Type 1 diabetes in Kenya: treatment options and emerging trends

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Introduction

Diabetes mellitus is a chronic, metabolic disorder resulting from insulin hyposecretion and/or insulin resistance leading to elevated glucose levels in the bloodstream. Diabetes comprises a group of disorders classified according to their aetiology. Type 1 diabetes is caused by an autoimmune destruction of the pancreatic beta cells, resulting in absolute insulin deficiency. It affects 5–10% of diabetic patients worldwide. Leonard Thompson was the first to be treated by insulin injection on 11th January 1922, marking the onset of an insulin era before which the prognosis of these patients was grim.[1] Type 1 diabetes requires lifelong treatment with exogenous insulin for survival. Insulin, which is a polypeptide hormone, undergoes degradation in the gastrointestinal tract and therefore can only be delivered parenterally. It is administered subcutaneously in routine management and intravenously in emergencies (e.g. diabetic ketoacidosis). Type 1 diabetes has an early age of onset often presenting in children and adolescents. Interestingly some studies have shown that children in Africa tend to develop the condition almost a decade later than their European counterparts.[2]

Type 2 diabetes may result from predominant insulin resistance with relative insulin deficiency, or predominant insulin secretory defects with insulin resistance. It is the most common form of diabetes and accounts for 90% of diabetes cases worldwide. Type 2 diabetes often has a late age of onset (>40 years), although it is increasingly being observed in the young. It is often related to lifestyle and obesity. This form of diabetes is managed by diet, exercise, oral hypoglycemic agents and/or exogenous insulin.

Gestational diabetes refers to glucose intolerance occurring during pregnancy. It often resolves after birth, though these patients have a higher risk for type 2 diabetes later in life. Other specific types of diabetes are associated with genetic defects of beta cells or insulin action, diseases of the exocrine pancreas, endocrinopathies, infections, drugs/chemicals and other genetic syndromes. Variants of diabetes described specifically in Africa are ketosis-prone and malnutrition-related diabetes.[3]

The prevalence, incidence, history, pattern and outcomes of diabetes in many parts of sub-Saharan Africa, including Kenya, have not been well elucidated. The International Diabetes Federation (IDF) in 2007 estimated a 3.3% prevalence of diabetes in Kenya; though the actual figure is expected to be much higher as about two-thirds of patients may go undiagnosed.[4]

Diabetes is an expensive disease posing serious challenges to the healthcare system in Kenya. The high incidence of complications, such as lower limb amputations, blindness, renal failure and cardiovascular disease, often among the working class, leads to a decrease of productivity of the nation. In addition, diabetes increases the susceptibility of patients to communicable infections such as tuberculosis (TB) and pneumonia, further straining the healthcare budget. Studies in India showed that 20% of smear-positive TB cases were attributable to diabetes.[5] In Kenya, epidemiological studies on the association between diabetes and TB are lacking.

Despite this, diabetes in Kenya has often received less attention than infectious diseases such as HIV/AIDS, malaria, and tuberculosis. It was only in 2010 that Kenya launched its first ever National Diabetes Strategy,[6] which promoted provision of high quality, accessible, affordable, and evidence-based diabetes prevention and care services for all people living in Kenya. The key strategies include advocacy, empowerment, resource mobilisation and prioritisation, capacity building, partnership and coordination, control of policies/regulations and research.

Type 1 diabetes, which often receives less focus (perhaps due to its lower prevalence) than type 2 diabetes, presents a unique management challenge due to its earlier onset and hence longer duration of illness and high cost of insulin relative to oral hypoglycaemic agents. This article focuses on insulin pharmacotherapy of type 1 diabetes in Kenya, exploring the insulin types and regimens available, their pharmacokinetic profiles, indications, advantages, and disadvantages. Particular emphasis is given to the use of continuous subcutaneous insulin infusion (CSCII) therapy, an emerging trend in the management of type 1 diabetes in Kenya.

