Diabetic complications and glycaemic control in remote North Africa

G Gill, A Gebrekidan, P English, D Wile, and S Tesfaye

Summary

Background: Delivery of diabetes services in resource-poor areas of Africa is difficult. Control is often poor and complications are common. However, adequate robust surveys are uncommon, particularly in remote rural areas. This makes needs assessment difficult and healthcare planning impossible.

Aim: To accurately assess the glycaemic control and burden of complications in a group of diabetic patients from a remote area of a resource-limited north African country.

Design: Prospective cohort study.

Methods: Over a 6-week period, all patients attending the diabetic clinic at Mekelle Hospital in northern Ethiopia were intensively assessed, using imported western technology as necessary. Glycated haemoglobin (HbA_{1c}), lipid profile, serum creatinine and urinary albumin–creatinine ratio were measured. Complications were assessed as accurately as possible, including examination of fundi by an ophthalmic specialist, and biosthesiometry for neuropathy.

Results: There were 105 patients, mean (±SD) age 41 ±16 years and diabetes duration 7±6 years. There were 74 (70%) males, and 69 (66%) on insulin. Median body mass index was low at 20.6 kg/m^2, but mean HbA_{1c} high at 11.3±2.8% (68% had an HbA_{1c} over 100%). Cataract (12%), retinopathy (21%), neuropathy (41%) and microalbuminuria (51%) were common; but nephropathy (2%) was rare, as was large vessel disease (6% had peripheral vascular disease, and none had coronary artery disease or cerebrovascular disease). Risk factors such as hypertension (5%) and smoking (2%) were uncommon, and lipid profiles were generally good.

Discussion: We conclude that in this severely resource-limited area of North Africa, glycaemic control amongst diabetic patients is very poor. Neuropathy, retinopathy and microalbuminuria are common; but large vessel disease risk factors are beneficial, and macroangiopathy prevalence is low. Scattered populations, shortage of drugs and insulin and lack of diabetes team care are major factors behind these serious issues of diabetic control and complications.

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Introduction

Diabetes mellitus is a chronic incurable disease associated with significant morbidity and mortality. Diabetes is rapidly increasing in prevalence worldwide, particularly so in developing countries which are least able to cope with this complex and serious disease.[1] Shortage of insulin, other drugs, monitoring and laboratory facilities and trained staff all lead to serious shortfalls in diabetes care in resource-poor countries.[2] These factors potentially lead to poor glycaemic control and a high burden of complications.[3]

Despite numerous observational studies from various parts of Africa,[4] few reports have assessed complications using modern criteria and equipment, or glycaemic control using updated standardised glycated haemoglobin (HbA_{1c}) levels. Additionally, most publications on the burden and shortfalls of diabetes care in Africa come from the sub-Saharan region, though North Africa also includes severely resource-restricted countries with highly problematic diabetes care delivery.[4,5]

Ethiopia is one of the poorest countries in the world, and in the remote and rural northern areas, access to diabetes services is particularly difficult.[6] We have therefore investigated complication status in detail and glycaemic control in a group of diabetic patients attending a diabetic clinic in northern Ethiopia.

Patients and methods

We investigated in detail 105 consecutively attending patients, over a 6-week period, at the diabetic clinic of Mekelle Hospital in northern Ethiopia. The hospital has 200 beds and serves a population of about 150 000 over a very wide geographical area. The region is poor and remote with very limited facilities, serious famines have occurred in the past and food supplies remain poor at present. In the hospital diabetic clinic, HbA_{1c} cannot be measured and blood glucose only occasionally. Self-glucose monitoring is not possible, and supplies of insulin and syringes are erratic. Glibenclamide is the only oral hypoglycaemic agent available. Patients receive all medical supplies exclusively from the hospital and usually attend monthly. They often travel great distances from their home to Mekelle (not uncommonly over 100 km).

Demographic data

Patients were seen by one physician, data was recorded onto a proforma and in the UK it was transferred to a computer database. Age, sex, diabetes duration, family history, smoking status and diabetic treatment was recorded. Body mass index (BMI) was calculated from

weight (kg) in light clothing without shoes, and height (metres) without shoes. Blood pressure (BP) was measured with the patient seated, using a mercury sphygmomanometer.

