PAMJ Clinical Medicine
Pan African Medical Journals

Research

Post-meal Urinary C-peptide creatinine ratio is a moderate measure of insulin secretion in diabetes patients in Cameroon: results from a cross-sectional study

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Received: 20 Mar 2020 - Accepted: 09 May 2020 - Published: 13 May 2020

Domain: Diabetes care

Keywords: UCPCR, insulin secretion, diabetes patients, Cameroon

Abstract

Introduction: Urinary C-peptide creatinine ratio (UCPCR) measured in urine collected at home after a meal has been shown to correlate strongly with stimulated blood C-peptide in European populations. This association and the clinical utility of UCPCR in a sub-Saharan African clinical setting has not been described before. We aimed to assess performance of UCPCR as a measure of endogenous insulin secretion in Cameroon. **Methods:** UCPCR was measured on two separate days before and after a standard mixed-meal tolerance test (MMTT), after lunch and after supper in 14 patients with diabetes and 14 healthy control individuals. Blood C-peptide was measured serially during a standard 75g oral glucose tolerance test (OGTT) every 30 minutes, on a separate day. The primary outcome was the correlation between stimulated blood C-peptide levels and post-meal UCPCR values. **Results:** stimulated blood C-peptide was significantly lower in participants with diabetes vs controls; median (IQR) 719 (110-999) pmol/l vs 1080 (934-1820) pmol/l, p=0.04. Fasting and post-MMTT UCPCR correlated strongly with stimulated blood C-peptide measurement in participants with diabetes (r= 0.71, p= 0.005) and (r=0.71, p=0.004) respectively. Post-meal UCPCR showed a moderate or poor correlation with stimulated blood C-peptide levels (supper r=0.56, p=0.04, lunch r=0.31, p=0.29). In participants without diabetes, UCPCR showed no relationship with stimulated blood C-peptide (supper r= -0.03, p=0.92, lunch r= -0.06, p=0.83). **Conclusion:** these results suggest that post-meal UCPCR performs less well in this population compared to European populations and may not be useful to assess endogenous insulin secretion in participants without diabetes in Cameroon.

Research | Volume 3, Article 12, 13 May 2020 | 10.11604/pamj-cm.2020.3.12.22419

Available online at: https://www.clinical-medicine.panafrican-med-journal.com/content/article/3/12/full

Introduction

Differences in endogenous insulin secretion are the major determinant of the different treatment requirements between type 1 and 2 diabetes [1]. In patients with insulin treated diabetes, endogenous insulin secretion is best assessed using C-peptide; a peptide secreted in equal amounts with insulin [2]. The longer half-life of C-peptide (20-30 minutes) compared to that of insulin (3-5 minutes); and the negligible hepatic first pass clearance makes C-peptide a more consistent assessment of insulin secretion that the direct measurement of insulin [3]. C-peptide testing can assist clinical diabetes classification and management of patients with insulin treated diabetes and is regularly used to assess insulin secretion in research settings [1]. In a research setting the gold standard method of assessing endogenous insulin secretion is by the measurement of C-peptide during the mixed meal tolerance test (MMTT), with insulin withheld. This is both expensive and time consuming, and results in marked hyperglycaemia [2] and a pragmatic alternative would be desirable. The UCPCR measured on spot urine is stable for 72 hours at room temperature in boric acid preservative, in contrast to blood C-peptide, which when collected in EDTA tube, is stable for a maximum 24 hours [1,4,5]. Studies in a white European population have shown that a post-meal home collection of urine for UCPCR measurement is highly correlated with blood C-peptide in a mixed meal tolerance test in patients with diabetes [6-8]. UCPCR after a post-meal home collection also strongly correlated with serum insulin and blood C-peptide in non-diabetics suggesting its utility in population-based epidemiological studies [9]. However the utility of post-meal UCPCR measurement has never been assessed in a clinical setting in sub-Saharan Africa. We therefore aimed to investigate the association between post-meal UCPCR and a stimulated blood C-peptide measurement in individuals with and without diabetes in Cameroon.

