

Basal and Postglucagon C-Peptide Levels in Ethiopians with Diabetes

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OBJECTIVE — To study basal C-peptide (BCP) and postglucagon C-peptide (PGCP) levels in Ethiopians with diabetes.

RESEARCH DESIGN AND METHODS — A total of 56 subjects with type 1 diabetes, 97 subjects with type 2 diabetes, and 50 control subjects were recruited from a hospital in Ethiopia. BCP was determined in all subjects and PGCP in 86 subjects.

RESULTS — Mean (\pm SEM) BCP, PGCP, and the increment after glucagon in type 1 diabetic subjects (0.14 ± 0.04 , 0.22 ± 0.11 , and 0.08 ± 0.05 nmol/l, respectively) were lower ($P < 0.001$) than those in type 2 diabetic subjects (0.66 ± 0.04 , 1.25 ± 0.10 , and 0.56 ± 0.06 nmol/l, respectively) or control subjects (0.54 ± 0.04 , 1.52 ± 0.26 , and 1.11 ± 0.24 nmol/l, respectively). The mean BCP level was higher in type 2 diabetic subjects than control subjects ($P = 0.015$), whereas the mean increment was lower ($P = 0.005$). Insulin-treated type 2 diabetic subjects, compared with non-insulin-treated type 2 diabetic subjects, had lower mean BCP (0.55 ± 0.08 nmol/l [$n = 37$] vs. 0.73 ± 0.04 [$n = 60$], $P = 0.001$), lower PGCP (0.97 ± 0.20 nmol/l [$n = 18$] vs. 1.40 ± 0.11 [$n = 35$], $P = 0.010$), and a lower C-peptide increment (0.34 ± 0.06 [$n = 18$] vs. 0.67 ± 0.07 nmol/l [$n = 35$], $P = 0.003$). In both the type 1 and type 2 diabetic groups, those with BCP levels < 0.2 nmol/l had lower BMI than those with higher BCP levels ($P = 0.023$ and $P < 0.001$, respectively).

CONCLUSIONS — Combined with clinical criteria, C-peptide levels are good discriminators between type 1 and type 2 diabetes in Ethiopians and may also be useful in identifying subjects with type 2 diabetes who require insulin therapy. There is a subgroup of type 2 diabetic subjects with features of type 1 diabetes.

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Determination of fasting basal C-peptide (BCP) and stimulated (with glucose or glucagon) C-peptide levels has been used to determine β -cell secretory activity. The C-peptide response to glucagon correlates well with the β -cell response to mixed meals or to other stimuli commonly used to characterize endogenous insulin secretion and has the

advantage of shorter duration and simple standardization (1).

Several studies used these tests to determine whether β -cell function shows concordance with the clinical classification of diabetes into type 1 and type 2 diabetes as described by the World Health Organization (WHO) in 1980 (2) and 1985 (3) and the National Diabetes Data Group (NDDG)

in 1979 (4). Although different thresholds for BCP and postglucagon C-peptide levels (PGCP) have been used, most studies concluded that there is a high degree of concordance, ranging between 86 and 89%, between C-peptide levels and type of diabetes (5–8). Some (5,8) have suggested that the postglucagon level is the better discriminator. Moreover, BCP and particularly PGCP levels have been found to predict the need for insulin treatment in type 2 diabetes (5,7–12).

Studies from South Africa (13,14), Nigeria (15), Uganda (16), Ethiopia (17), and Tanzania (18) have found that Africans with type 2 diabetes seem to have comparatively lower levels of C-peptide than those reported in Caucasians, East Indians, or African-Americans. In Ethiopian subjects, Abdulkadir et al. (17) reported that basal as well as glucose-stimulated C-peptide levels were highest in type 2 diabetic subjects, followed by control subjects, those with suspected malnutrition-related diabetes, and type 1 diabetic subjects.

The limitations of most of those studies in African populations include relatively small sample sizes (ranging between 24 and 57 subjects) and failure to differentiate clearly between type 1 and type 2 diabetes. In one recent larger ($n = 310$) study (19), control subjects were not included.