Laboratory measurements
Blood was taken by venepuncture and an aliquot put into a fluoride-oxalate tube for blood glucose analysis (all patients attended fasting). This was measured by a private laboratory in Mekelle by a glucose oxidase method, specially funded for the project. HbA_{1c} was measured on a finger prick blood sample using a portable meter with reagent cartridges, brought from the UK and again specifically funded for the project. The meter was a Haemaquant (Provalis Diagnostics Ltd, Queensferry, Wales, UK), which uses boronate affinity chromatography and is diabetes control and complications trial (DCCT)-aligned.[7] The non-diabetic reference range was 4.5–6.2%, and the meter gave a result in 4 min. This HbA_{1c} system has been pilot-tested in the area and found to be robust and reliable.[8] Separated serum was stored at –20°C, and later transported to the UK on dry ice. Fasting lipids were measured by standard laboratory techniques – cholesterol, HDL cholesterol and triglycerides on a Hitachi 747 automated analyser (Roche Diagnostics, Lewes, Sussex, UK), and LDL cholesterol was calculated using the Friedewald equation.

Complication assessment
Retinopathy
Patients were assessed for retinopathy by a private ophthalmologist in Mekelle. Fundi were examined with dilatation, cataract was noted if present and any retinopathy graded as either background, pre-proliferative or proliferative.

Neuropathy
This was assessed using a hand-held biosthesiometer (Bio-Medical Instrument Company, Newbury, Ohio, USA) brought from the UK for the project. Vibration perception threshold (VPT) was measured 3 times at the right great toe, and the average was calculated. Neuropathy was defined as a VPT over 15 V.

Nephropathy
Patients provided a morning urine sample into a clear container, which was 'dipstixed' (Multistix, Bayer PLC, Newbury, Berkshire, UK) for semiquantitative assessment of glucose, ketones, protein, blood, nitrite and leucocytes. A plastic-cupped sample tube was filled 'brim-full' (to prevent evaporation) with urine, deep-frozen and transferred to the UK in the same way as the serum samples. Urine in which dipstix analysis suggested infection (positive for nitrite and eucocytes) were excluded from urinary microalbumin analysis, as were samples with haematuria (bladder and renal stones, as well as schistosomiasis are common in the Mekelle area). Urinary albumin–creatinine ratio (ACR) was measured on the remaining samples and serum creatinine on all patients – both by standard laboratory methods. Nephropathy was considered present if the urinary ACR was >25.0 mg/mmol and retinopathy was present. Microalbuminuria was diagnosed if the ACR was >25 and <25.0 mg/mmol in men and >3.5 and <25.0 mg/mmol in women.

Peripheral vascular disease (PVD)
This was diagnosed if typical claudication was present, or both the dorsalis pedis and posterior tibialis pulses were absent.

Ischaemic heart disease (IHD)
There were no ECG facilities available, so IHD was diagnosed if the patient had a history of chest pain compatible with angina and/or had a documented past myocardial infarction.

Cerebrovascular disease (CVD)
This was considered present if the patient had suffered a previous stroke, or if there was a history compatible with current or past transient cerebral ischaemic attacks (TIA).

Statistics and ethics
Ethical approval for the study was obtained from the Ethical Committee of the Mekelle Health Board. Statistical analysis was performed using StasDirect statistical software, version 2.4.4. Quantitative data was expressed as mean±standard deviation, and as medians with interquartile ranges if non-normally distributed.

Results

Demographic data
This is shown in Table 1. Patients were generally of short diabetes duration and there were over twice as many males as females.

