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**EDITORIAL**

- 1309** From non-obese diabetic to Network for the Pancreatic Organ Donor with Diabetes: New heights in type 1 diabetes research

Ramirez L, Hamad ARA

ORIGINAL ARTICLE**Basic Study**

- 1312** Simple calculator to estimate the medical cost of diabetes in sub-Saharan Africa

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Contents

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From non-obese diabetic to Network for the Pancreatic Organ Donor with Diabetes: New heights in type 1 diabetes research

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Abstract

Since the discovery of therapeutic insulin in 1922 and

the development of the non-obese diabetic spontaneous mouse model in 1980, the establishment of Network for Pancreatic Organ Donor with Diabetes (nPOD) in 2007 is arguably the most important milestone step in advancing type 1 diabetes (T1D) research. In this perspective, we briefly describe how nPOD is transforming T1D research *via* procuring and coordinating analysis of disease pathogenesis directly in human organs donated by deceased diabetic and control subjects. The successful precedent set up by nPOD is likely to spread far beyond the confines of research in T1D to revolutionize biomedical research of other disease using high quality procured human cells and tissues.

Key words: Type 1 diabetes; Network for the Pancreatic Organ Donor with Diabetes; Non-obese diabetic mouse; Transitional type 1 diabetes research

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Core tip: Type 1 diabetes (T1D) strikes early in life with monumental impact on life style and long term health of affected children. There is currently no cure for T1D or mechanisms to protect at risk individuals. A major obstacle is the difficulty in translating the interventions that succeeded in preventing or reversing the disease in the non-obese diabetic mouse model into human immunotherapies. Network for Pancreatic Organ Donor with Diabetes has been established in 2007 to study the disease directly in humans by procuring and offering well preserved tissues to investigators. These efforts, as indicated by published results, are paying off by providing critical new insights that are expected to facilitate development of efficacious immunotherapies.

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MAIN TEXT

Type 1 diabetes (T1D) is a form of diabetes mellitus that results from the autoimmune destruction of the insulin-producing beta cells in the pancreas, manifested clinically as hyperglycemia. T1D accounts for 5% to 10% of diabetes cases in the world and about 80000 children develop the disease each year. During the last century, research of T1D passed through several critical milestones (Table 1). Prior to the discovery and use of insulin as a replacement therapy in 1922, T1D was invariably fatal^[1,2]. Advances in insulin delivery and formulation are allowing many patients to live out their respective life expectancies. Nonetheless, insulin replacement is not a cure and it has to be taken daily. In addition, the dose needs to be adjusted frequently for successful management of blood glucose levels and their maintenance within an acceptable range. Achieving these goals is challenging and patients develop bouts of hypo- and hyper-glycemia as well as serious long term cardiovascular complications^[3]. To alleviate these problems, there have been intensive and sustained efforts to develop a cure that protects high risk individuals and perhaps reverses hyperglycemia in new-onsets. For this purpose, scientists have been using small animals to understand disease pathogenesis better, which is critical for finding a cure. Indeed, the discovery of the pancreas as the sole source of insulin almost a century ago was based on the development of severe diabetes in depancreatized experimental animals^[2]. In the 1980s, these efforts were seriously boosted by the development of the non-obese diabetic (NOD) mouse as a spontaneous model of the diseases^[4]. Extensive studies of NOD mice over the years led to significant understanding of the disease pathogenesis and identification of large numbers of molecules and cell types that stood out as potential therapeutic targets^[5]. Clinical relevance of the findings derived from NOD mice are substantiated by identification of their counterparts in humans. Strategies to block or reverse disease in NOD mice were mostly successful^[6], raising the hope of translating them into effective and safe immunotherapies. Results of clinical trials, however, were rather disappointing as they largely failed to achieve the expected efficacy to preserve C-peptide or protect high risk individuals, dashing hopes. There were several comprehensive reviews of the major trials and their outcomes including an excellent concise review by Atkinson *et al*^[7].