Management of type 1 diabetes: insulin therapy

Insulin therapy is the main tenet in the management of type 1 diabetes. Exogenous insulin, which is classified according to its source or duration of action, is routinely administered subcutaneously. Beef and pork insulin are extracted from beef and pork pancreas respectively, while human sequence insulin is produced by enzymatic modification of animal insulin or biosynthetically via recombinant

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Table 1 Types and properties of insulin available in Kenya[7]

Insulin preparation	Onset of action	Peak of action	Duration of action	Examples
Rapid-acting analogues	10–20 min	1–2 hrs	3–5 hrs	Lispro (Humalog) Aspart (Novorapid)
Short-acting (Soluble)	30–60 min	2–4 hrs	6–8 hrs	Ilentin II Regular Wosulin-R
Intermediate (NPH)	1–2 hrs	5–7 hrs	13–18 hrs	Ilentin II NPH, Wosulin-N
Biphasic mixtures	30 min	2–8 hrs	14–16 hrs	Wosulin 30/70, Wosulin 50/50
Premixed insulin*				
Long-acting analogues	1–2 hrs	Peakless	24 hrs	Glargine (Lantus) Detemir (Levemir)

*Premixed insulin is a combination of short-acting and intermediate-acting insulin in one insulin vial or cartridge (the numbers following the brand name indicate the percentage of each type of insulin).

DNA technology using bacteria or yeast. Table 1 classifies the various insulin preparations available in Kenya according to their onset, peak, and duration of action.[7] It is worth noting that the actual pharmacokinetic profile of the various insulin types will vary from patient to patient, thus necessitating individual patient assessment.

In type 1 diabetes, the treatment goals are to achieve normoglycaemia with minimal risk of hypoglycaaaaemia. Patients should ideally self-test their blood glucose, calculate their carbohydrate intake, and adjust their insulin doses appropriately. Hypodermic devices available for insulin delivery include single-use syringes and pen injectors such as Humapen® and Opti Pen® Pro 1. Blood glucose measurement is important in assessing short-term (daily) glucose control, while glycosylated haemoglobin (HbA_{1c}) gives an indication of long-term (2–3 months) glucose control. HbA_{1c} is frequently used both as a clinical assessment tool and to predict the risk of diabetic complications.

In a non-diabetic individual, the pancreas releases about half of the total daily insulin as background insulin throughout the day, while the remainder of the day's insulin is released after meals, with insulin levels rising 5 to 10 fold within the first 30 minutes after a meal and returning to basal levels after approximately 2 hours.[8] This natural state outlines the two critical components of insulin supplementation in type 1 diabetes; namely basal and bolus insulin. The requirements of basal insulin, which is the background insulin tailored to maintain normoglycaemia in the absence of carbohydrate intake, tend to vary throughout the day, and are difficult to match with twice-daily (and sometimes even multiple) insulin doses. A particular problem is the 'Dawn Phenomenon' or 'Dawn Effect' – persisting morning hyperglycaemia (sometimes with nocturnal hypoglycaemia). This was previously thought to be due to night hypoglycaemia causing counter-regulatory hormone release, and rebound morning hyperglycaemia ('the Somogyi Effect'). It is now thought that this pattern of glucose control is mainly due to 'run out' of intermediate or long-acting insulin taken the previous evening, possibly also with variation in baseline insulin requirements which cannot be matched by standard subcutaneous injection. The main recommended insulin regimens are discussed below.

Conventional insulin therapy. Conventional insulin (CI) therapy involves the use of a mixture of intermediate-acting and rapid/short-acting insulin (usually premixed) given twice a day before meal times. CI therapy, one of the oldest insulin regimens, does not always give good glycaemic control as it does little to replicate the normal pancreatic function. Patients on CI therapy may be predisposed to the 'Dawn Phenomenon' as their basal requirements are not tailor met. In addition, hypoglycaemic events tend to be more frequent with CI therapy and are worsened if patients delay or skip meals. A key advantage of CI therapy, however, is the low number of injections required daily. Examples of biphasic insulin used for CI therapy include Novolin® 70/30, Humulin® 70/30 and Novolog® 70/30.

Multiple daily injections. Multiple daily injections (MDI) or intensive insulin therapy optimises diabetes treatment by incorporating the use of once- or twice-daily long-acting basal insulin with short-acting bolus insulin at meal times. MDI involves the use of a minimum of four injections per day, but offers advantages such as better glycaemic control and more flexibility with regard to meal times, in comparison to CI therapy. Examples of basal insulin used in MDI include Glargine® and Defemir®, while bolus insulin used in MDI include Lispro® and Aspart®. The main disadvantage of MDI is the number of injections making it less favourable with patients. However, despite the use of MDI, some patients are still not able to achieve optimal glucose control, and some of these patients may be suitable candidates for continuous subcutaneous insulin infusion therapy.

Continuous subcutaneous insulin infusion. Continuous subcutaneous insulin infusion (CSII) also known as insulin pump therapy was first introduced in the 1970s at Guy's Hospital, London as an approach to help achieve normoglycaemia in type 1 diabetes.[9] CSII, which entails the use of an external mechanical device for continuous subcutaneous delivery of insulin, is designed to closely mimic the normal pancreas delivering small amounts of basal insulin throughout the day and patient-activated bolus insulin at meal times. Only soluble short-acting insulin can be used for CSII.