Our objective was to determine BCP and PGCP levels in a larger sample size that consisted of three groups, type 1 diabetic, type 2 diabetic, and control subjects, in an Ethiopian population. We examined whether C-peptide levels discriminate among the WHO/NDDG categories of diabetes and whether C-peptide levels help to identify a subgroup of subjects with type 2 diabetes who require insulin treatment. Lastly, we addressed the issue of whether Ethiopians with type 2 diabetes are hyperinsulinemic.

RESEARCH DESIGN AND METHODS

Subjects

From May to July 1993, 56 subjects with type 1 diabetes and 97 subjects with type

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Abbreviations: BCP, basal C-peptide; NDDG, National Diabetes Data Group; PGCP, postglucagon C-peptide levels; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

2 diabetes (37 on insulin, 53 on oral agents, and 7 on diet alone) from the Diabetes Clinic of the Black Lion Hospital, Addis Ababa University, Addis Ababa, Ethiopia were included in the study. All subjects with either type 1 or type 2 diabetes who volunteered to participate in the study and were available for laboratory examination were included. None took a morning dose of insulin or oral agents on the day of examination.

Based on the WHO criteria (2,3), subjects with acute onset of classical symptoms who required insulin therapy from the onset to control hyperglycemia or had an episode of ketoacidosis during the course of their illness were classified as type 1 diabetic subjects. The rest were classified as type 2 diabetic subjects.

In addition, 50 nondiabetic subjects were included as control subjects. These were healthy medical student volunteers ($n = 6$) or outpatients in the hospital being treated for minor medical problems ($n = 44$).

Collection of information

After obtaining informed consent from each subject, demographic information was collected by personal interview. Additional clinical information was collected from medical records.

Body measurements, ratios, and indexes

Blood pressure, height, weight, and waist and hip circumferences were measured. Previously described techniques for measuring waist and hip circumferences were used (20). BMI and waist-to-hip ratio (WHR) were calculated.

C-peptide measurements and the glucagon test

A sample of 5–10 ml venous blood was withdrawn from each subject in the fasting state for BCP measurement. In 86 subjects (22 type 1 diabetic, 53 type 2 diabetic, and 11 control subjects), the glucagon test was performed by injecting 1 mg glucagon intravenously, followed 6 min later by a second blood-draw of 5–10 ml from a separate venous site. The selection of subjects for the glucagon test was based simply on their agreement to have the test done.

After centrifugation of the blood samples, the sera were isolated and then frozen at -20°C . In September 1993, the transportation of the sera to Germany was

performed using dry ice-filled containers at temperatures reaching -70°C . Within <24 h, the specimens reached their destination and were kept frozen at -20°C .

Laboratory analysis

The C-peptide assays were performed within 1–2 months of receipt at the Endocrine Laboratory of the Center for Internal Medicine, University of Leipzig, Leipzig, Germany, using radioimmunoassay kits from Diagnostic Systems Laboratories (Webster, TX). Assays were performed in duplicate using the 4-h assay protocol. The assays were run in several batches with deliberate mixing of groups. In those subjects in whom the glucagon test was performed, both the basal and postglucagon sera of each patient were simultaneously analyzed in the same assay run. The performance characteristics of the assay were: minimum detection limit of 0.003 nmol/l, intra-assay variability of $<10\%$, and interassay variability of $<9\%$.

Statistical analysis

Quantitative data were summarized by means, SEs, and percentiles, whereas frequencies and percents summarized the categorical data. Group comparison with respect to quantitative and categorical data were performed using the Wilcoxon's rank-sum test and χ^2 test, respectively. The cutoff values of 0.2 nmol/l for BCP and 0.32 nmol/l for PGCP were used in assessing concordance with the clinical classification of diabetes. These values, which have been shown by Gjessing et al. (5) to be good discriminators between type 1 and type 2 diabetes, were selected after demonstrating their agreement with our own receiver-operator curve data.

