Immunological and C-peptide studies of patients with diabetes in northern Ethiopia: existence of an unusual subgroup possibly related to malnutrition

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Abstract

Aims/hypothesis Surveys in northern Ethiopia have demonstrated that apparent type 1 diabetes occurs more frequently than elsewhere in Africa and, indeed, in other parts of the world. We therefore investigated in detail a cohort of diabetic patients from this region to clarify the nature of this type of diabetes.

Methods All patients attending the diabetic clinic at Mekelle Hospital in the Tigray region of northern Ethiopia were investigated over a 6 week period. Clinical, demographic and anthropometric data were collected, as well as measurements of HbA_{1c}, fasting lipid profile, fasting serum C-peptide and serum markers of beta cell autoimmunity, i.e. islet antigen-2 and GAD antibodies (GADA).

Results Of 105 patients seen, 69 (66%) were on insulin treatment and had been from or close to diagnosis. Their median age and diabetes duration were 30 and 5 years,

respectively, with a male excess of 2:1. Median BMI was 20.6 kg/m². Despite these clinical characteristics suggestive of type 1 diabetes, only 42 of 69 (61%) patients were C-peptide-negative and 35% GADA-positive. Overall, 38 (36%) of the total group ($n=105$) had immunological or C-peptide characteristics inconsistent with typical type 1 or type 2 diabetes. The clinical characteristics, local prevalence of undernutrition, and GADA and C-peptide heterogeneity suggest a malnutrition-related form of diabetes. **Conclusions/interpretation** Not all patients in northern Ethiopia with apparent type 1 diabetes appear to have the form of disease seen in Europeans; their disease may, in fact, be related to malnutrition.

Keywords Atypical diabetes mellitus · C-peptide · Diabetes mellitus · GAD antibodies · Malnutrition-related diabetes mellitus · Type 1 diabetes · Type 2 diabetes

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Abbreviations

GADA GAD antibodies
 IA-2 Islet antigen 2
 IA-2A IA-2 antibodies

Introduction

The provision of diabetes care in Africa, the world's poorest continent, is a major challenge. Inadequate resources and shortage of insulin are a constant barrier to effective care delivery [1]. In addition, patient characteristics sometimes challenge standard classifications of diabetes [2]. An example is 'malnutrition-related diabetes mellitus', a form of diabetes that is characterised by varying degrees of insulin dependence and is often reported in young men from localised geographical areas, sometimes accompanied by pancreatic calcification [3]. More recently, an 'atypical type 2' syndrome has been described in Africa, where initial insulin-dependence may later remit [4]. A viral aetiology for this type of diabetes has been suggested [5].

For some time, unusual phenotypes of diabetes have been observed in northern Ethiopia, but have never been intensively investigated. In the central capital city (Addis Ababa) and surroundings, Lester reported childhood diabetes to be 'typical type 1' and 'clinically similar to elsewhere' [6]. Similarly, standard type 2 diabetes, often accompanied by being overweight, is also seen in this area [7, 8]. However, in the remote and poor northern areas most diabetic patients seen are young, thin and apparently have type 1 diabetes. This has been reported from Mekelle [9] and also from Gondar [10, 11], with an even higher proportion in rural areas [11]. Although no accurate incidence figures exist, this frequency of type 1 diabetes has been described as 'astonishing' [11] and is in marked contrast to observations from sub-Saharan Africa, where the vast majority of diabetic patients have type 2 disease [2, 12]. Interestingly, however, these young and thin northern Ethiopian diabetic patients rarely, if ever, suffer diabetic ketoacidosis and frequently survive despite absent supplies of insulin [9]. A recent survey from rural Ethiopia again confirmed the existence of unusually large numbers of young (peak age 25 to 29 years) insulin-treated patients (45% of the diabetic population of the clinic) with low BMI [13]. Most of these patients were poor subsistence farmers or were unemployed.