The first pumps were very large but several improve-

ments have since been made to develop the current pager-sized insulin pumps produced by companies such as Medtronic MiniMed, Animas Corporation, and Roche Diagnostics among others. Insulin pumps are used in the management of type 1 diabetes throughout the world in Europe, America, Asia, and Africa.

The insulin pump consumables, namely the insulin reservoirs (which store the insulin) and infusion sets (through which insulin is delivered) are changed every 2 to 3 days. Modern pumps may be very sophisticated, some also combining continuous glucose monitoring, programmed variability of basal insulin infusion rates,[10] and alarms for hypo- or hyperglycaemia. An overview of current insulin pumps available worldwide is presented in Table 2.[11]

Indications and effectiveness of insulin pump therapy

The UK National Institute for Health and Clinical Excellence (NICE) guidelines recommend CSII therapy for the management of type 1 diabetes in adults and children 12 years and over under the following conditions:[12]

- Attempts to reach target HbA_{1c} with MDI results in the patient having disabling hypoglycaemia which impacts negatively on their quality of life.
- HbA_{1c} levels have remained high (8.5% or more) with MDI. CSII is also recommended as a possible treatment for type 1 patients under 12 years. In cases where MDI is unsuitable or impractical. Contraindications to insulin pump therapy include psychiatric illness, lack of motivation, inaffordability, lack of skilled healthcare personnel, and blindness.

In a meta-survey comparing the use of MDI and CSII, Pickup et al found that CSII offered a slight advantage over MDI in glycaemic control. CSII was particularly beneficial only in sub-groups of patients with specific problems such as morning hyperglycaemia and unpredictable hypoglycaemia.[13] The insulin pump allows programming of increased basal insulin rates during the morning hours effectively counteracting the 'Dawn Effect', whose prevalence is reported to be as high as 54% in type 1 diabetes.[14]

The advantages of CSII include potentially better glycaemic control, increased flexibility with regard to meals and exercise, less variability in blood glucose levels, reduction of hypoglycaemic events, and improved quality of life. Reduction in the number of injections is

Pump type	Dimensions (mm)	Weight (oz)	Extra features
MiniMed Paradigm® Revel 523/723, Medtronic MiniMed, USA* (523 holds the 1.76 ml reservoir while 723 holds either the 1.76 ml or the 3.00 ml insulin reservoir)	50.8×76.2×20.3 (523) 50.8×91.4×20.3 (723)	3.53 3.81	Enhanced continuous glucose monitoring feature with REAL-time trend graphs, predictive alerts for hypoglycemia, hyperglycemia and rapid changes in blood glucose, bolus calculator, remote control. MiniMed Paradigm® Veo pumps have an additional low glucose suspend feature which shuts off insulin supply when hypoglycemia is detected.
Accu-Chek® Spirit Combo, Roche Diagnostics, USA	80 × 47 × 24	4.8	Icon and menu driven programming, reversible display screen, meter remote offers wireless bolus calculation and delivery, option of 12 languages.
OneTouch® Ping, Animas Corporation (Johnson & Johnson), USA	51 × 77 × 18	3.9	Meter remote offers wireless bolus calculation and delivery, integrated database with carbohydrate counts of up to 500 food items.
OmniPod®, Insulet Corporation, USAS (consists of the pod which holds and delivers insulin and the PDA which programmes insulin delivery)	41 × 61 × 18 (Pod) 66 × 110 × 26 (PDA)	1.2 4.0	World's first tubeless pump, the PDA (personal digital assistant) has an integrated blood glucose meter and and a reference library with carbohydrate counts of over 1000 common foods.
DANA Diabecare® IIS, Sooil Development, USA	46 × 77 × 19	2.3	Built-in glucose meter, carbohydrate counting programme auto dose capabilities, bolus frequency restrictions PIN programming to access functions, option of 12 languages.
t:slim®, Tandem Diabetes Care, USA	79.5 × 50.8 × 15.2	3.95	Colour touch screen, slim sleek design; resembles a smart phone, USB connectivity, rechargeable battery.
*Medtronic MiniMed insulin pumps are locally available via Cardiac Implant Systems Limited, Kenya.			

Table 2 Current insulin pumps available worldwide[11]

also a key benefit; with CSII patients only required to change their infusion sets every 2 to 3 days. A summary of the advantages and disadvantages of CSII and other insulin regimens is shown in Table 3.