Assessment of the reasons behind the failure of the selected agents in the clinic is leading to more appreciation of biological differences between the highly heterogeneous human population and the NOD inbred mouse and to the role of the environment as barriers that challenge the assumption that “what works in NOD mice will work in humans”. Changes in environmental

factors (including viral infections, changes in diet) rather than changes in allele frequency, which would not occur so rapidly, are likely responsible for the rapid increase of the incidence of T1D in western countries. Together these factors pointed to the importance of studying the disease directly in humans. However, regular access to well characterized human organs has been very difficult and not available at central facilities. Consequently, most of the clinical research has been limited to the analysis of peripheral blood mononuclear cells. Facing the reality that most if not all of what worked in NOD mice failed in the clinic, a foresighted group of researchers conceived and implemented the idea of studying the disease directly in humans using donated organs. This led to the established of the Network for Pancreatic Organ Donors with Diabetes (nPOD). For complete information about nPOD, supporting agencies and how to get involve, please visit: <http://www.jdrfnpod.org/>. As indicated in their website, nPOD biobank receives organs from donors, worldwide, and distributes tissues and cells to nPOD researchers. These efforts are allowing scientific investigation of T1D directly in well-preserved high quality human tissues and organs by researchers with diverse scientific specialties and interests. The ultimate goal of this diverse group of research converges on studying and understanding different aspects of the disease and eventually developing therapeutic modalities to protect high risk individuals and perhaps reverse disease at onset. Fruitfulness of these efforts are indicated by a stream of new discoveries some of which confirmed similarities to what have been known in the NOD mouse, whereas others identified significant departures (for complete list of these publication, please visit nPOD website). Most of these notable differences, particularly in the pancreas and potential roles of viral infections in driving disease pathogenesis have been elegantly described in recent reviews by Pugliese *et al*^[8] and Kaddis *et al*^[9].

CONCLUSION

Access to donated human organs procured by nPOD is providing the opportunity to study the disease directly in humans. Studies of these organs is already leading to new critical insights that are expected to help better understanding of T1D and development of new modalities that can prevent T1D or preserve C-peptide in new-onset patients. However, NOD mouse still remain valid model for identification of new targets such as FasL^[10] and for functional understanding of observations made in humans. Particularly useful will be development of robust humanized mice that can be reconstituted by lymphocytes isolated from different human organs, particularly the pancreas. In addition, new innovative studies are directed towards combining reconstitution of humanized mice with peripheral mononuclear cells (PMNCs) with transplanted organs. At least but not least, success of the nPOD model is likely to inspire establishment of similar networks to study various

Table 1 Milestones in type 1 diabetes research

Use of depancreatized mice showed that T1D is due to the absence of internal pancreas secretion (1889)
Identification and synthesis of insulin for therapy (1922)
Development of spontaneous NOD mouse model (1980)
Establishment of nPOD to study disease using organs and tissues procured from patients, high risk individuals and non-diabetic controls (2007)

T1D: Type 1 diabetes; NOD: Non-obese diabetic; nPOD: Network for Pancreatic Organ Donors with Diabetes.

human diseases.

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Basic Study

Simple calculator to estimate the medical cost of diabetes in sub-Saharan Africa

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of hospital department heads in all four countries (members of the working group) and these professors of medicine have the required authority to collect and use the data. Furthermore, the identity of the hospitals and pharmacies where price information was collected was not divulged. Additionally, the prices are known to the public and displayed in hospitals and pharmacies. Therefore, no further authorization or special permission to use the data was necessary.

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Abstract

AIM: To design a medical cost calculator and show that diabetes care is beyond reach of the majority particularly

patients with complications.

METHODS: Out-of-pocket expenditures of patients for medical treatment of type-2 diabetes were estimated based on price data collected in Benin, Burkina Faso, Guinea and Mali. A detailed protocol for realistic medical care of diabetes and its complications in the African context was defined. Care components were based on existing guidelines, published data and clinical experience. Prices were obtained in public and private health facilities. The cost calculator used Excel. The cost for basic management of uncomplicated diabetes was calculated per person and per year. Incremental costs were also computed per annum for chronic complications and per episode for acute complications.

RESULTS: Wide variations of estimated care costs were observed among countries and between the public and private healthcare system. The minimum estimated cost for the treatment of uncomplicated diabetes (in the public sector) would amount to 21%-34% of the country's gross national income per capita, 26%-47% in the presence of retinopathy, and above 70% for nephropathy, the most expensive complication.

CONCLUSION: The study provided objective evidence for the exorbitant medical cost of diabetes considering that no medical insurance is available in the study countries. Although the calculator only estimates the cost of inaction, it is innovative and of interest for several stakeholders.

Key words: Diabetes; Non-communicable diseases; Africa; Advocacy; Cost-of-illness

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Core tip: The costs of medical treatment of diabetes are poorly documented in sub-Saharan Africa, while such data are of interest for several stakeholders and useful for advocacy. There is a lack of tools to make these estimations. We describe a standardized, innovative and user-friendly medical cost calculator and provide the results of its use in four countries. It was developed in West-Africa but it is also relevant for other African countries and perhaps even in Asia provided the standard treatment protocol is deemed appropriate.