Methods

Study design, setting and population: we carried out secondary analysis on data obtained from 28 participants (14 with diabetes and 14 healthy controls matched for age, sex, and BMI) at the National Obesity Centre of the Yaoundé Central Hospital from August 2009 and March 2010.

Ethical consideration: this study was approved by the National Obesity Centre and the National Ethics Committee for Health and Human Research in Cameroon (No122/CNE/SE/09). All subjects provided a signed written informed consent for all the procedures and biological investigations.

Study visits: on day 1 of investigation, fasting blood and urine samples were collected from the participants in the morning into Sodium fluoride (5mL) tube and sterile urine collection container for blood glucose and C-peptide measurement respectively. All participants received a locally-prepared standard liquid meal (MMTT) containing 33g of carbohydrates, 15g of proteins and 6g of fat corresponding to 240Kcal. Another urine sample was collected 2 hours after the ingestion of the standard meal. These urine samples were stored within 24 hours at -20°C for C-peptide and creatinine determination. On day 2 of the investigation, each participant collected at home a 2 hour post-meal urine sample after lunch and supper in a sterile urine collection container provided by the investigators. The participant brought their home collected urine samples the following day to the research facility. On day 3 of investigation, each participant received the same standard meal (mixed-meal tolerance test) as in day 1 with urine collection before and 2 hours after the test. On day 4 of investigation, all participant underwent an oral glucose tolerance test (OGTT) after an overnight fast of 8 hours following standard procedures with measurement of the

stimulated blood C-peptide levels at 30, 60, 90 and 120 minutes post ingestion of the glucose load.

Laboratory analysis: both serum and urine C-peptide were measured by direct electrochemiluminescence using an automated Roche diagnostics (Manheim, Germany) E170 with intra-assay CV of 3.7 - 6.6% and inter-assay CV of 4.4 - 8.0%. Urinary creatinine was measured by kinetic method (Jaffe´s method). These analyses were performed at Royal Devon & Exeter Hospital Blood Sciences Department, United Kingdom.

Calculations and definitions: UCPCR was calculated as the ratio of Urinary C-peptide (nmol/L)/ creatininuria (mmol/L). The 2 hours (120 minutes) stimulated (OGTT) blood C-peptide levels was considered as the standard measure of insulin secretion for test comparisons [9].

Statistical analysis: we compared the clinical characteristics and UCPCR values between the 2 groups (diabetes vs controls) using the Mann Whitney U test and correlation coefficient between the post-meal UCPCR and stimulated blood C-peptide after the OGTT using Spearman´s rank correlation.

Funding: JCK is supported by NIHR grant reference 17/63/131. A.G.J. is supported by an NIHR Clinician Scientist award (17/0005624). TJM is an NIHR Senior Clinical Senior Lecturer. Data analysis and article preparation was supported by the NIHR Global Health Group at University of Exeter: Improving outcomes in sub-Saharan African diabetes through better diagnosis and treatment (grant reference 17/63/131). The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or Department of Health. The funders had no role in any part of the study or in any decision about publication.

Results

Clinical and biophysical characteristics of the participants: participant characteristics are shown in Table 1. Participants with diabetes had a median age of 29 (20-51) years with a median duration of diabetes of 2 (2-4) years and 07/14 were insulin treated. Stimulated blood C-peptide was significantly lower in participants with diabetes vs controls; 719 (110-999) pmol/l vs 1080 (934-1820) pmol/l, p=0.04.

Impact of stimulus on UCPCR levels: Table 1 and Figure 1 show the UCPCR levels at different meal points in participants with diabetes and healthy controls. UCPCR was substantially higher after the mixed meal tolerance test than when measured after a home meal or fasting (Figure 1).