Type of diabetes
The majority (66%) were on insulin, mostly from or close to diagnosis. Arbitrarily defining type 1 diabetes as onset <30 years of age and needing insulin from diagnosis, 42 (40%) were type 1 and 63 (60%) type 2 (36 on oral agents and 27 on insulin). However, many apparent type 1 patients had been without insulin in the past for several weeks (due to supply and shortage problems), and had not developed ketoacidosis, raising the possibility of 'malnutrition-related diabetes mellitus'.[5,9]

Occupation and location
There were 68 (65%) patients from Mekelle and 37 (35%) from outside. Many of the latter came from very distant locations. Thus, 28 travelled to clinic on foot, taking an average 25 h (ranging from 2 h to 3 days) to reach Mekelle. Nine travelled by bus, the journey being on average 14 h long (ranging from 30 min to 1.5 days). The major occupations were housewives [25 (24%)], farmers [20 (19%)], merchants [15 (14%)], students [8 (8%)], labourers [6

Table 1 Demographic and glycaemic control data in northern Ethiopian diabetic patients (n=105)

	Whole group	Males	Females
Age (years)	41±16 (16–77)	40±16 (16–77)	41±15 (17–65)
Diabetes duration (years)	7±6 (1–27)	8±6 (1–27)	7±5 (1–20)
Gender	M:F = 74:31 (2.4:1.0)	74 (70%)	31 (30%)
Family history	10 (9)	9 (12)	1 (3)
BMI (Kg/m^2)	20.6 (5.4)	20.0 (4.8)	22.7 (5.7)
Treatment			
Diet (%)	1 (1)	1 (1)	0 (0)
Drugs (%)	35 (33)	21 (28)	14 (45)
Insulin (%)	69 (66)	52 (70)	17 (55)
Fasting BG (mmol/l)	12.0±5.1	11.6±5.5	12.6±4.8
HbA_{1c} (%)	11.3±2.8	11.6±2.8	10.5±2.7
HbA_{1c} >10.0%	73%	78%	61%

Results are means ± 1SD, except for BMI which is median with IQR. Insulin treament was once-daily isophane or lente insulin in 30 patients (43%) and twice-daily in 39 (57%). Glibernclamide was the sole oral agent used.
BMI: Body Mass Index; BG: blood glucose.

(6%)], civil servants [5 (5%)], teachers [4 (4%)] and tailor [1 (1%)]. There were 21 (19%) unemployed or retired.

Glycaemic control

Both fasting blood glucose (FBG) and HbA_{1c} were markedly high (Table 2). Only 27 (26%) had FBG <8.0 mmol/l; and only 6 (6%) had HbA_{1c} <7.0% – the standard target HbA_{1c} level from the DCCT[7] and United Kingdom prospective diabetes study (UKPDS)[10] – for types 1 and 2 patients respectively. Most patients (71 or 68%) had very poor long-term glycaemic control with an HbA_{1c} level >10.0%.

Risk factor data

Risk factor data are shown in Table 2. Levels of hypertension and smoking were very low (5 and 2%, respectively). The fasting lipid profiles were generally good (no patient was on lipid-lowering therapy which is unavailable in Mekelle), and no patient had a diagnosable hyperlipidaemia.

Table 2 Risk factor data in northern Ethiopian diabetic patients (n = 105)

Hypertension (BP >140/90)	5 (5%)
Systolic BP	108±17 mmHg
Diastolic BP	72±11 mmHg
Smoking	2 (2%)
Fasting lipids	
Cholesterol (mmol/l)	4.6±1.4
Triglycerides[a] (mmol/l)	1.5 (1.4)
HDL-C (mmol/l)	1.0±0.3
LDL-C (mmol/l)	2.8±1.1

[a]Results are means±SD, except for triglyceride which is median with IQR. HDL-C is high density lipoprotein cholesterol, and LDL-C is low density lipoprotein cholesterol.

Complication data

There was an apparent low rate of large vessel disease (though diagnostic facilities were limited) – no patients had IHD or CVD, and only 6% had PVD. Cataract was common (23%), as were retinopathy (21%) and neuropathy (41%). Nephropathy was uncommon (2%), perhaps related to the short mean duration of diabetes in the group; but microalbuminuria was very common (51%) (Table 3).