The phenotype of apparent type 1 diabetes in this area therefore appears unusual. Several authors have suggested a direct link with malnutrition [9, 13], particularly as famine is common in the area. We therefore undertook a detailed clinical, biochemical and immunological study of a group of these patients from Mekelle, northern Ethiopia.

Methods

Location The research site was the diabetic clinic, held weekly at Mekelle Hospital in Mekelle, in the Tigray region of northern Ethiopia. Mekelle has a population of 200,000 and has the central referral hospital for Tigray region, which has a population of about 4 million. Much of Tigray is semi-desert, with low rainfall and difficult unsurfaced roads. Most inhabitants are subsistence farmers with very low income. Serious food shortages due to crop failures are common, and particularly severe famines occurred in the mid and late 1980s. Transport is difficult and patients often have to travel large distances on foot (often 50 to 100 km or more) for medical services. The study was not carried out in the rainy season, when patients from rural areas find it especially difficult to reach the hospital due to impassable roads and tracks. Even when patients do reach hospital, essential drugs and equipment (including insulin and syringes) may be unobtainable.

Patients The diabetic clinic at Mekelle Hospital is the only care facility for diabetic patients in the area. Consecutively attending patients at the diabetic clinic were studied over a 6 week period, amounting to 105 patients. Patients were diagnosed by WHO criteria [14], using a portable blood glucose meter. The type of meter and quality control systems available varied according to supply. In practice, most patients originally presented with obvious osmotic symptoms and marked hyperglycaemia. A written proforma was filled in for each patient recording name, age, location of residence, duration of diabetes, family history of diabetes, treatment, known complications and other illnesses. Patients were divided into 'insulin-treated' and 'non-insulin treated'. The decision to treat with insulin was made by one clinician (A. Tekle), an experienced provider of diabetes care in the area. Each patient was later given a code number and anonymised data were entered on to an Excel computer spreadsheet.

Anthropometric data BMI was determined by dividing weight in kg by height in metres squared. Weight was measured in light clothes on standard scales to the nearest 0.1 kg. Height was measured to the nearest centimetre using a wall-mounted measuring rod. Blood pressure was measured with a standard mercury sphygmomanometer with the patient in a sitting position and the arm at mid-thoracic level. Measurement was made to the nearest mmHg and the diastolic level was recorded as complete disappearance of sounds.

Laboratory data No hospital-based laboratory services (including blood glucose and HbA_{1c}) were available. Patients attended the clinic in a fasted state and blood was

taken into plain tubes. A finger prick blood sample was used to measure HbA_{1c} with a portable analyser (Glycosal; Provalis Diagnostics, Queensferry, UK) provided for the study. This system uses boronate affinity chromatography and is aligned to Diabetes Control and Complications Trial criteria [15]. The technique has been shown to work well in tropical field conditions [16]. Blood taken into the plain tube was allowed to clot and the serum was separated by centrifugation at 2,000g and stored frozen at –40°C. Later, one of the researchers transported the samples on dry ice to the UK. The samples arrived fully frozen and in good condition. Cholesterol, HDL-cholesterol and triacylglycerol were measured by standard laboratory methods on an automated analyser (Hitachi 747; Hitachi, Bohemia, NY, USA) at the Aintree University Hospital, Liverpool, UK. LDL-cholesterol was calculated by the Friedewald equation. C-peptide was measured by radioimmunoassay at the Royal Liverpool University Hospital, Liverpool (an accredited national centre for this assay). The assay is WHO-standardised, with undetectability defined as a level of <183 pmol/l. The intra-assay coefficient of variability was 1.3% and precision was 1.8%. Patients with undetectable C-peptide were considered ‘C-peptide-negative’ and all others ‘C-peptide-positive’. The latter group had levels ranging from 225 to >7,282 pmol/l, but 80% had values over 400 pmol/l. GAD antibodies (GADA) and islet antigen 2 (IA-2) antibodies were measured at the Department of Diabetes and Metabolism, Southmead Hospital, University of Bristol, UK, as previously described [17, 18] and using ³⁵S-labelled full-length GAD65 or IA-2 (605-979). Results were expressed in WHO units/ml derived from a standard curve and samples were considered positive if above the 97.5th centile (14.0 WHO units/ml for GADA, 6.0 WHO units/ml for IA-2 antibodies [IA-2A]). The GADA and IA-2A assays achieved a laboratory-defined sensitivity of 94% and 69%, with 96% and 98% specificity, respectively in the Fourth Diabetes Antibody Standardisation Program [19].