RESULTS

Subject characteristics

In the group with type 2 diabetes, there was a female preponderance, whereas in the group with type 1 diabetes and the control group, there was a male preponderance. Subjects with type 2 diabetes were on average older than those with type 1 diabetes and control subjects. Type 2 diabetic subjects were relatively more obese (higher BMI) and had a greater degree of upper-body obesity (higher WHR) than type 1 diabetic or control subjects. In all three groups, women were more obese (higher BMI) but had a lesser degree of

upper-body obesity (lower WHR) than men (data not shown). The mean systolic and diastolic blood pressure readings were higher in type 2 diabetic subjects than type 1 diabetic or control subjects. Of the 97 subjects with type 2 diabetes, 37 were on insulin, 53 were on oral agents, and 7 were exclusively on diet. Comparison of socioeconomic variables such as occupation and educational level between control and diabetic subjects (both groups) did not reveal any significant differences (data not shown), suggesting that they had similar nutritional status (Table 1).

Comparison of baseline characteristics of the 86 subjects who had the glucagon test with the 117 who did not revealed no significant differences, with the exception of age in the type 2 diabetic group, in which those who had the glucagon test were younger (48.6 ± 1.46 vs. 53.7 ± 1.7 years, $P = 0.04$).

Comparison of C-peptide levels among the three groups of subjects

The distribution of BCP values in the three groups of subjects is shown in Fig. 1A. Whereas 96% of control subjects and 93% of subjects with type 2 diabetes had BCP levels ≥ 0.2 nmol/l, only 16% of those with type 1 diabetes attained this level.

Figure 1B shows the PGCP levels and Fig. 1C shows the C-peptide increments in the 86 subjects who had the glucagon test performed. All control subjects, 92% of type 2 diabetic subjects, and 14% of type 1 diabetic subjects had PGCP levels ≥ 0.32 nmol/l. With the exception of a single control subject, all subjects with PGCP levels ≥ 0.32 nmol/l had BCP values ≥ 0.2 nmol/l (data not shown). In type 2 diabetic subjects, BCP level was positively correlated with BMI and duration of diabetes but had no correlation with age, sex, and systolic blood pressure (data not shown).

C-peptide level comparisons in type 2 diabetic subjects according to type of treatment

Of the 97 subjects with type 2 diabetes, 37 were on insulin therapy, whereas 60 were managed without insulin. As compared with the non-insulin-treated subgroup, the insulin-treated subgroup had lower BCP levels, lower PGCP levels, as well as a lower C-peptide increment (Table 2).

Table 1—Characteristics of the three groups of subjects

	Type 1 diabetic subjects (A)	Type 2 diabetic subjects (B)	Control subjects (C)	P
n	56	97	50	
Sex (M/F)	34/22	37/60	29/21	A vs. B = 0.011 A vs. C = 0.844 B vs. C = 0.024
Age (years)	30.0 ± 1.4	51.5 ± 1.0	29.0 ± 1.5	A vs. B <0.001 A vs. C = 0.502 B vs. C <0.001
BMI (kg/m ²)*	20.2 ± 0.4	24.6 ± 0.5	20.3 ± 0.4	A vs. B <0.001 A vs. C = 0.992 B vs. C <0.001
WHR*	0.88 ± 0.01	0.94 ± 0.01	0.83 ± 0.01	A vs. B <0.001 A vs. C <0.001 B vs. C <0.001
Systolic blood pressure*	114.8 ± 2.8	133.7 ± 2.1	120.2 ± 2.1	A vs. B <0.001 A vs. C = 0.015 B vs. C <0.001
Diastolic blood pressure*	76.4 ± 1.3	81.4 ± 1.1	78.7 ± 1.8	A vs. B = 0.003 A vs. C = 0.301 B vs. C = 0.079

Data are means ± SEM. *Although statistically significant differences were observed among groups, multivariate analysis indicated that these differences were not statistically significant when adjusted for differences in age, sex, and/or BMI.

BMI in different BCP categories

In both the type 1 and type 2 diabetic groups, subjects with BCP levels <0.2 nmol/l had lower mean BMI than those with higher levels. All six type 2

diabetic subjects with BCP levels <0.2 nmol/l were on insulin therapy (Table 3).

