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ORIGINAL ARTICLE

Insulin-requiring diabetes in Ethiopia: associations with poverty, early undernutrition and anthropometric disproportion

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Background/Objectives: Most insulin-requiring diabetes patients in Ethiopia have an atypical form of the disease, which resembles previous descriptions of malnutrition-related diabetes. As so little is known about its aetiology, we have carried out a case–control study to evaluate its social and nutritional determinants.
Subjects/Methods: Men and women with insulin-requiring diabetes ($n=107$), aged 18–40 years, were recruited in two centres, Gondar and Jimma, 750 km northwest and 330 km southwest of the capital, Addis Ababa, respectively. Controls of similar age and sex ($n=110$) were recruited from patients attending other hospital clinics.
Results: Diabetes was strongly associated with subsistence farming, odds ratio = 3.5 (95% confidence interval: 1.5–7.8) and illiteracy/low levels of education, odds ratio = 4.0 (2.0–8.0). Diabetes was also linked with a history of childhood malnutrition, odds ratio = 5.5 (1.0–29.0) the mother's death during childhood, odds ratio = 3.9 (1.0–14.8), and markers of poverty including poorer access to sanitation ($P=0.004$), clean water ($P=0.009$), greater overcrowding ($P=0.04$), increased distance from the clinic ($P=0.01$) and having fewer possessions ($P=0.01$). Compared with controls, people with diabetes had low mid upper arm circumference, body mass index (BMI) and fat/lean body mass ($P<0.01$). In addition, men with the disease tended to be shorter, were lighter ($P=0.001$), with reduced sitting height ($P=0.015$) and reduced biacromial ($P=0.003$) and bitrochanteric ($P=0.008$) diameters.
Conclusions: Insulin-requiring diabetes in Ethiopia is strongly linked with poor education and markers of poverty. Men with the disease have associated disproportionate skeletal growth. These findings point towards a nutritional aetiology for this condition although the nature of the nutritional deficiency and its timing during growth and development remains obscure.
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Keywords: diabetes; insulin-dependent; malnutrition; ethiopia; anthropometry; poverty

Introduction

A recent survey suggests that an atypical form of the disease accounts for the majority of cases of insulin-requiring diabetes presenting in rural areas of Ethiopia (Alemu *et al.*, 2009). The phenotype differs from the classical type 1 disease encountered in westernized populations. Peak disease incidence is in the 25–29 years age group, and it is only rarely observed in children and adolescents. This is in marked contrast to the pattern of disease reported from diabetes registries in the United States, Europe and Japan, which show a peak at the age of puberty, together with a lesser peak in young children aged 0–4 years (LaPorte *et al.*, 1995). It also affects people of low socioeconomic status and is seen most frequently in men. This again differs from conventional type 1 diabetes, which is a disease of the advantaged (LaPorte *et al.*, 1995), with sex ratios close to unity among cases presenting under the age of 15 years (Gale and Gillespie, 2001). The sparse epidemiological data from other countries in

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sub-Saharan Africa suggest a high prevalence of a similar disease pattern (Levitt, 2008; Gill *et al*., 2009). Previous studies have shown that markers of islet cell autoimmunity are detectable in much <50% of insulin-requiring diabetic patients in Ethiopia and other African countries, a frequency considerably lower than that of Caucasian populations where these markers are typically found in 80–90% of newly diagnosed cases (Peters *et al*., 1986; McLarty *et al*., 1990; Lutale *et al*., 2007). Thus, although autoimmune type 1 diabetes does occur in sub-Saharan Africa, the Ethiopian data suggest that the most prevalent form of insulin-requiring diabetes is a non-autoimmune condition. This most closely resembles previous descriptions of malnutrition-related diabetes (Hugh-Jones, 1955; Abu-Bakare *et al*., 1986), a poorly characterized and controversial condition not recognized in the current WHO diabetes classification (WHO, 1999).