UCPCR is correlated with blood C-peptide in participants with diabetes but not without diabetes: correlations of stimulated (120 minutes OGTT) blood C-peptide with UCPCR measures are shown in Figure 2. Fasting UCPCR correlated strongly with stimulated blood C-peptide measurement in participants with diabetes (r= 0.71, p= 0.005) but showed no correlation in participants without diabetes (r= -0.12, p= 0.69). The 2 hours post MMTT UCPCR also correlated strongly with stimulated blood C-peptide measurements in participants with diabetes (r= 0.71, p= 0.004) but showed no correlation in healthy controls (r= -0.34, p= 0.24).

Post-meal (supper) UCPCR showed a moderate significant correlation with stimulated blood C-peptide levels with r=0.56, p= 0.04 in participants with diabetes while there was no significant correlation between post-lunch UCPCR and stimulated blood C-peptide levels (r=0.31, p=0.29) in the same group of patients with diabetes.

Discussion

We have shown that fasting UCPCR and post-MMTT UCPCR are strongly correlated with stimulated blood C-peptide in Cameroonian participants with diabetes. However a UCPCR sample collected at home was moderately (supper) or poorly (lunch) correlated with stimulated blood C-peptide. Fasting or post MMTT UCPCR may therefore offer a practical means of assessing endogenous insulin secretion in patient with diabetes, but use of post home meal samples is not supported by these findings. In contrast to those with diabetes, in participants without diabetes these tests were poorly related to stimulated blood C-peptide.

This is the first study to formally investigate the utility of post-meal UCPCR measurements against a standard stimulated blood C-peptide as a surrogate of insulin secretion in a sub-Saharan African clinical setting. Previous studies in European population have shown that UCPCR is strongly correlated with blood C-peptide in insulin treated patient with diabetes whether collected after MMTT ($r= 0.64$, $p= <0.001$) or after a home meal ($r=0.54$, $p= <0.001$), however correlations are lower in those treated without insulin and with renal impairment [6].

However, we found a lower correlation with home meals than previously described. This may potentially result from differences in meals between populations, including inclusion of low numbers of patients with insulin treatment and severe insulin deficiency, or other population differences such as presence of renal dysfunction, which is common in the many sub-Saharan African populations [10] and not assessed this cohort. It is also possible that sample stability may have affected home results (see limitations below).

A key limitation of this study is the small sample size, with only 7 insulin treated participants we are unable to fully examine test performance in the patient group where C-peptide measurement has clinical utility (insulin treated diabetes), or examine performance of UCPCR for clinically relevant thresholds such as the suggested test cut off for differentiating type 1 and 2 diabetes (600pmol/L) [1]. Another limitation is that urine samples were also not collected in boric acid urine collection containers given that UCPCR stability is lower in plain samples. While previous research in Europe suggests stability of 24 hours in plain samples, it is possible that stability may be lower at the higher temperatures seen in Cameroon [4].

Conclusion

Our findings suggest that UCPCR may not be a robust method of assessing endogenous insulin secretion in non-diabetic individuals in Cameroon and that the use of home meal stimulation may also not be appropriate in patients with diabetes. Further larger studies using appropriate stable urine collection techniques are needed in patients with insulin treated diabetes to accurately determine whether home UCPCR samples can be used to robustly detect severe insulin deficiency in this population.

What is known about the topic

- Endogenous insulin secretion is best assessed using C-peptide; a peptide secreted in equimolar concentration with insulin from the beta cells of pancreatic islets;
- The gold standard method of assessing endogenous insulin secretion in patients with diabetes is by measuring C-peptide during the mixed meal tolerance test (MMTT). This method is however expensive, time consuming and mostly used in research;

- Urinary C-peptide creatinine ratio (UCPCR) offers a more simple and practical measure of endogenous insulin secretion in clinical settings.

What this study adds

- Fasting UCPCR and post-MMTT UCPCR are strongly correlated with stimulated blood C-peptide in patients with diabetes in Cameroon;
- Post meal UCPCR only moderately correlates with stimulated blood C-peptide in patients with diabetes;
- UCPCR performs poorly when compared to stimulated blood C-peptide in non-diabetic participants and therefore may not be used to assess endogenous insulin secretion in the general population

Competing interests

The authors declare no competing interests.