Statistics Statistical evaluation was done using a StatsDirect package. Mean and standard deviations were calculated for normally distributed data; for skewed data, medians with inter-quartile ranges were calculated. Groups were compared for significance by Student’s unpaired *t* test (normal data) or the Mann–Whitney *U* test (non-normal data). Fisher’s exact test was used to compare proportionate variables. The Kruskal–Wallis test was used for comparison between groups. A value of *p*<0.05 was taken to indicate statistical significance.

Ethics We obtained approval for the project from the Ethics Committee of the Mekelle Health Board. Due to the high level of illiteracy, verbal consent only was obtained from patients, who were universally enthusiastic to take part, as

for the first time they were able to have detailed biochemical assessment of their diabetes (HbA_{1c}, lipids, etc.).

Results

Patient details Of the 105 patients, 74 (68%) were men, mean (± SD) age was 41±16 years and diabetes duration (median [interquartile range]) was 5 (3–10) years. A family history of diabetes was present in ten (9%) patients; median (interquartile range) BMI was 20.6 (18.5–23.9). Treatment was with diet (*n*=1), oral agents (*n*=35) and insulin (*n*=69). Only 5% of patients were hypertensive (BP>140/80). Glycaemic control was poor with HbA_{1c} high at 11.3±2.8%.

Comparison of insulin-treated and non-insulin treated patients As shown in Table 1, two-thirds of the group were on insulin treatment. They were significantly younger, although of similar diabetes duration to those on oral agents and diet. BMI and both systolic and diastolic BP were also highly significantly lower in those on insulin than in those on other treatments, but glycaemic control was worse (HbA_{1c} 11.9 vs 10.0%, *p*=0.002). The lipid profiles were better in the insulin-treated group, with lower total cholesterol and LDL-cholesterol, higher HDL-cholesterol and lower triacylglycerol (all statistically significant except for HDL-cholesterol). Although all these characteristics suggest that the group studied had predominantly or entirely type 1 diabetes, only 35% were either GADA- or IA-2A-positive. In addition, although C-peptide levels were lower and significantly more patients were C-peptide-negative, 39% of those on insulin still had detectable levels of fasting serum C-peptide.

Analysis of GADA and C-peptide status Analysis showed that 29 (28%) patients were GADA-positive and 45 (43%) were C-peptide-negative. Only four patients were IA-2A-positive, two of whom were also GADA-positive. Table 2 divides the total group into patients who were GADA-positive or -negative, and those who were C-peptide-negative or -positive. Most (83%) but not all GADA-positive patients were on insulin, and only 62% were C-peptide-negative. Similarly, some (7%) C-peptide-negative patients were not on insulin and only 40% were GADA-positive. The C-peptide-positive and GADA-negative groups showed similar heterogeneity. This led us to arbitrarily group the patients into: (1) ‘definite’ type 1 diabetes (defined as GADA-positive, C-peptide-negative and on insulin treatment); (2) ‘definite’ type 2 diabetes (defined as GADA-negative, C-peptide-positive and on any treatment); and (3) an ‘uncertain’ group (Table 3). This ‘uncertain’ group contained 38 (36%) patients. They were of similar age, diabetes duration, BMI and HbA_{1c} as the type 1 group. In addition, four (11%) were not on

