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Assessing Utilisation and Expenditure on Long-Acting Insulin Analogues in Kenya; Findings and Implications for the Future

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Abstract **Original Research Article**

Prevalence rates for patients with diabetes mellitus are rising across countries including sub-Saharan African countries, which will continue. As a result, there are an increasing number of patients with insulin-dependent diabetes across sub-Saharan Africa including Kenya. Growing prevalence rates are increasing the costs of treating patients with diabetes enhanced by associated complications. These include both microvascular and macrovascular complications, with hypoglycaemia and generally poor control of diabetes contributing to the burden. Long-acting insulin analogues were developed to reduce rates of hypoglycaemia associated with insulin usage, including nocturnal hypoglycaemia, and improve adherence through improving patient convenience. As a result, they are now included in the Kenyan Essential Medicines List. However, long-acting insulin analogues are typically considerably more expensive than standard insulins limiting their use in practice, especially in countries such as Kenya with concerns with affordability even for standard insulins such as Mixtard®. Consequently, a need to ascertain current utilisation and expenditure patterns for the different insulins including long-acting insulin analogues across Kenya starting with leading referral hospitals. Research in Kenyatta National Hospital (KNH) showed growing use of insulin glargine reaching up to 3.4 to 3.6% of total insulin utilisation in 2019 and 2020. However, prescribing was limited by considerably higher prices (3.4 fold higher) than standard insulins on a defined daily dose basis. Considerably higher prices resulted in no utilisation of long-acting insulin analogues in another leading referral hospital in Kenya. Overall, appreciably lowering the prices of long-acting insulin analogues through instigating local production and other activities should increase their use benefiting patients and the healthcare system in Kenya and wider. These are considerations for the future.

Keywords: Affordability, biosimilars, diabetes, drug utilisation, essential medicine lists, long-acting insulin analogues, Kenya, pharmaceutical health policy.

INTRODUCTION

The prevalence of diabetes mellitus continues to rise across countries including sub-Saharan African countries enhanced by rising incidence rates [1-5], with the number of patients with diabetes in sub-Saharan Africa likely to reach 34.2 million by 2040, and potentially up to 42 to 47 million across Africa by 2045 [5-7]. These growing prevalence rates will have an appreciable impact on morbidity, including health-related quality of life, mortality and costs across sub-Saharan Africa and wider [2,8-12], building generally on the growing burden of non-communicable diseases (NCDs) across sub-Saharan Africa [13,14]. We already see NCDs accounting for an appreciable number of in-patient beds in sub-Saharan Africa, and this will grow [15]. The actual burden of diabetes is also likely to be considerably higher in sub-Saharan Africa than current published rates given the appreciable number of undiagnosed patients [16]. This burden is enhanced by the associated micro- and macrovascular complications with diabetes, which include diabetic retinopathy, coronary vascular disease (CVD), chronic kidney disease (CKD), heart failure and ulceration including diabetic foot ulceration [2, 8, 10, 17-19], with

hypoglycaemia and generally poor control of diabetes contributing to this burden [20-22].

Kenya is no exception with rising rates of NCDs, which will become the greatest disease burden by 2027 overtaking infectious diseases, and include patients with diabetes [15, 23]. There are differences in prevalence rates between rural and urban populations in Kenya; however, current estimates are likely to be under-estimates given the considerable number of undiagnosed patients among the population [15].

Whilst the majority of patients with diabetes in sub-Saharan Africa, including Kenya, have type 2 diabetes (T2DM) as opposed to Type 1 diabetes (T1DM) [5, 24], an appreciable number of patients with diabetes are insulin dependent across low- and middle-income countries (LMICs) including sub-Saharan African countries [25-28]. This is a concern given the high costs of insulin and accompanying monitoring equipment among patients with diabetes mellitus in Kenya and wider with high co-payment levels outside of hospital, which can be catastrophic for some families [29]. Medicine costs are currently the greatest contributor to total direct costs among patients with diabetes in Kenya, accounting for an average 52.4% of total costs for those attending public healthcare facilities in Kenya [29]. Costs are enhanced by high levels of co-morbidities among patients with diabetes mellitus including hypertension, CVD and CKD, adding to the burden of the disease as well as access and affordability of medicines to treat diabetes and associated complications [5, 24, 30].

Access and availability of insulins generally is a continuing issue across low- and middle-income countries (LMICs) [31], highlighted in the studies by the ACCISS (Addressing the Challenge and Constraints of Insulin Sources and Supply) group [32-34]. There are similar concerns with the availability and costs of glucagon to treat any resultant hypoglycaemia among African countries [35].