Very little is known about its epidemiology. Early descriptions and case series remark on the low socioeconomic status of most patients (Rao, 1984; Abu-Bakare *et al*., 1986). However, there are no control data and these findings may merely reflect the very high prevalence of poverty where the patients live and may not necessarily be a feature of the disease. Likewise, the role of malnutrition in insulin-dependent diabetes is poorly documented. Although there is strong evidence from animal experiments that protein-calorie malnutrition in early life damages the endocrine pancreas and leads to permanent diabetes (Desai *et al*., 1995; Gatford *et al*., 2008), the human evidence is restricted to the observation that people with the disease live in communities where malnutrition is prevalent and tend to have very low body mass index (BMI) on presentation (Rao, 1984). We have therefore carried out a case–control study to determine whether the disease is associated with poverty and markers of prior undernutrition. The study was performed in the two areas of Ethiopia where we previously carried out an incidence study. (Alemu *et al*., 2009).

Patients and methods

The study was based in two zones of Ethiopia, Gondar and Jimma, 750 km northwest and 330 km southwest of the capital, Addis Ababa, respectively. Each zone has a central university hospital, which together with satellite/peripheral health centres provides care for patients with diabetes.

Patients

Patients, aged 18–40 years, with diabetes requiring insulin treatment from diagnosis were recruited from diabetic clinics in and around Gondar and Jimma. An approximately equal number of controls of the same age and a similar gender distribution were recruited from patients or relatives of patients attending general medical clinics for conditions other than diabetes in both communities. Of these, 45 were relatives and the remainder patients from gastroenterology (16); respiratory clinics (10); neurology including epilepsy (11); cardiovascular clinics (10); otolaryngology (8); dermatology (3); genito-urinary, infectious disease and rheumatology clinics (2 each) and gynaecology (1). A questionnaire was verbally administered in Amharic or Oromifa (the local languages) to define the social and medical history of the cases and controls. Cases were asked about the duration of their disease and the amount of insulin they were currently taking. The controls were asked about the reason for their attendance at the hospital. The patients and controls were asked about their level of education (elementary, secondary or higher education) and their current occupation. They were also asked whether they had been treated for malnutrition in childhood and whether a parent had died when they were children. Details of their housing were recorded including the number of rooms, number of people living in the house, type of construction of the house and whether animals slept in the same room as the occupants. The patients were asked about the source of their drinking water (whether this was a piped or protected supply or whether water was obtained directly from the river), and whether they had access to a toilet. The participants were also asked about the ownership of common household items (electric stove, bicycle, clock, cart, plough, bednet, table, chair, sofa or spring/foam mattress): this was used to create a possessions score.

Height and sitting height were measured with a portable stadiometer and weight with digital electronic scales to the nearest 0.1 kg. Bitrochanteric and biacromial diameters were measured with a Harpenden Anthropometer (Holtain Ltd, Crymych, Pembrokeshire, UK). Mid upper arm circumference was measured with a nylon tape measure midway between the acromion and olecranon. Waist and hip circumferences were also measured with a nylon tape measure. Waist circumference was measured midway between the lower rib margin and the superior anterior iliac spine. Hip circumference was taken at the widest point over the great trochanters. Skinfold thicknesses were measured in triplicate with the use of Harpenden skinfold callipers (British Indicators, Luton, UK) at the triceps, biceps, sub-scapular and suprailiac sites. Whole-body bioelectric impedance was measured using a Bodystat meter (Bodystat Ltd, Douglas, Isle of Man, UK) and gel-coated aluminium foil electrodes were used to attach the electrodes to the non-dominant hand and foot. A fingerprick sample of blood was obtained from the controls for the measurement of blood glucose, which was carried out using a glucose monitor (Boots Ltd, Nottingham, UK).

The interviewers were trained to ensure that accurate and comparable anthropometric measurements were obtained. A senior investigator (DIWP) performed 10% of the measurements in each centre. The scales and measuring equipment were calibrated before use and regularly checked during the study. Studies comparing the performance of the interviewers were also carried out. The between-observer coefficients of variation were <2.5% for the measurements of length or circumference and between 8 and 19% for the

skinfold measurements. The study protocol was approved by the local research ethics committees and both patients and controls gave informed consent.