Discussion

Our results show that this diabetic population in northern Ethiopia is lean (median BMI 20.6) with very poor

Table 3 Complication details in northern Ethiopian diabetic patients (n = 108)

Retinopathy	22 (21%)
Background	18
Preproliferative	2
Proliferative	2
Cataract	13 (12%)
Neuropathy	43 (41%)
Nephropathy[a]	1 (2%)
Microalbuminuria[a]	35 (51%)
Serum creatinine	72 (22) μmol/l (range 10–145)
Creatinine >120 μmol/l	2 (2%)
Peripheral vascular disease	6 (6%)
Foot ulcer	4 (4%) – past foot ulcer 7 (7%)
Ischaemic heart disease	0 (0%)
Cerebrovascular disease	0 (0%)

Creatinine is median with IQR. [a]Urinary ACR levels (to assess microalbuminuria and nephropathy) were done on 59 patients, as those with haematuria and/or urinary infection were excluded (see Patients and Methods section).

glycaemic control – mean fasting glucose 12.0±5.1 mmol/l and HbA_{1c} 11.3±2.8%. Over two-thirds had an HbA_{1c} level over 10.0% and these levels are directly comparable to European and North American levels, as the assay was DCCT-standardized.[7] Probably related to this poor glycaemic control, we found rates of diabetic complications to be high, despite a mean duration of diabetes of only 7 years. Thus retinopathy was present in 21%, cataract 12%, neuropathy 41% and microalbuminuria in 51%. Only one patient had nephropathy, presumably because of the mean short diabetes duration (7 years). Though we do not have definitive supportive data, our impression is that the short diabetes duration of our patients is likely to be due to high and early mortality. This makes the complication rates observed of particular concern, and presumably reflect the markedly poor glucose control.

We had no adequate investigative facilities for large vessel disease, so our estimates must be interpreted with caution. Nevertheless, it is remarkable that in this population no patients had symptoms of angina, or a past history of myocardial infarction, stoke or TIA. Rates of hypertension (5%) and smoking (2%) were extremely low, and lipid profiles generally good.

Large vessel disease has also been reported to be uncommon in diabetic populations both from Ethiopia and sub-Saharan Africa,[11,12] though it is certainly now rapidly emerging in urban 'westernised' areas such as Johannesburg.[13]

Interestingly, as in our study, PVD has previously been recorded in African diabetic patient as the predominant form of large vessel disease[11,12] though the small numbers and relatively crude diagnostic criteria make such data a little difficult to interpret. The general rarity of large vessel disease in African diabetic patients may represent ethnic protection reflecting the traditional African lifestyle (with low BMI and BP, beneficial lipid profiles and low smoking rates). Comparative studies on microangiopathic complications are difficult to find, because of variations in diagnostic methods and accuracy. A careful, though now rather dated study from Zambia by Rolfe, showed a retinopathy prevalence of 34% with a diabetes duration similar to our study at about 6 years.[14] There was no information available on glycaemic control (comparable to our study), which may explain the higher retinopathy rate in Zambian series. Also in the Zambian study the prevalence of peripheral neuropathy was 31%[15] – lower than our figure of 41%, but our diagnostic criteria were more sensitive. Nephropathy prevalence was low in our study, as well as in other reports elsewhere in Africa,[4] almost certainly because of the generally short mean duration of diabetes. However, reports from Nigeria[16] and South Africa[17] suggest that at least in some parts of the continent, diabetic nephropathy is emerging as a growing cause of end-stage renal failure. We found only one case of nephropathy in our series, but many patients (51%) had microalbuminuria. This is higher than most other African studies (e.g. 11% in a recent Tanzanian study[18]), though our figure may be a little exaggerated as diagnosis was based on a single urine measurement only. The apparent low level of progression from microalbuminuria to nephropathy in our patients may be related to short mean diabetes duration and/or the unusually low blood pressure levels.

Markers of glycaemic control (mean HbA_{1c} 11.3% and mean fasting blood glucose 12.0 mmol/l) in our patients were very poor. Given their relatively short duration of diabetes (mean 7 years), and low rates of smoking, hypertension and dyslipidaemia, it seems likely that hyperglycaemia is the most important factor accounting for the high prevalence of diabetic complications seen in our study. Access to diabetes care for many of our patients is difficult – of the 35% who lived outside Mekelle, the mean journey time to clinic was over one day. In addition, food supplies are erratic, and insulin and syringe availability intermittent. No monitoring facilities or diabetes nurse support networks exist. These are problems shared with other parts of northern Ethiopia.[6,19]

There are no recent surveys of diabetes prevalence or incidence in Ethiopia. Prevalence of clinic cases in Gondar compared with the local population size gives a figure of 0.2%, though this is certainly an underestimate.[20] Whatever the prevalence, local experience is that it is increasing, and thus the problems of control and complications we have reported here will rise in importance.