Alouki K, Delisle H, Besançon S, Baldé N, Sidibé-Traoré A, Drabo J, Djrolo F, Mbanya JC, Halimi S. Simple calculator to estimate the medical cost of diabetes in sub-Saharan Africa. *World J Diabetes* 2015; 6(16): 1312-1322 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v6/i16/1312.htm> DOI: <http://dx.doi.org/10.4239/wjcd.v6.i16.1312>

INTRODUCTION

Non-communicable diseases (NCDs) including diabetes

pose a serious challenge to health systems already overstretched with acute and infectious diseases in Africa^[1]. Following the High Level Meeting of the United Nations on NCDs in New-York in 2011^[2], heads of governments made commitments towards prevention and control. However, the misconception that NCDs are diseases of the affluent is still widespread in low-income countries in spite of accumulating evidence against this myth. Strong advocacy is therefore required and the International Diabetes Federation (IDF), for instance, has developed a series of tools and guidelines to influence decision makers^[3]. The following definition of advocacy is relevant for all health professionals^[4]: "Blending science, ethics and politics, advocacy is self-initiated, evidence-based, strategic action that health professionals can take to help transform systems and improve the environments and policies which shape their patients' behaviours and choices, and ultimately their health". Simple and culture-sensitive advocacy tools are direly needed to foster the prevention and control of chronic diseases such as diabetes.

Several methods for identifying the economic consequences of diseases have been defined. Standard costs of diabetes in Africa, including the direct and indirect costs of the illness, have been estimated based on secondary data^[5]. Such cost-of-illness (COI) studies, in addition to direct and indirect costs, may also include the intangible costs although these are seldom measured owing to the complexity of such measurements^[6]. COI methods are simpler than, and very different from, the macro- and micro-economic models that have been developed to estimate the economic burden of the disease (cost of inaction) and the cost-effectiveness of action, such as CORE^[7] and other Markov-based models, and WHO CHOICE^[8]. Markov models are computer simulations of probabilistic progression of a disease in a hypothetical cohort which have been adapted to forecast mortality and complications of diabetes, as well as medical costs^[9]. WHO CHOICE has been used to estimate the cost-effectiveness of interventions to combat chronic diseases, including diabetes, at the regional level, thereby assisting decision makers^[10]. Comprehensive computer models of diabetes economic burden are many and they are in constant evolution^[11,12]. However, such models are highly complex and ill-suited to the field.

As part of a university partnership project on the double burden of malnutrition in French-speaking West-Africa^[1], diabetes advocacy instruments that are more specific to sub-Saharan African countries were developed. The principal tool was a simple medical cost calculator which is described and the results discussed in the present paper.

MATERIALS AND METHODS

The process and the study sites

A Diabetes Advocacy Working Group was set up among the partnership project institutions, with members from Benin, Burkina Faso, Mali, Guinea and Canada (University of Montreal). The focus on diabetes, rather than obesity, was a strategic choice because obesity is not as yet

commonly perceived as a health problem while diabetes certainly is.

The working group held regular sessions between 2009 and 2014. A medical cost calculator for diabetes treatment, in the absence or presence of complications, was designed. The team was inspired by the positive experience with PROFILES in the area of nutrition for advocating investments to eradicate malnutrition and micronutrient deficiencies^[13]. The costing tool was applied after pretesting in the four West-African countries represented on the working group. A training workshop on diabetes advocacy with the introduction of this tool was held in Benin for members of the project's institutional partners and for graduate students in health and nutrition.

The definition of a realistic diabetes care protocol

The approach was based on COI, which is quite different from a cost-effectiveness approach^[6,14]. In our study, the COI included only medical care from the patient perspective, that is, estimated individual, out-of-pocket expenditures. Medical cost estimates would also be relevant for third-party payers if and when health insurance becomes available. Other direct costs, for instance for transportation, are highly variable across individual patients and cannot be estimated in a standardized fashion. Although the instrument was based on the PROFILES conceptual model^[13], only the first component was considered at the present stage, that is, the cost of the disease (cost of inaction), as there are as yet insufficient relevant data for Africa on the cost-effectiveness of primary prevention, screening and secondary prevention to also include the cost of action.