Statistical methods

BMI was calculated as weight (kg) divided by height squared (m^2). Leg length was calculated from the difference between sitting and standing height. The averages of triplicate skinfold-thickness measures at each site were used to calculate percentage of body fat (Durnin and Womersley, 1974), a method applicable in non-Caucasian populations (Zillikens and Conway, 1990). Fat mass was derived by multiplying the body weight by the percentage body fat and fat-free mass by subtracting fat mass from body weight. The bioimpedance measurements were used to calculate percentage body fat and lean body mass using equations developed for non-Caucasian populations (Kotler *et al*., 1996). Non-normal variables were transformed appropriately. Unconditional logistic regression was used to estimate multivariate-adjusted odds ratios and 95% confidence intervals. Multiple linear regression was used to estimate adjusted case–control differences and 95% confidence intervals for continuously distributed outcomes.

Results

A total of 107 cases and 110 controls were recruited. Gondar contributed 52 cases and 53 controls, whereas the remaining 55 cases and 57 controls were from Jimma. As the characteristics of the cases and controls were similar in Gondar and Jimma, the data for the two centres were combined. Seventy-eight (73%) of the cases and 75 (68%) of the controls were males. Their ages ranged from 18 to 40 years, with a similar mean age in cases, 26.6 (s.d. 6.2) years and controls, 26.0 (s.d. 5.9) years. Thirty-five (33%) cases and 49 (45%) controls lived in the urban areas of Gondar and Jimma, the remainder were from the surrounding rural areas. The diabetic patients reported a mean age of onset of 23.5 (s.d. 6.5) years and a median duration of diabetes of 1.7 (interquartile range: 0.67–4.9) years. The total dose of insulin ranged from 12 to 120 units per day, with a mean of 47.7 (21.3) units per day. Among the 110 controls, the random blood sugar ranged from 2.6 to 7.6 mmol/l (mean 5.1 mmol/l).

Table 1 shows that diabetes was strongly associated with unskilled occupations or working as a subsistence farmer. Diabetes was also strongly associated with the level of education. People with diabetes were much more likely to be illiterate or able to read or write only and much less likely to have completed secondary or higher levels of education. Findings were similar in the Gondar and Jimma centres. The association between diabetes and poor education was observed in both genders, but the occupational associations were only observed in men. Although relatively few of the cases or controls reported a history of childhood malnutrition, this was more evident in the patients with diabetes than the controls. They were also more likely than controls to report that they had experienced the loss of a mother when they were $\leqslant$10 years but not more likely to report the death of a father.

Table 2 shows the data obtained about the type of housing of the cases and controls. The diabetic patients reported that they were less likely to have a toilet in their house and had poorer access to piped or clean water. They had a greater density of people per room, and a significantly longer journey to get to the diabetes clinic (either the central clinic or one of the peripheral satellite clinics). The diabetic patients also reported a lower possessions index than the controls. Again the findings were similar in men and women and in both Gondar and Jimma.

Table 1 Occupation, level of education and history of early malnutrition or loss of a parent in the cases and controls

Variable	*Cases* (N = *107*) N *(%)*	*Controls* (N = *110*) N *(%)*	*Odds ratio (95% CI)*	P-*value**
Occupation[a]				<0.001
Farmer/unskilled	53 (55)	27 (28)	3.5 (1.5–7.8)	
Housewife	9 (9)	10 (11)	1.6 (0.5–5.7)	
Student	19 (20)	30 (32)	1.0 (0.4–2.6)	
Government/business	15 (16)	28 (30)	1.0	
Not known/unemployed	11	15		
Education[a]				<0.001
Illiterate or read/write only	46 (43)	22 (20)	4.0 (2.0–8.0)	
Elementary	28 (26)	26 (24)	2.0 (1.0–4.0)	
Secondary/higher education	33 (31)	62 (56)	1.0	
Childhood malnutrition	8 (8)	2 (2)	5.5 (1.0–29.0)	0.047
Mother died child <10 years	12 (11)	3 (3)	3.9 (1.0–14.8)	0.046
Father died child <10 years	14 (13)	11 (10)	1.4 (0.6–3.3)	0.49

Abbreviation: CI, confidence interval.
**P*-values adjusted for interviewer, location, gender and age.
[a]Entered as categorical variables with four levels (occupation) or three levels (education).