Table 1 Comparison of insulin- and non-insulin-treated diabetic patients in northern Ethiopia

Characteristic	Insulin-treated	Non-insulin treated	<i>p</i> value
<i>n</i> (%)	69 (66)	36 (34)	
Age (years)	30 (22–48)	50 (40–60)	0.0001
Duration diabetes (years)	5 (3–10)	6 (2–11)	NS
BMI (kg/m ²)	19.3 (16.6–21.3)	24.0 (21.2–25.7)	0.0001
BP systolic (mmHg)	100 (90–110)	120 (110–130)	0.0001
BP diastolic (mmHg)	70 (60–80)	80 (70–90)	0.0002
HbA _{1c} (%)	11.9 (10.1–14.2)	10.0 (8.6–11.8)	0.0002
Cholesterol (mmol/l)	4.4±1.3	5.1±1.4	0.01
Triacylglycerol (mmol/l)	1.3 (0.9–2.2)	1.8 (1.4–2.7)	0.003
HDL-cholesterol (mmol/l)	1.0 (0.8–1.2)	0.9 (0.8–1.1)	NS
LDL-cholesterol (mmol/l)	2.6±0.9	3.2±1.3	0.007
C-peptide (pmol/l)	477 (286–845)	788 (586–1,136)	0.003
C-peptide-negative, <i>n</i> (%)	42 (61)	3 (8)	0.0001
GADA-positive, <i>n</i> (%)	24 (35)	5 (14)	0.023

Unless otherwise indicated, data are means±SD for normally distributed data and median (interquartile ranges) for non-normally distributed data

insulin, only 11 (29%) were GADA-positive and 11 (29%) were C-peptide-positive.

Discussion

Our study was stimulated by empirical clinical observations by ourselves [8] and others [9, 10, 20] suggesting a remarkably high proportion of apparent type 1 diabetic patients in northern Ethiopia. Accurate epidemiological studies of type 1 diabetes are rare in Africa, but from the data available, results are lower than in western countries. Incidence rates of 1.5 per 100,000 per year have been reported from Tanzania [21] and 10.1 per 100,000 per year from Sudan [22] (differences possibly reflect varying ethnicity of the study populations). A weakness of our study and others [9–11, 13, 20] is that it was hospital, rather than community-based. However, hospital surveys have been previously used as an argument for the unusually low proportionate rates of type 1 diabetes in sub-Saharan

Africa, perhaps due to deaths of type 1 patients outside hospital [21, 23]. A strength of our study is that it was conducted in a poor, rural area, whereas most other type 1 research in the continent has been in urban African centres, where nutrition is likely to be at least reasonable [21, 22].

It has long been known that a number of the phenotypic type 1 diabetic patients in northern Ethiopia are very thin, predominantly male [9, 10, 13, 20] and ‘frequently discontinued insulin but seldom developed ketoacidosis’ [20]. We and others have surmised that because of these clinical observations and the marked past and present undernutrition in the area, these patients may have malnutrition-related diabetes mellitus [9, 13, 24]. The present study measured GADA and IA-2A to internationally accepted specifications [17–19], as well as fasting C-peptide. Although we did not determine glucagon-stimulated C-peptide, there is evidence that fasting C-peptide correlates well with post-stimulation levels [8, 25]. We also found a clear separation of C-peptide positivity and negativity in our patients.

Our results confirm a previously observed 2:1 male: female ratio and low BMI in rural Ethiopian diabetic patients. Comparison of insulin- and non-insulin-treated patients (Table 1) showed higher age, BMI and BP, and lower HbA_{1c} in the non-insulin treated group, suggestive of type 2 diabetes features. Indeed, BMI in particular showed almost complete separation between the two groups, perhaps supporting differing aetiologies. However, at 66% the proportion of apparent type 1 diabetes patients remains surprising. Moreover, GADA and C-peptide characteristics by no means always fitted with these categories. Thus, 39% of the insulin-treated group were C-peptide-positive, and only 35% were GADA-positive. The failure of C-peptide negativity and GADA positivity to correlate is explored further in Table 2, and led us to subdivide our group into: (1) ‘definite’ type 1 diabetes (GADA-positive, C-peptide-