Prior to data collection on medical costs, a detailed protocol for the basic treatment of type-2 diabetes and for the treatment of main complications was developed by the working group. Components of care were listed under physicians and allied health professionals' services, hospital care, lab tests and controls, and drugs and medical supplies, first for uncomplicated diabetes and then for each of the main acute and chronic complications. Acute complications included ketoacidosis, acute diabetic foot, kidney failure and stroke. Chronic complications were proliferative retinopathy, hypertension, nephropathy, cardiac ischemia, foot ulcer and the chronic phase of stroke. These complications were considered as the most common according to published data^[15-19]. The treatment protocol was based on realistic medical care for uncomplicated and complicated diabetes in the African context, rather than on optimal care as may be available in high-income countries. The working group selected the components of care based on the latest IDF clinical guidelines^[20], on IDF guidelines for Africa in 2006^[21] taking account of needed update, as well as on a thorough literature review and on the clinical experience of endocrinologists of the group. Standards of care of the American Diabetes Association^[22] were also examined for their relevance. The level of medical care was usually between "standard" and "minimal" as defined by IDF^[20]. The care components as detailed for

the basic treatment of uncomplicated type-2 diabetes and its complications are shown in Table 1. The frequency of medical check-ups, controls and tests is indicated, as well as drug posology. It will be noted that there are some alternatives, for instance, for hypoglycemic agents, as well as for drugs for complications. This is so because a cheaper alternative and a more expensive one are provided in order to estimate a range of medical costs instead of a single value such as the mean. Regarding tests, medical supplies, specialized treatments and drugs, two alternatives are also sometimes listed, a cheaper and a more expensive one.

Price data collection

Diabetes care costs were computed from price data (in local currency) collected in hospitals, clinics and pharmacies of the targeted countries, and not on the basis of actual patients' expenditures. Unit prices or rates for services and supplies were collected and entered in the tally forms designed for the purpose and including each care component previously identified. Prices were retrieved in public hospitals, private clinics, hospital pharmacies and private pharmacies of the capital city. The two hospitals included a university hospital (there is usually only one, serving as reference hospital) and a secondary hospital. Price data were also collected in two private clinics, including one offering specialized diabetes care if available. Prices for drugs and medical supplies were obtained in the pharmacies of the selected public hospitals and in two private pharmacies. Prices or rates were as charged to patients, irrespective of government subsidies that may exist in a given country. Forms for entering price data were designed (available from the corresponding author upon request). Unit costs were entered in the unshaded parts of the forms. If an element of care was only offered in one public hospital or only in one private clinic, the same price was entered for the other public or private structure. In public pharmacies, prices of available generic drugs were collected. If a given drug was only available in private pharmacies, the same price would be entered for the public pharmacies as well. The cost of drugs was to be entered for the number of units as generally packaged, but if the number was different, it had to be specified on the form. General and specific guidelines were developed to assist the users of the cost calculator in filling the forms.

Estimating medical costs for individuals living with diabetes

A user-friendly software was designed on Excel 2010 for Windows with the assistance of a computer specialist in order to compute the medical costs of diabetes, in the absence or presence of complications. The estimated costs per individual are given as a range in the public and private health sector of a given country. It was hypothesized that incurred costs would be higher in the private healthcare sector and this was the rationale for collecting data in the public and private sectors. The cost data could be entered directly in the Excel software,

Table 1 Care parameters for basic treatment of uncomplicated diabetes and for the treatment of chronic and acute complications