Costs and problems of insulin pumps. CSII, however, is not without challenges, the most obvious being the very high cost. The initial cost associated with insulin pump therapy varies with the pump manufacturer. An estimated cost of US$5475 for Animas pumps, US$5495 for Medtronic MiniMed pumps and US$4995–5495 for Disetronic Medical Systems (now Roche Diagnostics) pumps has been reported.[15] In addition there is the ongoing cost of pump consumables namely insulin reservoirs and infusion sets (~ $1,500 per annum). Kanakis et al[15] estimated the annual cost of CSII consumables to be $1554 to 2160 compared with an annual cost of $288-332 and $336 for insulin pen needles and insulin syringes respectively in the USA. Following a UK-based Health Technology Assessment in 2004; Colquitt et al[16] estimated the additional cost of CSII (including the cost of the insulin pump, consumables and initial patient education) over MDI to be approximately £1091 to 1680 per annum depending on the make of the insulin pump and the estimated life of the device. Most insulin pump models have a warranty of 4 years, after which patients replace them. In another study based in South Africa, Brown[17] estimated a total cost (including the cost of insulin and insulin delivery devices namely pen injectors and needles or insulin pump and pump consumables) of R672 and R2477–3178 for MDI and CSII respectively. CSII also requires intensive training and a highly motivated patient, and cannot be used in the absence of skilled health personnel. Insulin pumps may also not be acceptable to some patients who feel uncomfortable having an attached device. Finally, patients on CSII rely solely on the pump for insulin, therefore in case of pump malfunction or failure, hyperglycaemia and diabetic ketoacidosis could develop rapidly. Therefore, patients on CSII must monitor their blood glucose levels frequently and may require insulin vials and syringes for back-up purposes.

New advances in insulin pump therapy

In 2006, Medtronic Diabetes (Northridge, CA) launched the MiniMed Paradigm REAL-time system, the first system to integrate real-time continuous glucose monitoring sensors (CGMS) with insulin pump therapy.[18] The CGMS feed-back glucose data to the insulin pump in real-time thereby optimising therapy; the patient is able to view changes in glucose levels and take corrective action. Furthermore, some of the latest insulin pumps have automatic shut-off mechanisms which stop insulin delivery when hypoglycaemia is detected – an indispensable advantage for those prone to nocturnal hypoglycaemia. CGMS are changed every few days and present an added expense (US$4930 to US$7120 per annum).[19]

Although the utilisation of insulin pump therapy and continuous glucose monitoring in the treatment of type 1 diabetes in Kenya has been described previously,[20] a review of the literature did not reveal any published scientific reports involving larger groups of patients.

Socioeconomic factors

In Kenya, socioeconomic status plays a major role in determining the access to various healthcare services[21] and the access to diabetes care is no exception. There are reports of patients in both rural and urban settings being unable to afford basic modalities of diabetes care such as insulin, blood glucose monitoring, and HbA_{1c} testing.[22,23] Although the cost of insulin is highly subsi-

Therapy	Conventional (CI)*	Multiple daily injections (MDI)†	Insulin pump (CSII)††
Advantages	Only two injections required per day	Better flexibility in terms of meal times and potentially improved glycaemic control when compared to CI[2]	Reduced hypoglycaemia and improved overall glycaemic control. Improved life quality. Greater meal flexibility
Disadvantages	Lack of flexibility in terms of meal times, frequent hypoglycemia, non-optimal control in patients prone to the Dawn Phenomenon	Increased number of injections	Cost of pump and pump consumables, risk of infusion site infections, patient discomfort with attachment to a device
Insulin delivery device	Insulin syringes or pen injectors	Insulin syringes or pen injectors	Insulin pump and pump consumables (infusion sets and reservoirs)

Notes
* Conventional insulin.
† Multiple daily injections.
†† Continuous subcutaneous insulin infusion.

Table 3 Comparison of insulin regimens for type 1 diabetes

dised in government health facilities, a regular supply of insulin in these facilities is not guaranteed.

The utilisation of CSII in the management of type 1 diabetes is an emerging trend in Kenya, with the advent of specialised clinics dealing with insulin pump therapy. Socioeconomic status will however be a main determinant in accessing CSII considering the great cost of an insulin pump, continuous glucose sensors and pump consumables, which exceed an average Kenyan's salary. In addition to these basic costs, significant expert health worker input is needed, in terms of support and education.