CONCLUSIONS— To our knowledge, this is the first large study to analyze

the basal and stimulated C-peptide levels in groups of type 1 diabetic, type 2 diabetic, and control subjects in an African population. Our findings demonstrate that C-peptide levels clearly distinguish, albeit not completely, between type 1 and type 2 diabetic subjects. Multivariate analysis revealed that sex was not correlated with C-peptide levels; therefore, it is unlikely that the differences in C-peptide levels among the groups are due to differences in sex distribution.

The fact that virtually all subjects with PGCP values ≥0.32 nmol/l also had BCP values ≥0.2 nmol/l indicates the equivalence of both cutoffs in differentiating between type 1 and type 2 diabetes. Using these cutoffs, however, there was discordance between C-peptide levels and type of diabetes in 14–16% of type 1 diabetic subjects and 7–8% of type 2 diabetic subjects. The most likely explanation for the discordance is misclassification using the WHO clinical criteria. In particular, all of the six subjects with type 2 diabetes having BCP <0.2 nmol/l, who were on insulin and had lower BMI values, may have been misclassified.

The six type 2 diabetic subjects having BCP levels <0.2 nmol/l had a lower mean BMI value compared with that of subjects with higher BCP levels, and all were on insulin therapy. Moreover, in another study in which we tested for antibodies against GAD (21), 2 of those same

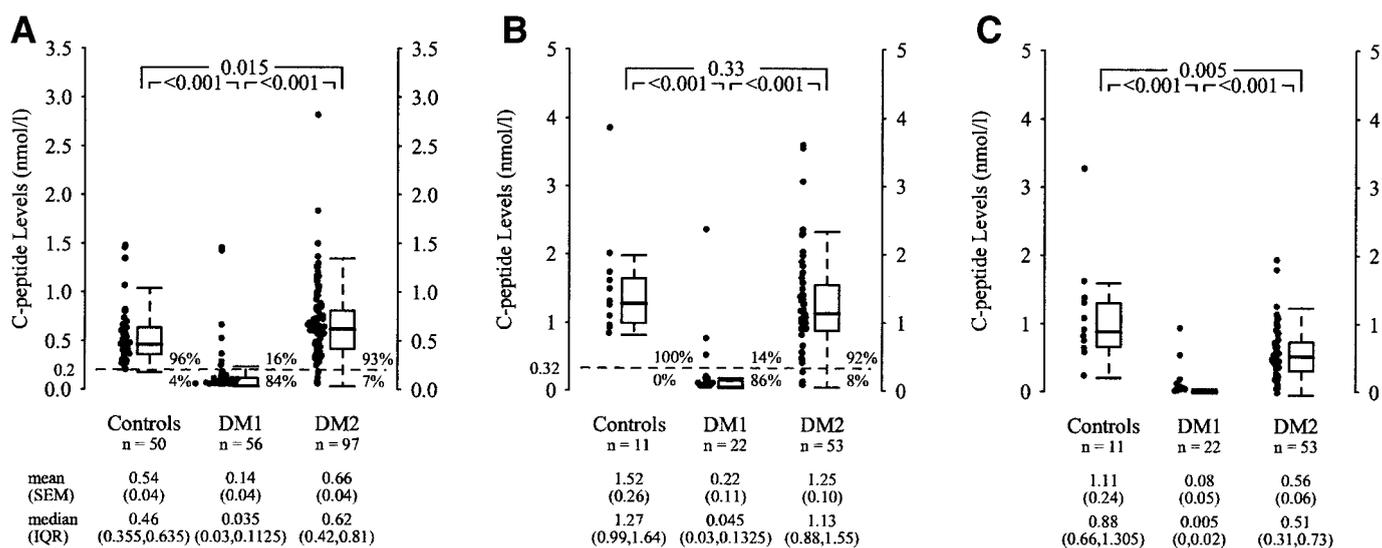


Figure 1—Distribution of C-peptide levels (nmol/l) in the three groups of subjects. A: BCP levels. B: PGCP levels. C: Increment in C-peptide levels after glucagon. In A and B, within each group, percentages above and below the cutoff values of 0.2 and 0.32 nmol/l, respectively, are displayed. Box and whisker plots: the box gives the median as well as the 25th and 75th percentiles (denoted q1 and q3), whereas the whiskers extend to the furthest observation within 1.5 × (q3 – q1) of the adjacent quartile. DM1, type 1 diabetic subjects; DM2, type 2 diabetic subjects; IQR, interquartile range.