Medical conditions	Care component	Guidelines
Uncomplicated diabetes	Consultation of diabetes specialist or a general practitioner	4/yr
	Fasting glucose test	4/yr
	Urine glucose test	6/yr
	Glycated hemoglobin	2/yr
	Proteinuria test	1/yr
	Blood lipid test TG, HDL-cholesterol, LDL-cholesterol	1/yr
	Electrocardiogram	1/yr
	Chest X-ray	1/yr
	Ophthalmology consult	1/yr
	Oral hypoglycemic agents	
	Glibenclamide 5 mg OR in combination with metformin	3 tablets/d
	Metformin® 500 mg	3 tablets/d
	Glucophage® 850 mg OR in combination with Amarel®	3 tablets/d
	Amarel® 4 mg	1 tablet/d
	For insulin users	
	Syringes	1/wk (min)-1/d (max)
	Insulin	30 UI (min) et 60 UI (max)/d
	Strips for blood glucose control	1 strip/d (min) 3 strips/d (max)
	Glucometer	1 (Duration: 2 yr)
Chronic complications		
Proliferative retinopathy	Consultation in ophthalmology	3/yr
	Retinography	1/yr
	Laser photocoagulation	1/yr
Overt nephropathy	Consultation in nephrology	2/yr
	Blood creatinine test	2/yr
	Serum protein test	2/yr
	Serum electrolytes test (sodium, potassium)	2/yr
	Urinary electrolytes test (sodium, potassium)	2/yr
	Urine creatinine test	2/yr
	Proteinuria	2/yr
	Hemogram	2/yr
	Urine bacteriology	4/yr
	Urine culture (ECBU)	1/yr
	Antiplatelet drugs	
	Aspirin® 100 mg OR	1 tablet/d
	Plavix® 75 mg	1 tablet/d
	Antihypertensive (ARA2)	
	Valsartan® 80 mg	1 tablet/d
	Diuretics:	
	Laxilix® 40 mg OR	3 tablets/d
	Laxilix® special 500 mg	Half tablet/d
	Calcium carbonate (added to antiplatelet therapy, maximum cost)	2 tablets/d
	Statin (added to antiplatelet therapy, maximum cost)	1 tablet/d
Renal failure	Dialysis	2 session/wk
	Potex® 4000 UI (EPO)	50 UI/kg weight (max) 2 sessions/wk
	Calcium carbonate 500 mg	1.5 g or 3 tablets/d (max)
Ischemic heart disease	Consultation in cardiology	2/an
	Antiplatelet drugs	See under nephropathy
	Statins	
	Simvastatin (Zocor®) OR	1 tablet/d
	Atorvastatin (Tahor®)	1 tablet/d
	Exercise electrocardiogram testing	1/yr
	Echo doppler	1/yr
	Cardiac ultrasound	1/yr
	Coronarography	1/yr
Hypertension	Consultation in cardiology	1/yr
	Antihypertensive drugs (ACEI)	
	Captopril® 25 mg OU	3 tablets/d
	Ramipril® 5 mg	1 tablet/d
	Diuretics	See under nephropathy

Diabetic foot	Aggregation inhibitors	See under nephropathy
	Semi quantitative urine protein test	2/yr
	Blood creatinine test	2/yr
	Proteinemia	2/yr
	Blood electrolytes test (Na, K, Ca)	2/an
	Stroke (chronic phase)	
	Consultation in cardiology	2/yr
	Antiplatelet drugs	See under nephropathy
	Consultation in podiatry	1/yr
	Arteriography of the lower limbs	1/yr
Acute complications	Physiotherapy sessions	10-20 sessions/yr
	Echo doppler	1/yr
	Statins	See under ischemic heart disease
	Antiplatelet drugs	1 tablet/d
	Orthopedic shoes	2 pairs/yr
	Ketoacidosis	
	Hospitalization	7 d
	Blood glucose test	Done once during hospitalization
	Glycated hemoglobin	Done once during hospitalization
	Hemogram	Done once during hospitalization
Diabetic foot (acute)	Blood lipids test	Done once during hospitalization
	Blood electrolytes test (Na, K)	Done once during hospitalization
	Blood creatinine test	Done once during hospitalization
	Blood urea test	Done once during hospitalization
	Electrocardiogram	Done once during hospitalization
	Chest X- ray	Done once during hospitalization
	Echo doppler	Done once during hospitalization
	Keto-Diastix® box of 50 strips (blood biology)	3 times/d for 3 d
	Perfusion	3 d
	Hospitalization	90 d
Foot surgery	Antibiotics	
	Oxaciline® 500 mg	4 tablets/d
		3 wk of treatment without bone involvement (min); 10 wk when bone involved (max)
	Vasodilator: Vastarel® 35 mg	2 tablets/d, 22 wk
	Biopsy	Done once during hospitalization
	Antibiogram	Done once during hospitalization
	Bone radiography	Done once during hospitalization
	Vascular ultrasound	Done once during hospitalization
	Dressings	1/wk, 22 wk
	Minor surgery (56%)	
End stage renal disease	Major surgery, amputation (44%)	
	Prosthesis	
	Hospitalization	30 d
	Ultrasound	Done once during hospitalization
	Electrolytes blood test (Na, K)	Done once during hospitalization
	Creatinine blood test	Done once during hospitalization
	Proteinemia	Done once during hospitalization
Stroke	Hospitalization	18 d
	Vasodilator: Vastarel® 35 mg	2 tablets/d, 18 d
	Anticoagulants	1 tablet/d, 18 d
	Rehabilitation/physical therapy	18 d
	Scanner	1 examination during hospitalization