Table 2 Household amenities in the cases and controls

Variable	*Cases (N = 107)* N *(%)*	*Controls (N = 110)* N *(%)*	*Odds ratio (95% CI)*	P-*value**
Animals sleep in the same room	20 (19)	16 (15)	1.0 (0.4–2.0)	0.90
No access to toilet	26 (24)	11 (10)	3.6 (1.5–8.8)	0.004
No access to piped/clean water	44 (41)	28 (26)	2.3 (1.2–4.1)	0.009
Hatched (vs corrugated) roof	35 (33)	24 (22)	1.8 (0.9–3.3)	0.075
	Mean (s.d.)	*Mean (s.d.)*	*Difference (95% CI)*	
No. of people/house	4.9 (2.2)	4.6 (2.2)	0.3 (−0.3–0.9)	0.28
No. of people/room[b]	2.4 (1.9)	2.0 (1.9)	0.4 (0.02–0.9)	0.04
Distance from clinic, km[b]	6.6 (3.2)	4.1 (3.8)	2.5 (0.6–5.2)	0.01
Possessions index[a]	3.4 (1.4)	3.9 (1.5)	0.5 (0.1–0.9)	0.01

Abbreviation: CI, confidence interval.
**P*-values adjusted for interviewer, location, gender and age.
[a]See section Patients and methods.
[b]Geometric mean and s.d.

Table 3 Anthropometric differences between cases and controls (s.d. shown in parentheses)

	Men		P-*value**	*Women*		P-*value**
	Cases (n = 78)	*Controls (n = 75)*		*Cases (n = 29)*	*Controls (n = 34)*	
Height, cm	167.2 (7.1)	169.3 (5.8)	0.057	158.3 (6.7)	156.2 (5.4)	0.11
Weight, kg	53.1 (7.7)	57.1 (7.0)	0.001	50.4 (6.8)	53.8 (9.6)	0.085
Sitting height, cm	82.4 (3.7)	83.8 (3.6)	0.015	78.1 (3.1)	78.8 (3.6)	0.38
Leg length, cm	84.8 (5.7)	85.5 (4.5)	0.46	80.3 (6.5)	77.4 (4.5)	0.03
Biacromial, cm	36.2 (2.6)	37.3 (2.0)	0.003	33.4 (2.1)	34.3 (1.9)	0.09
Bitrochanteric, cm	29.3 (2.1)	30.2 (1.7)	0.008	29.7 (1.5)	30.5 (2.6)	0.15
Mid-upper arm, cm	23.1 (2.6)	24.9 (2.4)	<0.001	24.2 (3.3)	25.5 (3.2)	0.06
Waist, cm	73.9 (5.5)	74.4 (6.4)	0.53	74.2 (8.4)	74.2 (9.7)	0.80
Hip, cm	85.0 (6.1)	88.4 (4.8)	<0.001	88.2 (7.0)	90.5 (7.5)	0.15
BMI, kg/m^2	18.9 (2.1)	19.9 (2.2)	0.004	20.1 (3.0)	22.0 (3.4)	0.017
Skinfold						
Body fat, %	11.8 (4.4)	13.3 (4.9)	0.03	24.6 (7.3)	27.3 (5.4)	0.10
Fat mass, kg	6.4 (3.2)	7.8 (3.6)	0.011	12.8 (4.8)	15.0 (5.3)	0.07
Fat-free mass, kg	46.7 (5.8)	49.2 (5.0)	0.002	37.7 (3.4)	38.8 (5.1)	0.21
Bioimpedance						
Body fat, %	12.5 (4.0)	14.0 (5.1)	0.06	21.1 (9.2)	27.6 (7.5)	0.004
Fat mass, kg	6.8 (3.0)	8.3 (3.6)	0.014	11.0 (5.9)	15.3 (6.7)	0.008
Fat-free mass, kg	46.3 (5.4)	48.8 (4.3)	0.001	39.1 (3.9)	38.5 (4.5)	0.525