High costs of insulin have been exacerbated by the lack of competition with three principal manufacturers globally accounting for up to 96% of the global market by volume and up to 99% by value [32, 34, 36, 37]. Having said this, we are seeing a range of initiatives among sub-Saharan African countries to enhance diagnosis and affordability of insulins, and this is likely to continue. Initiatives include the Changing Diabetes in Children' (cCDiC) initiative launched in 2010 in Cameroon to offer free diabetes care to children and adolescents with T1DM as access and availability to insulins, as well as blood glucose monitoring equipment, had been a major issue [38-40]. There are similar initiatives in Nigeria with Novo Nordisk looking to offer insulin free to children during 2021 [41]. The International Insulin Foundation has also worked with governments in Mozambique and Zambia to enhance access to insulin [42], and in Tanzania, Biocon is looking to take part in a pan-African project entitled 'Mission 10 cents' whereby insulins, including recombinant human insulin (rh-insulin), will be sold at a cost of less than 10 US cents per day [43].

There have also been a number of initiatives in Kenya to enhance the affordability of medicines to treat patients with NCDs [30,44]. This includes the Base of Pyramid (BoP) project, which aimed to enhance the diagnosis of patients with diabetes as well as establish a ceiling price of KSh 500–600 (US$5) for insulin Mixtard® among participating healthcare facilities as well as surrounding markets and private pharmacies [45]. This should enhance affordability of medicines including insulins for patients with diabetes as this equates up to a two-thirds price reduction [45].

With respect to insulins, we have seen the development of long-acting insulin analogues to reduce rates of hypoglycaemia, especially nocturnal hypoglycaemia, and improve adherence through improved patient comfort [2,46-53]. This is welcomed given, as mentioned, concerns with the availability and costs of glucagon to treat hypoglycaemia when this occurs among African countries [35]. However, other authors are less certain of the patient benefits of long-acting insulin analogues versus standard insulins such as Neutral Protamine Hagedorn (NPH) insulin, which combined with appreciably higher costs, has resulted in concerns with their availability and funding within healthcare systems especially in LMICs [31,54-57]. Despite these concerns, there has been continued growth in the utilisation of long-acting insulin analogues in high and high-middle income countries, and they are now the most prescribed insulin in these countries [31, 58]. There has also been continued growth in their use in Bangladesh with perceived benefits on patient care outweighing additional costs [59]. This has been helped by increasing use of biosimilars at lower costs [59].

Whilst long-acting insulin analogues are listed in the Kenyan Essential Medicine List (KEML) [60], there is likely to be limited use and funding in view of considerable price differences with NPH and other insulins along with affordability concerns [30, 45, 61]. Biosimilars offer a way forward to increase competition and potentially lower prices of long-acting insulin analogues as seen in Bangladesh [59]. However, this has not been the case to date among a number of LMICs where biosimilar insulin glargine can be more expensive than the originator [31]. There have also been more limited price reductions for biosimilar insulin glargine among some European countries, impacting on their use in practice [62, 63]. However, this may change with the introduction of the World Health Organisation (WHO) prequalification initiative [64]. In addition, we

are aware of initiatives across Africa to stimulate local production of medicines to lower their costs and reduce shortages following challenges seen with the recent COVID-19 pandemic [65-67], especially given the potential low costs of goods for biosimilar insulin glargine [68].

Consequently, given current challenges and controversy, we wanted to investigate current insulin utilisation and expenditure patterns in Kenya. In addition, ascertain potential measures that could be undertaken if pertinent in Kenya to enhance future availability and funding for long-acting insulin analogues including biosimilars to benefit patients.

METHODOLOGY

We assessed current utilisation and expenditure patterns for insulins among two major hospitals in Kenya. These included Kenyatta National Hospital (KNH) and Embu County Referral Hospital (ECRH). KNH is a 2000 bed national teaching and the largest public referral hospital in the region, offering quality specialized healthcare to patients across Kenya and wider [69, 70]. ECRH is a level 5 regional teaching referral hospital located in Embu County offering high quality health care delivery and training of healthcare professionals [71]. Embu is located in Central Kenya, a region with high prevalence of diabetes mellitus. Consequently, both hospitals can provide good insight into the current situation in Kenya with respect to long-acting insulin analogues starting with key referral hospitals.