Conclusions

A wide variety of insulin preparations exist, classified by source or duration of action. There are also a number of possible insulin regimens in type 1 diabetes, namely conventional insulin therapy, multiple daily injections, and continuous subcutaneous insulin infusion therapy. Continuous subcutaneous insulin infusion offers promising benefits, but the cost of this therapy will limit its utilisation for the foreseeable future.

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References

1. Burrow G, Hazlett BE, Phillips MJ. A case of diabetes mellitus. *N Engl J Med* 1982; 306: 340–3.
2. Kalk WJ, Huddle KRL, Raal FJ. The age of onset and sex distribution of insulin-dependent diabetes mellitus in Africans in South Africa. *Postgrad Med J* 1993; 69: 552–6.
3. Hall V, Thomsen RW, Henriksen O, Lohse N. Diabetes in sub-Saharan Africa 1999-2011: Epidemiology and public health implications. A systematic review. *BMC Public Health* 2011; 11: 564.
4. *Diabetes Atlas*. 3rd Edition. International Diabetes Federation, Brussels, Belgium, 2006.
5. Stevenson CR, Forouhi NG, Roglic G, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health* 2007; 7: 234–42.
6. Kenya National Diabetes Strategy 2011-2015. Available online at http://diabetes-communication.org/wordpress/wp-content/uploads/2012/09/Kenya-National-Diabetes-Strategy-2010-2015-Complete.pdf. Accessed 13/08/2012.
7. Pharmacy and Poisons Board database of human pharmaceuticals registered in Kenya. http://www.pharmacyboardkenya.org/index.php?id=56. Accessed 13/08/2012
8. Emilien G, Maloteaux JM, Ponchon M. Pharmacological management of diabetes: recent progress and future prospective in daily drug treatment. *Pharmacol Ther* 1999; 81: 37–51.
9. Pickup JC, Keen H, Parsons JA, Alberti KGMM. Continuous subcutaneous insulin infusion: an approach to achieving normoglycemia. *Brit Med J* 1978; 1: 204–7.
10. Walsh J, Roberts R. *Pumping insulin: everything you need for success on a smart insulin pump*, 4th Edition. Torrey Pine Press, 2006; pp 25-52.
11. Current insulin pumps available worldwide. http://www.diabetesnet.com/diabetes-technology/insulin-pumps/current-pumps/pump-comparison. Accessed 13/08/2012
12. National Institute of Health and Clinical Excellence (NICE) technology appraisal guidance 151. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. Available online http://www.nice.org.uk/nicemedia/live/12014/41300/41300.pdf. Accessed 13/08/2012
13. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomized controlled trials. *Brit Med J* 2002; 324: 705-8.
14. Carroll MF, Schade DS. The dawn phenomenon revisited: implications for diabetes therapy. *Endocr Pract* 2005; 11: 55–64.
15. Kanakis SJ, Watts C, Leichter SB. The business of insulin pumps in diabetes care: clinical and economic implications. *Clinical Diabetes* 2002; 20: 214-6.
16. Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technol Assess* 2004; 8: 53-71.
17. Brown VJ. An overview of insulin pump therapy: appropriate use of an expensive resource. *J End Metab Diab Sth Afr* 2012; 17: 122–6.
18. Mastrototaro J, Scott L. The integrated MiniMed Paradigm REAL-Time insulin pump and glucose monitoring system: implications for improved patient outcomes. *Diab Tech & Therapy* 2009; 11: S37–S43.
19. Hermanides J, Phillip M, DeVries JH. Current application of continuous glucose monitoring in treatment of diabetes. Pros and Cons. *Diabetes Care* 2011; 34: S197–S201.
20. Mohamed G. Care of children with diabetes. Diabetes Leadership Forum - Africa 2010. Available online at http://174.132.77.189/~tktsco/diabetesforum/images/ppt/25-Dr-Ali-Mohamed-Gaman.pdf. Accessed 13/08/2012.
21. Chuma J, Okungu V. Viewing the Kenyan health system through an equity lens: implications for universal coverage. *Int J Equity Health* 2011; 10: 22.
22. Pastakia SD, Karwa R, Kahn CB, Nyabundi JS. The evolution of diabetes care in the rural, resource-constrained setting of western Kenya. *Ann Pharmacother* 2011; 45: 721–6.
23. Otieno FCF, Ng'ang'a L, Kariuki M. Validity of random blood glucose as a predictor of the quality of glycaemic control by glycated haemoglobin in out-patient diabetic patients in Kenyatta National Hospital. *East Afr Med J* 2002; 79: 491–5.