Table 2 Inter-relations between GADA and C-peptide status in 105 Ethiopian diabetic patients

Variable	Negative	Positive	<i>p</i> value
C-peptide			
<i>n</i>	45	60	
GADA-positive, <i>n</i> (%)	18 (40)	11 (18)	0.04
On insulin, <i>n</i> (%)	42 (93)	27 (45)	0.0001
GADA			
<i>n</i>	29	76	
C-peptide-negative, <i>n</i> (%)	18 (62)	27 (35)	0.016
On insulin, <i>n</i> (%)	24 (83)	45 (59)	0.037

Table 3 Comparison of demographic and biochemical characteristics of definite type 1, definite type 2 and uncertain types of diabetes in northern Ethiopia

Characteristics	Definite type 1 ^a	Definite type 2 ^b	Uncertain type ^c	<i>p</i> value
<i>n</i> (%)	18 (17)	49 (47)	38 (36)	
Age (years)	27 (22–38)	53 (40–60)	29 (22–45)	0.0001 ^d
Age at diagnosis (years)	22 (14–29)	43 (35–52)	24 (16–34)	0.0001 ^d
Duration diabetes (years)	5 (4–8)	7 (3–13)	5 (3–9)	NS ^e
BMI (kg/m ²)	18.8 (17.2–20.1)	23.1 (21.1–25.3)	19.2 (16.5–20.7)	0.0001 ^d
HbA _{1c} (%)	12.0 (10.0–14.2)	10.2 (8.8–12.0)	11.6 (10.2–14.2)	0.0113 ^f
Insulin treatment, <i>n</i> (%)	18 (100)	19 (38)	34 (89)	0.01 ^g
GADA-positive, <i>n</i> (%)	18 (100)	0 (0)	11 (29)	0.01 ^h
C-peptide-negative, <i>n</i> (%)	18 (100)	0 (0)	27 (71)	0.01 ⁱ

Data are medians (interquartile range), unless indicated otherwise

Statistical comparison was by Kruskal–Wallis test as non-parametric ANOVA between groups

^a GADA-positive, C-peptide-negative and on insulin

^b GADA-negative, C-peptide-positive and any treatment

^c For all comparisons

^d For type 2 vs type 1 and uncertain diabetes type; type 1 vs uncertain diabetes type NS

^e For all comparisons

^f For type 1 vs type 2 diabetes; $p=0.0292$ for type 2 vs uncertain diabetes type; type 1 vs uncertain NS

^g For type 1 vs type 2 diabetes; type 1 vs uncertain diabetes type NS

^h For type 2 vs uncertain diabetes type; $p=0.0001$ for type 1 vs uncertain diabetes type and for type 1 vs type 2 diabetes

ⁱ For type 2 vs uncertain diabetes type and for type 1 vs uncertain type; $p=0.0001$ for type 1 vs type 2 diabetes

negative and on insulin); (2) ‘definite’ type 2 diabetes (GADA-negative, C-peptide-positive and on any treatment); and (3) ‘uncertain’ (all other patients) (Table 3). We accept that this categorisation is arbitrary, and that GAD and C-peptide status are not exclusive markers of type 1 and type 2 diabetes. However, although GADA positivity declines after diagnosis of type 1 diabetes, such low rates in a group with median diabetes duration of only 5 years is unusual. In one European study, two-thirds of a type 1 diabetes cohort were still positive for either islet cell antibodies or GADA at 10 years after diagnosis [26]. Also, type 1 diabetic patients elsewhere in Africa, including urban Ethiopia, have been shown to be positive for GADA or islet cell antibodies [27, 28].

