addition to the standard Beta-score (Supplementary Fig. 2).

When patients were divided into tertiles of mean postmeal UCPCR,

clinical score increased across the three groups (Fig. 1C). When patients were grouped according to poor graft function (sCP90 <200 pmol/L, replacement dose insulin), moderate graft function (sCP90 >200 pmol/L on insulin treatment), and good graft function (insulin independent), there was also a significant increment in UCPCR across the groups (Fig. 1D).

UCPCR results were higher in those who were insulin-independent (Fig. 1E). A cutoff of ≥0.82 nmol/mmol was 100% sensitive and 64% specific for detecting insulin independence. Analysis of impaired graft function using an MMTT serum C-peptide cutoff of 200 pmol/L demonstrated that UCPCR was much lower in the impaired graft function group (Fig. 1F), with a UCPCR of ≤0.35 nmol/mmol being 100% specific and 88% sensitive for detecting impaired graft function.

Single most recent home UCPCR sample correlated with sCP90 and clinical measures, but this was consistently less strong (Supplementary Fig. 3) and more variable (coefficient of variation: 35%) than a mean of three samples (coefficient of variation: 19%).

Reanalysis excluding islet after kidney recipients did not affect correlations, and no overt impact of serum creatinine over the range studied (Supplementary Table 1) was seen (Supplementary Fig. 4).

CONCLUSIONS

In islet transplant recipients, 120-min UCPCR samples provide a valid measure of graft function within an MMTT. Mean of three postmeal urine samples sent from home reflects both serum C-peptide in the MMTT and clinical status. UCPCR may be a useful method to monitor graft insulin production regularly from home.

We have shown strong correlation between UCPCR120 and sCP90 during MMTT in islet transplant recipients. This concurs with published studies in people with type 1 and type 2 diabetes (8–10). Correlations appear to be stronger in type 1 ($r = 0.94$; $P < 0.0001$) (8) than type 2 diabetes ($r = 0.64$; $P < 0.0001$) (10). This may be explained by serum and urine measures of C-peptide being less variable when absolute levels are low. Median UCPCR in islet recipients was 0.73 (IQR 0.28–1.62) nmol/mol,

compared with 0.34 (IQR 0.04–1.41) nmol/mol in the nontransplanted type 1 diabetes study (8).

Results for single and repeated home samples in this study support work showing that a home postmeal sample could be used as a measure of endogenous insulin production (8). By analyzing repeated UCPCRs, we found that a mean of three home samples was less variable than a single sample and had a stronger relationship with clinical and serum markers of islet function. A mean of mailed urine samples may provide a better representation of underlying insulin production in view of intrinsic variability in C-peptide secretion. The nonstandardization of breakfast was designed to make the samples less disruptive for patients and provide a real-world test of home UCPCR collections. A standard breakfast at home could reduce intraindividual variability further and merits further study. Home UCPCR tests are easy to perform and offer the opportunity for repeated measurement of C-peptide without the need for travel to a hospital. This may be of particular use for centers providing care for patients over a wide geographic area.

Analysis of mean home postmeal UCPCRs against clinical features showed correlation with recipient insulin dose, glycemic control, and impaired graft function. Home UCPCR may be most useful in conjunction with other markers of islet function such as insulin dose and glucose values/variability, which could be then used to trigger further investigations to facilitate early detection of changes in graft function.

This study is limited by small numbers and use of repeated tests within individuals. Weighted Spearman correlation was used to account for this but does not assess within individual variation. A larger prospective study with more individuals or observations for each individual patient would be best to test this. We performed a cross-sectional analysis of home UCPCR against clinical score, but a prospective study is needed to assess whether UCPCR can inform treatment decisions in combination with other clinical features. The group of islet patients studied had good renal function, and further work is needed to determine whether UCPCR is valid in those with significant renal impairment.