Table 2—C-peptide levels (in nmol/l) in subjects with type 2 diabetes according to type of treatment

	Insulin	Oral agents and/or diet	P
BCP	0.55 ± 0.08 (37)	0.73 ± 0.04 (60)	0.001
PGCP	0.97 ± 0.20 (18)	1.40 ± 0.11 (35)	0.010
Increment	0.34 ± 0.06 (18)	0.67 ± 0.07 (35)	0.003

Data are means ± SEM (n).

6 subjects were positive, whereas only 1 of 80 subjects with BCP ≥ 0.2 nmol/l was positive. These findings are in agreement with observations made elsewhere regarding the existence of a subgroup of type 2 diabetes that exhibits several features of type 1 diabetes (6,22), which has been named latent autoimmune diabetes in adults (23).

The mean BCP level in type 2 diabetic subjects was only marginally higher (though statistically significant) than that of control subjects. Only 4 of the 97 subjects with type 2 diabetes (4%) had C-peptide values above the upper limit of normal (1.3 nmol/l). These findings suggest that hyperinsulinemia, as estimated by C-peptide measurements, may not be a major feature of type 2 diabetes in Ethiopians. In contrast, results from the developed world as well as from other ethnic groups (24–26) and African-Americans (27) demonstrate that type 2 diabetic subjects are characterized by hyperinsulinemia. On the other hand, studies from Africa (13,14,27,28) indicate that African blacks (with and without diabetes) have lower levels of C-peptide when compared with Caucasians, Indians (East), and African-Americans. Other studies conducted in different parts of Africa, including Ethiopia (15–17,19), demonstrate no convincing evidence of hyperinsulinemia in type 2 diabetes. In the current study, the low prevalence of obesity in type 2 diabetic subjects (average BMI < 25 kg/m²) may be a major reason for the lack of hyperinsulinemia.

Our study also demonstrated that

insulin-requiring type 2 diabetic subjects have significantly lower BCP, PGCP, and C-peptide increments after glucagon than those on either dietary treatment alone or oral agents. These findings are supportive of numerous reports in the literature (8–12,15,29) and suggest that determination of basal or stimulated C-peptide levels, in concert with clinical criteria, may prove useful in the early identification of subjects with type 2 diabetes who will require insulin therapy.

In agreement with our findings, previous studies of several populations, including Ethiopia, have demonstrated that subjects with type 2 diabetes have higher BMI and/or WHR compared with type 1 diabetic or control subjects (30–33). Thus, as in other populations, obesity, in particular upper-body obesity, appears to be a risk factor for the development of type 2 diabetes in Ethiopians.

In summary, our study of 203 Ethiopian subjects allows us to make the following conclusions: 1) in concert with clinical criteria, BCP and PGCP levels are good discriminators between type 1 and type 2 diabetes in Ethiopians and may also be useful in identifying those subjects with type 2 diabetes who will require insulin therapy; 2) in contrast to studies elsewhere, type 2 diabetic subjects in Ethiopia are not hyperinsulinemic (as gauged by C-peptide levels); and 3) type 2 diabetic subjects with low BCP levels exhibit features of type 1 diabetes and may have been misclassified by WHO criteria.

Table 3—BMI (in kg/m²) according to BCP categories*

Groups	BCP level categories		P
	< 0.2 nmol/l	≥ 0.2 nmol/l	
Type 1 diabetic subjects	19.7 ± 0.36 (46)	22.4 ± 1.13 (9)	0.023
Type 2 diabetic subjects	18.6 ± 0.92 (6)	25.0 ± 0.46 (84)	< 0.001

Data are mean ± SEM (n). *Analysis performed in 90 type 2 and 55 type 1 diabetic subjects in whom reliable BMI data were available.

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