**P*-values adjusted for age, interviewer and location.

Table 3 shows the anthropometric measurements obtained in the cases and controls. Because of the differences between men and women, the data for the genders are shown separately. Men with diabetes tended to be shorter and were lighter than the controls. Although their sitting height, biacromial and bitrochanteric diameters were reduced, the leg length was similar in cases and controls. The cases had similar waist size but their hip size was smaller than the controls. Cases had a reduced mid upper arm circumference, lower BMI, and both fat mass and lean body mass were lower. The trends were similar whether composition was measured using the skinfold technique or by means of bioimpedance.

The anthropometric contrasts between diabetic patients and controls differed in women. Cases were slightly taller than controls with significantly longer leg length while the sitting height was similar. Cases had a lower BMI and lower body fat whether expressed absolutely or in percentage terms but lean body mass was similar to the controls. None of the other measurements differed significantly.

Discussion

This study shows that insulin-dependent diabetes in Ethiopia is strongly associated with low socioeconomic

status, poor levels of education and markers of poverty. In both study areas, diabetes was much more likely to occur in people who were unemployed or peasant farmers and less frequently among the more affluent. It was also associated with lower levels of education and markers of poverty such as poorer housing, overcrowding and having few possessions.

We selected diabetic patients in the 18–40 years age group as our previous study of diabetes in Ethiopia showed that disease rates were highest in this age group (Alemu *et al*., 2009). The age and sex distribution of our cases is typical of the pattern seen in other studies of insulin-dependent diabetes in sub-Saharan Africa (Kalk *et al*., 1993; Habtu *et al*., 1999), and in our previous study in Ethiopia (Alemu *et al*., 2009), and is likely to be representative. We selected as controls patients or relatives of patients attending local general medical clinics as they would have reached the hospital through similar referral processes, which would therefore reduce the chance of differences arising between cases and controls through selective access to medical care. The controls were of a very similar age and sex to the cases.

The association with poverty accords with the impressions of previously published clinical case series of malnutrition-related diabetes both in the early literature (Belcher, 1970; Abdulkadir *et al*., 1987) and subsequently. Among 100 cases collected in Mekelle, Northern Ethiopia, most patients were farmers in rural areas and 45% were illiterate (Habtu *et al*., 1999), whereas a small study of 12 patients in India found that all were of low socioeconomic status (Tripathy and Samal, 1997). It is possible that the association with markers of poverty observed is a result of reverse causation—that poverty is a result of having diabetes. Although this cannot be excluded as an explanation, we think this is unlikely as first, we found no association between these markers of poverty and the duration of the diabetes and, second, we found associations with events that had occurred before the onset of diabetes such as the premature death of a patient's mother or poor level of education.