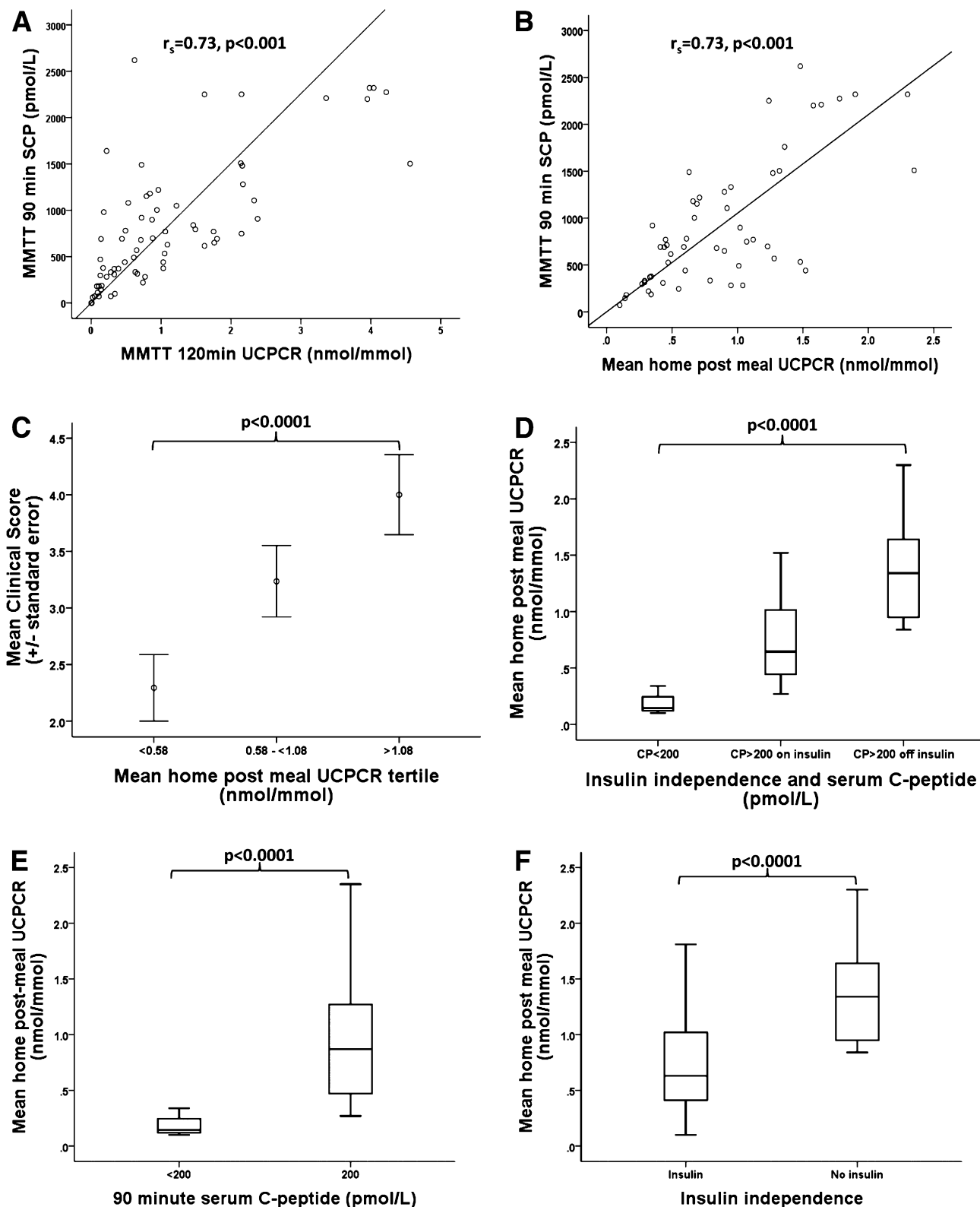


Figure 1—Scatterplots, error bar plot, and box plots demonstrating relationship of UCPCR with serum C-peptide (SCP) and clinical markers of islet transplant function. Relationship of 120-min post-MMTT UCPCR (A) and mean home postmeal UCPCR with sCP90 (B) in islet transplant recipients. Both were correlated with sCP90 ($r_s = 0.73$, $P < 0.001$ [$n = 68$]; and $r_s = 0.73$, $P < 0.001$ [$n = 54$], respectively). C: Relationship of mean home postmeal UCPCR tertile with clinical score. Error bars represent SEM. Clinical score increased as UCPCR group increased ($P < 0.0001$; $n = 51$). D: Box plot showing UCPCR levels across groups defined by increasing SCP and insulin independence, UCPCR increase with SCP and insulin independence ($P < 0.0001$; $n = 51$). E: Box plot of mean home postmeal UCPCR for recipients divided by insulin independence. F: Box plot of mean home postmeal UCPCR in those with sCP90 <200 pmol/L and ≥ 200 pmol/L. Boxes show IQR, and whiskers show range excluding outliers (defined as $> 1.5 \times$ IQR away from Q1 or Q3).

UCPCR offers a method for regular assessment of C-peptide from home even when patients live large distances from their transplant center. The ability to test C-peptide frequently with minimal inconvenience to patients will allow closer monitoring of C-peptide than has previously been possible and could ultimately lead to earlier recognition of changes in β -cell function following islet transplantation.

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Research Centre, Core Biochemical Assay Laboratory, in addition to contributing to data analysis and interpretation. T.J.M. performed all UCPCR analysis, contributed to writing the manuscript, analyzed and interpreted data, and reviewed multiple versions of the manuscript. J.A.M.S. contributed to study design, recruited patients, provided samples for analysis, analyzed and interpreted data, and reviewed multiple versions of the manuscript. A.T.H. analyzed and interpreted data and reviewed multiple versions of the manuscript. All authors contributed to and approved the final version of the manuscript. J.A.M.S. 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.

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