Current utilisation patterns were broken down into the various insulin types including rapid acting, standard, longer-acting and long-acting insulin analogues, as well as mixed preparations [72]. Utilisation was documented in vials and packs as well as defined daily doses (DDDs) in order to track specific patterns over time. We have used this approach in an earlier paper documenting medicine utilisation patterns in KNH as well as utilisation and cost patterns in Bangladesh and generally across countries [59, 70, 73, 74]. Expenditure patterns were kept in local currency (Ksh) without conversion to US dollars as we wanted to track changes over time without worrying about currency conversions. We have used this approach before [75, 76].

RESULTS

We have seen variable utilisation and expenditure on insulins over time in KNH (Table 1) depending on current affordability and other issues, with patients subsequently purchasing their insulins from community pharmacies when stocks run out.

Utilisation patterns reflect those listed in the Kenyan EML, which includes ultra short acting insulin (Rapid); short acting insulins (soluble), intermediate acting insulins, premixed insulins and insulin glargine [60].

Table-1: Utilisation and expenditure on insulins in KNH 2015 to 2020

	2015		2016		2017		2018		2019		2020 (Jan to Oct)	
Insulin Name	DDDs	Exp	DDDs	Exp	DDD	Exp	DDD	Exp	DDD	Exp	DDD	Exp
Rapid Acting												
Rapid acting insulin (Aspart® or Lispro®) Vial	950	85500	725	65250	1200	108000	2775	249750	1250	112500	300	27000
Rapid acting insulin (Aspart® or Lispro®) Flexpen - 3ml	0	0	0	0	0	0	0	0	7.5	1450	0	0
Standard insulins including intermediate and premixed insulins												
Insulin soluble cartridge	0		0	0	375	30600	75	6120	300	24480	37.5	3060
Soluble insulin vial	15800	227520	19025	273960	16300	234720	25400	365760	31625	455400	24350	350640
Intermediate acting insulin(Humalog® mix 75%/25%)cartridge	7582.5	1041330	7275	999100	5460	749840	5940	815760	5835	801340	1642.5	225570
Intermediate acting insulin(Humalog mix 75%/25%)vial®	0	0	0	0	2550	255000	10925	1092500	4700	470000	1950	195000
Intermediate acting insulin NPH vial	0	0	0	0	2675	47080	2550	44880	1950	34320	1825	32120
Human insulin isophane suspension (Humulin® N)	450		0		75		37.5		0		37.5	
Insulin Isophane 70% + Regular 30% Penfill single vial	0	0	0	0	50	7900	25	3950	0	0	0	0
Insulin Isophane 70% + Regular 30% vial (Mixtard®)	559825	7834050	306525	4291350	206400	2889600	212175	2970450	248125	3473750	205625	2878750
Premixed insulin 50%/50% vial	4125	181500	7250	319000	6750	297000	2625	115500	1850	81400	125	5500
Long-acting insulin analogues												
Long acting basal insulin (Lantus®) vial	0	0	0	0	975	46800	5800	278400	8000	384000	6775	325200
Basal analogue insulin glargine or equivalent (Lantus®) cartridge	3015		1260		2227.5		2880		3075		1470	
Total DDDs	591747.5		342060		245038		271208		306718		244138	
% long-acting insulin analogues (DDD)	0.51	0.00	0.37	0.00	1.31	1.00	3.20	4.68	3.61	6.58	3.38	8.04
Cost/ DDD												
Cost/DDD long acting basal insulin (Lantus®) vial						48.00		48.00		48.00		48.00
Cost/ DDD soluble insulin vial		14.40		14.40		14.40		14.40		14.40		14.40
Cost/ DDD Mixtard®		13.99		14.00		14.00		14.00		14.00		14.00

NB: Utilisation is in DDDs and expenditure in Ksh

The low use of insulin glargine, up to a maximum of 3.2 to 3.6% of total insulins in recent years, reflects issues of affordability especially given appreciable differences in procured costs (cost/ DDD) between soluble insulin and insulin Mixtard® versus those for insulin glargine (Table 1). The higher cost of insulin glargine (cost/ DDD) is reflected in a greater

contribution of insulin glargine to total expenditure than for total utilisation rising up to 8.0% in 2020 (Table 1).

Overall, it is likely there will be limited or no use of long-acting insulin analogues, including potential biosimilars, in public hospitals outside of KNH with patients in Kenya struggling to fund even insulin Mixtard® without specific access schemes [44, 45]. This was seen in ECRH where Mixtard® was the principal insulin dispensed with usage rising from 2061 packs in 2015 (511,360 Ksh) to 5627 packs in 2018 (1,800,640 Ksh) before falling to 4742 packs in 2019, with similar utilisation and expenditure patterns up to June 2020. There was no dispensing of any long-acting insulin analogue in this referral hospital in recent years.