Accepting these limitations, our revised groupings give a much more expectable proportion of type 1 diabetes patients at 17%, with type 2 diabetes comprising 47% and the ‘uncertain’ group 36%. Patients in the latter group were closer to type 1 than type 2 diabetes in terms of age (current and at diagnosis), BMI and HbA_{1c}, with 89% on insulin, 29% GADA-positive and 71% C-peptide-negative (Table 3). Although this cohort is undoubtedly heterogeneous and may include some GADA-negative type 1 and possibly some GADA-positive type 2 diabetic patients, it seems unlikely that this would account for more than a small proportion. The possibility that these patients may be

simply malnourished and poorly controlled type 1 diabetes patients is not supported by their frequency of occurrence or by the variable immunological and C-peptide status. We believe that most of this group represent an unusual form of ‘pseudo-type 1’ diabetic patients. Interestingly, Siraj and colleagues [8], reporting on C-peptide studies on diabetic patients in Addis Ababa, Ethiopia, commented that ‘there is a subgroup of type 2 diabetic subjects with features of type 1 diabetes’.

One distinct possibility is that our insulin-treated patients may have malnutrition-related diabetes [2, 3, 24]. This entity has been described for many decades and is based on the hypothesis that malnutrition in early life leads to pancreatic beta cell damage with varying degrees of insulin hyposecretion. The scenario in northern Ethiopia is certainly compatible with the existence of malnutrition-related diabetes mellitus, since serious famines occurred here in the mid-1980s (when most of our insulin-treated patients were children) and food shortages have continued since. Moreover, malnutrition-related diabetes mellitus has been described previously in Ethiopia [29] and, interestingly, a male excess, usually around a 2:1 ratio, is well described in the syndrome [3, 9, 24]. Due to male excess, low BMI, early onset, past (and often present) malnutrition, plus insulin requirement but not dependence, many of our insulin-treated patients fulfil current criteria for malnutrition-related diabetes mellitus. Of

the two described subgroups of malnutrition-related diabetes mellitus, i.e. fibrocalculous pancreatic diabetes and malnutrition-modulated diabetes mellitus [24], the latter would fit best with our patients. Although we did not perform abdominal x-rays or ultrasounds as part of our research protocol, pancreatic calcification is not seen in the Mekelle area and none of our patients had steatorrhea. Interestingly, immunological studies on patients with malnutrition-modulated diabetes mellitus in India have shown that many are positive for GADA [30]. In fact, at 23%, the figure is very similar to the 29% positive rate in our ‘uncertain’ type group (Table 3). Of further interest, and again similar to our own observations, was that IA-2 positivity was rare. Nevertheless, compelling as these arguments may seem, they are by no means conclusive, and further work is clearly required. One particular problem is that while undernutrition is highly prevalent in northern Ethiopia, the majority of people affected do not develop diabetes.

In conclusion, we believe that we have confirmed an unusual form of ‘pseudo-type 1’ diabetes from northern Ethiopia, which has clinical and immunological similarities to malnutrition-modulated diabetes mellitus. A wider community-based study of this diabetic population would be valuable, although given the highly scattered population and difficult terrain, such a study would not be easy. More practically, our results may have important implications for insulin treatment in the area and elsewhere. There are often critical shortages of insulin in northern Ethiopia, yet our data show that 40% of those on insulin treatment were C-peptide-positive and may therefore be potentially treatable with oral agents, leading to considerable financial savings and helping conserve precious insulin supplies for those who are truly insulin-dependent.

Finally, we agree with Alemu and colleagues that ‘the case for malnutrition-related diabetes’ should be re-opened [13]. This form of diabetes is no longer recognised by the WHO. We recognise that the observational studies of ourselves and others [3, 9, 11, 13], as well as the immunological and C-peptide data presented here, do not prove causal association. Nevertheless, the clear existence of this unusual type of diabetes in one of the poorest areas of the world makes a strong case for re-evaluating the link between malnutrition and diabetes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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