Authors' contributions

JCK, VPM and ES conceived the study. VMP collected the research data, VMP and TJM performed the biochemical examinations, JCK and AJ analyzed the data. JCK, AJ, TJM, ES wrote the manuscript. JCK, AN, WN, AJ, TJM, ES reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgments

All the staffs of the National Obesity Centre at the Yaoundé Central Hospital who contributed to patient orientation during this study.

Table and figures

Table 1: clinical and biophysical characteristics of the participants

Figure 1: differences in post MMTT UCPCR and post-lunch and post-supper UCPCR values in participants with diabetes

Figure 2: correlations between blood C-peptide levels and UCPCR values

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Table 1: clinical and biophysical characteristics of the participants			
Variables	**Diabetes (n=14)**	**Controls (n=14)**	**P value**
Age (years)	29 (20-51)	28 (23-53)	0.81
Gender (F/M)	5/9	5/9	/
Number of insulin-treated patients	7/14	/	/
Duration of diabetes (years)	2 (2-4)	/	/
SBP (mmHg)	126 (113-137)	112 (105-127)	0.09
DBP (mmHg	79 (67-85)	71 (68-83)	0.27
BMI (kg/m^2)	24.5 (22.1-20.9)	24.2 (22.5-27.0)	0.67
Waist circumference (cm)	79 (77-89)	82 (76-92)	0.59
Fasting glycaemia (mg/dL)	6.66 (6.30-10.44)	5.7 (5.35-5.94)	0.001
HbA1C (%)	10.5 (6.5-12.8)	/	/
Fasting UCPCR (nmol/mmol)	0.30 (0.18-0.51)	0.51 (0.29-0.68)	0.07
2h Post MMTT UCPCR (nmol/mmol)	1.11 (0.42-1.44)	1.63 (0.99-1.74)	0.08
Post Lunch UCPCR (nmol/mmol)	0.63 (0.36-1.34)	0.75 (0.27-1.75)	0.61
Post Super UCPCR (nmol/mmol)	0.66 (0.28-0.96)	0.96 (0.62-1.36)	0.24
Fasting blood C-peptide (pmol/L)	255 (55-341)	313 (263-412)	0.10
Stimulated (OGTT) blood C-peptide (pmol/L)	719 (110-999)	1080 (934-1820)	0.04