In conclusion, our study has used rigid and modern complication assessment systems and biochemical tools in a highly resource-limited region of North Africa. The results are likely to applicable to other similar areas, and indicate major deficiencies in glycaemic control and a consequent high burden of diabetes-related complications.

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Conflict of interest: None declared.

References

1. Beaglehole R, Yach D. Globalisation and the prevention and control of non-communicable disease: the neglected chronic diseases of adults. *Lancet* 2003; 362: 903–8.
2. Beran D, Yudkin JS. Diabetes care in sub-Saharan Africa. *Lancet* 2006; 368: 1689–95.
3. Gill GV. Outcome of diabetes in Africa. In: Gill GV, Mbanya J-C, Alberti KGMM, eds. *Diabetes in Africa.* FSG Ltd, Cambridge 1997; 65–71.
4. Gill GV, Mbanya J-C, Alberti KGMM. *Diabetes in Africa*. FSG Ltd, Cambridge 1997.
5. Habru E, Gill G, Tesfaye S. Characteristics of insulin requiring diabetes in rural Ethiopia – a possible link with malnutrition? *Ethiop Med J* 1999; 37: 263–7.
6. Alemu S, Watkins P. Access to diabetes care in northern Ethiopia. *Diab Voice* 2004; 49: 8–10.
7. Diabetes Control and Complications Trial Research Group (DCCT). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Eng J Med* 1993; 329: 977–86.
8. Gebrekidan A, Gill G, Wile D, Gill A, Tesfaye S. An accurate and

portable system for glycated haemoglobin measurement in the tropics. *Trop Doct* 2004; 34: 94–5.
9. Gill GV, Tekle A, Reja A, English PJ, Diver M, Tesfaye S. Malnutriton-related diabetes mellitus – evidence for its existence in northern Ethiopia. *Diab Metab* 2003; 29: 4S172.
10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53.
11. Lester FT, Keen H. Macrovascular disease in middle-aged diabetic patients in Addis Ababa, Ethiopia. *Diabetologia* 1998; 31: 361–7.
12. Rolfe M. Macrovascular disease in diabetics in Central Africa. *Brit Med J* 1988; 296: 1522–5.
13. Ntyintyane L, Panz VR, Raal FJ, Gill GV. Metabolic syndrome, undiagnosed diabetes mellitus and insulin resistance are highly prevalent in urbanised South African blacks with coronary artery disease. *Cardiovasc J South Africa* 2006; 17: 7–12.
14. Rolfe M. Diabetic eye disease in Central Africa. *Diabetologia* 1988; 31: 88–92.
15 Rolfe M. The neurology of diabetes mellitus in Central Africa. *Diab Med* 1988; 5: 399–401.
16. Alebiosu CO, Ayodele OE. The increasing prevalence of diabetic neuropathy as a cause of end-stage renal disease in Nigeria. *Trop Doct* 2006; 36: 218–9.
17. Gill GV, Huddle KR, Monkoe G. Long-term (20 years) outcome and mortality of type 1 diabetic patients in Soweto, South Africa. *Diab Med* 2005; 22: 1642–6.
18. Lutale J. Prevalence of microalbuminuria in people with diabetes in Dar es Salaam, Tanzania. *Diab Med* 2006; 23 (Suppl. 4): 245.
19. Watkins P, Alem S. Delivery of diabets care in rural Ethiopia: an experience from Gondor. *Ethiopia Med J* 2003; 41: 9–17.
20. Brown V, Alemu S, Wtkins P. Diabetes in Ethiopia: overcoming the problems of care delivery. *J Diabetes Nursing* 1998; 2: 28–31.

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