DISCUSSION

We believe this is the first study in Kenya to track the use of long-acting insulin analogues within the public healthcare system starting with leading referral hospitals. Overall, as envisaged, there is limited use of long-acting insulin analogues due primarily with issues of affordability given appreciably higher costs (Table 1) within these referral hospitals. This is different to Bangladesh where we have seen increasing use of long-acting insulin analogues in recent years [59]. The current price gap between the different insulins (Table 1) is likely to be greater among community pharmacies once dispensing and other costs are added in [77], further exacerbating issues of affordability for the general population unless actively addressed.

The principal goal in sub-Saharan African countries such as Kenya is to make sure appropriate healthcare facilities, personnel, and medicines are in place to manage patients with diabetes. This includes preventing patients with T2DM from becoming insulin dependent, as well as making sure once insulin is needed that there is access and availability to insulins such as NPH insulins and insulin Mixtard® as well as blood glucose monitoring equipment given current concerns [8, 24, 45, 61]. Following this, it is important that patients have a full range of insulins available to them to improve their care, building on those available in higher income countries [2, 31]. This is facilitated in Kenya by long-acting insulin analogues already listed in the Kenyan EML [60]. Compliance is a critical issue with treatments for patients with diabetes including insulins, with pharmacists also playing a role to improve the control of diabetes and its complications [78-80].

However, it is likely that prices of long-acting insulin analogues would need to fall to close to those for NPH insulins and insulin Mixtard® to enhance funding and usage, similar to ongoing regulations in LMICs such as Brazil and South Africa [81,82]. This could be achieved through potentially instigating local production of biosimilar insulin glargine, similar to initiatives in Malaysia through Biocon or other companies [83]. This also builds on suggestions by the East African Secretariat to enhance production of medicines in Africa to reduce future shortages as a result of pandemics and other circumstances [65, 66]. This could be in addition to the WHO prequalification initiative to enhance competition among insulin manufacturers to lower the price of biosimilars and break the near monopoly of the three main insulin manufacturers [34, 36, 37, 64]. Potentially similar, or slightly higher, cost of goods for insulin glargine versus NPH insulins should help here [68].

Once underway, key physician and pharmacy groups can educate all key stakeholders regarding similar safety and effectiveness between originator and biosimilar long-acting insulin analogues if this is perceived to be a problem to avoid/ reduce any negative nocebo effects [84-87]. This can be facilitated by pharmaceutical manufacturers and others instigating studies in sub-Saharan Africa to compare the effectiveness and value of biosimilar insulin glargine versus NPH and other insulins given the lack of such studies currently in sub-Saharan Africa. Physicians, pharmacists, and nurse practitioners can subsequently work with patients to ensure they are familiar with any difference in pens/ devices between the different insulin glargine preparations if this proves to be a concern. In addition, provide educational and other support to enhance adherence to regular administration of long-acting insulin analogues in patients' home to reduce any potential hypoglycaemia. Subsequently, routinely monitor patients and medicine use during follow-up visits to ambulatory care clinics in hospitals and primary healthcare centres to address key issues including HbA1c levels, hypertension and statin administration given ongoing concerns across sub-Saharan Africa [88].

We are aware of a number of limitations with this study. The principal ones are that the research was only undertaken in two leading hospitals in Kenya. However, this was deliberate since if there was limited use of long-acting insulin analogues in these facilities, these patterns would be seen throughout Kenya. We also did not explore rates of hypoglycaemia and other complications among diabetes patients attending clinics in these facilities. However, this was outside the scope of this paper. Similarly, we did not monitor current utilisation patterns within private hospitals in Kenya as our emphasis was on the public system where the vast majority of patients are treated. Despite these issues, we believe this paper provides a valuable insight into current insulin use among leading hospitals in Kenya.

In conclusion, there is currently limited use of long-acting insulin analogues in Kenya due primarily to issues of affordability. Biosimilars can potentially help. However, their prices need to be nearer to those for

NPH and other similar insulins to enhance future use and funding despite listing in the Kenyan EML. These are considerations for the future enhanced by ongoing WHO prequalification and other initiatives.

Conflicts of interest and funding

The authors declare they have no competing interests. This analysis was commissioned and paid for by the World Health Organization. The authors are totally responsible for the views expressed in this paper and they do not necessarily represent the decisions, policy or views of the World Health Organization.

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