The role of undernutrition is supported by our findings that the disease was associated with the loss of a mother under the age of 10 years and that more cases reported a history of being treated for childhood malnutrition. It is also supported by our anthropometric findings as skeletal growth and skeletal proportion reflect childhood nutrition. Men who had insulin-requiring diabetes showed evidence of disproportionate skeletal growth. Compared with the controls, they tended to be shorter with smaller biacromial and bitrochanteric diameters and reduced sitting height. These findings raise the possibility that exposure to undernutrition during the early growth period may be a key factor in the development of the disease although clearly they could result from influences related to undernutrition, for example infectious disease or parasite load. Although skeletal growth has both biological and socioeconomic determinants, socioeconomic factors seem to be more important in the early growth period (Victora *et al*., 2010), which is supported by the finding of a consistent association between reduced fetal or infant growth and reduced skeletal growth in both children and adults. This is independent of the genetic effects of parental height (Sayer *et al*., 2004; Elia *et al*., 2007). Reduced biacromial and bitrochanteric diameters, one of the strongest findings in this study, have been linked with reduced fetal growth in Western populations in both children (Elia *et al*., 2007) and adults (Kensara *et al*., 2005). The lower hip but not waist measurements in the men with diabetes is also likely to reflect the low bitrochanteric diameter. We found associations between diabetes and reduced sitting height but not leg length. This was somewhat unexpected as there is a considerable body of evidence, suggesting that leg length could act as a sensitive marker of the early environment. It may be an artefact resulting from low buttock fat thickness in the cases causing a reduction in sitting height (Bogin and Varela-Silva, 2008). However, as the correlation between trunk and leg length in our study ($r = 0.25$) and other studies (Li *et al*., 2007) is low and because leg and trunk length are both independently related to fetal growth (Wadsworth *et al*., 2002), these measures of body size may be sensitive to different exposures during growth. Finally, there is evidence suggesting that trunk length is independently affected by socioeconomic and dietary factors (Gunnell *et al*., 1998).

Many of the early case series of insulin-requiring diabetes in resource poor countries comment on the thinness of the patients (Belcher, 1970; Abdulkadir *et al*., 1987). In our study, the men with diabetes had low BMI compared with the controls. Our data show that the reason for this low BMI is a reduction in both lean body mass and fat mass (Table 3). Although the methods we used to estimate body composition have not been validated in Ethiopia, both the skinfold method and bioimpedance methods have been shown to be accurate in multiracial populations although with different normal ranges (Zillikens and Conway, 1990; Kotler *et al*., 1996). Furthermore, in the current study, we have compared people with diabetes with controls from the same ethnic and environmental background. Finally, the striking similarity of estimates of body fat and lean body mass and differences between the diabetic patients and controls using the skinfold and bioimpedance methods, suggests that the differences we are observing are real. The abnormal body composition of the patients with diabetes may reflect persistent poverty and malnutrition possibly in association with poor diabetic control. However, because of the associated patterns of skeletal disproportion, which would have been achieved before the onset of the diabetes, it is more likely that the differences are a consequence of poor nutrition in early life. This is supported by the results of several studies, which show that deficits of early growth are associated with altered body composition throughout life, particularly a reduction in lean body mass (Singhal *et al*., 2003; Sayer *et al*., 2004).

Women showed a somewhat different anthropometric contrast between diabetic patients and controls. Although there was a reduction in BMI and fat mass, lean body mass

was maintained and there was a tendency for them to be taller than the controls with longer leg length. Although the analysis among the women lacked statistical power because of the smaller number of cases and controls, these preliminary findings suggest that the anthropometric patterns associated with disease differ in women. A possible explanation is that because the atypical diabetes observed in Ethiopia is much more prevalent among men than women, there exists a greater case heterogeneity among the women, with a higher proportion of classical type 1 diabetes. This is commonly associated with excessive childhood growth (Blom *et al*., 1992), and might account for the greater linear growth in women with diabetes.

This study of insulin-dependent diabetes in Ethiopia has shown strong links between the disease and markers of poverty. It also shows that men with the disease have associated disproportionate skeletal growth. These findings point towards a nutritional aetiology for this condition although the nature of the nutritional deficiency and its timing during growth and development remain obscure. There is good experimental evidence that undernutrition *in utero* or during early life leads to permanent defects of insulin secretion and diabetes in animal models and this leads to a male preponderance of glucose intolerance/insulin resistance (Hay, 2006; Gatford *et al*., 2008). This offers a potential mechanism for the disease and raises the possibility that this type of diabetes, prevalent in Ethiopia and other countries in sub-Saharan Africa, may be part of the spectrum of diseases resulting from fetal programming. Studies are needed that concentrate particularly on the patterns of nutrition experienced in early life.

Conflict of interest

The authors declare no conflict of interest.

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