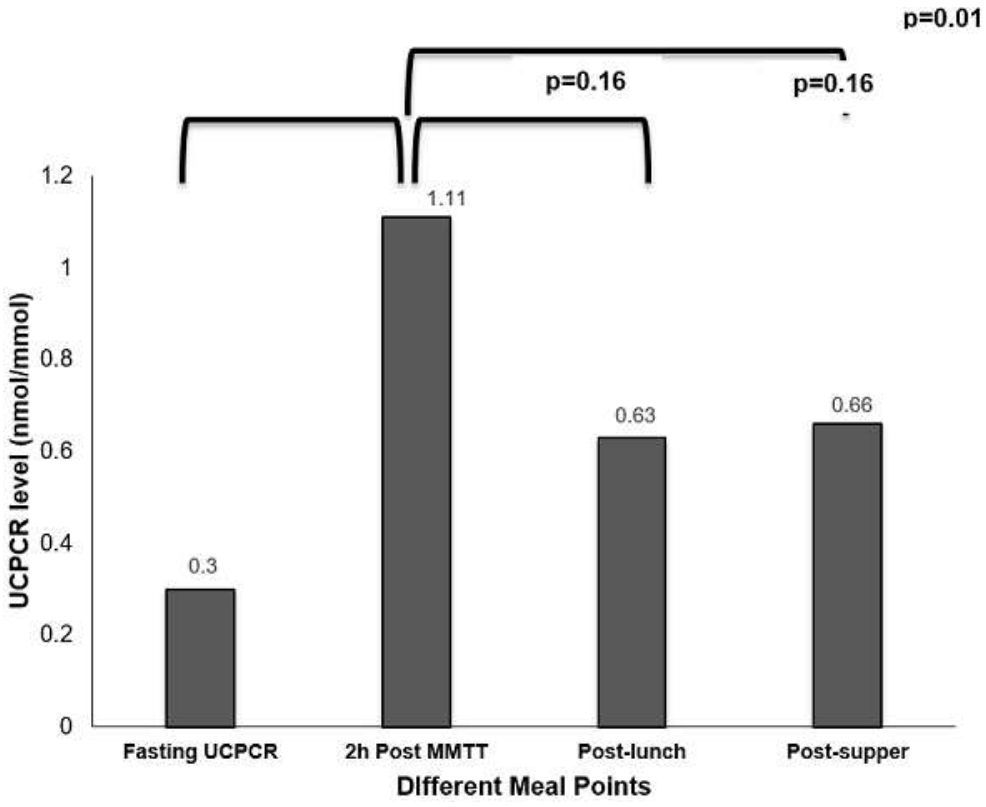

Figure 1: differences in post MMTT UCPCR and post-lunch and post-supper UCPCR values in participants with diabetes

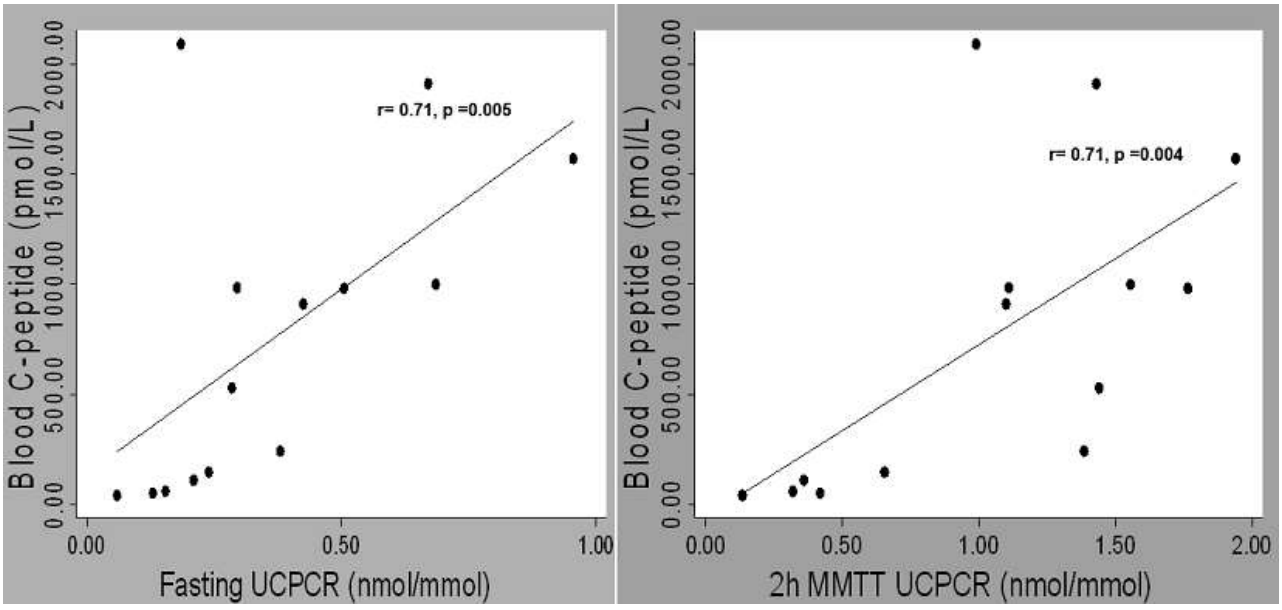

Figure 2: correlations between blood C-peptide levels and UCPCR values