TG: Triglycerides; HDL-cholesterol: High density lipoprotein cholesterol; LDL-cholesterol: Low density lipoprotein cholesterol; ARA2: Angiotensin receptor blocker; ACEI: Angiotensin converting enzyme inhibitors; EPO: Erythropoietin.

but the algorithms could not be changed. They are quite complex as several assumptions and empirical solutions had to be made. For instance, in computing the annual cost of basic care in the absence of complications, an

assumption had to be made regarding the proportion of subjects taking insulin since glucose monitoring regimen is different from those on oral hypoglycemic agents. It was estimated that roughly 20% of all patients were on

Table 2 Medical costs per individual per year for uncomplicated diabetes and for complications (in United States dollars) in the four countries

Medical condition	Bénin				Burkina Faso				Guinea				Mali			
	Public sector		Private sector		Public sector		Private sector		Public sector		Private sector		Public sector		Private sector	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Uncomplicated diabetes	212	542	310	828	224	451	363	859	126	422	437	1093	137	335	390	869
Chronic complications - Basic medical cost for uncomplicated diabetes plus additional annual cost for single complication																
Retinopathy	320	686	421	987	306	532	465	984	187	488	511	1243	177	374	524	1002
Stroke	233	576	672	1360	241	469	1644	2155	135	432	1267	1937	147	345	687	1850
Nephropathy	850	1920	1614	3198	783	1299	2578	3412	808	1578	2366	4256	491	1808	1516	4069
Hypertension	345	751	1256	2065	377	605	2074	2590	367	667	1784	2655	293	556	1212	2408
Ischemic heart disease	535	1297	1050	2188	496	785	1943	2577	313	612	1484	2553	441	1324	1002	2881
Diabetic foot	694	1533	1103	2386	923	1337	2447	4294	527	877	1717	3393	484	1424	1043	3172
Acute complications - Basic annual medical cost for uncomplicated diabetes plus additional cost per episode of acute complication																
Keto acidosis	406	802	576	1297	387	665	1036	1936	222	531	726	1758	243	463	606	1391
Infected diabetic foot requiring hospitalization	728	1539	1020	3860	729	1702	6886	12043	667	1129	2897	6679	698	1340	1709	5802
Stroke (acute phase)	637	1117	834	1935	576	1064	2316	4147	510	933	1427	3315	455	705	1003	2266

insulin, based on clinical practice and published data^[15]. Another example refers to dialysis. Some hospitals have a package rate, whereas others have a rate per session, with a separate charge for the catheter. For any care component, four prices were obtained; the software computed the range of cost per care item and for the total in the private and public sectors.

Based on the recommended frequency of "treatment" units, the total cost was computed per year and per individual for the medical cost of uncomplicated diabetes. Similarly, the additional annual cost for the treatment of chronic complications (one by one to prevent dual counting) was computed. For acute complications, the additional cost was calculated per episode. Costs were computed in local currency and they can then be converted automatically into Euros or United States dollars. The software provides the results in table and figure format. It is also possible to estimate with the software the total theoretical medical costs at country level, based on prevalence of diabetes and its main complications, but this is beyond the scope of the present paper (The software, which includes the spreadsheet for price data entry, is available from the corresponding author).

RESULTS

Individual medical costs for uncomplicated diabetes and additional costs associated with complications are shown in Table 2 for each study country (in United States dollars). Uncomplicated diabetes costs and chronic complication costs are given on an annual basis. Costs for acute complications include uncomplicated diabetes annual costs plus additional costs per episode of a given complication. Medical costs of uncomplicated diabetes ranged from 126 United States dollars to 1093 United States dollars in Guinea, 137 United States dollars to 869 United States dollars in Mali, 212 United States dollars to 828 United States dollars in Benin, and 224 United States dollars to 859 United States dollars in Burkina-Faso. Wide ranges were also observed within countries,

with at least a twofold increase from the minimum to the maximum cost in the public healthcare system as well as in the private sector. The minimum cost in the public sector was lower by a factor of 4 to 8 than the maximum cost in the private sector in all countries. In the treatment of uncomplicated diabetes, drugs and medical supplies represented the highest cost share, ranging from 52% to 75%. Figure 1 illustrates the range of medical costs per person per year for uncomplicated diabetes, in the public and private healthcare systems and for each study country. The medical costs increased steadily from the public to the private sector, except in Benin and Burkina-Faso where the maximum medical cost in the public sector was higher than the minimum cost in the private sector. Figure 2 provides illustrated examples of the software outputs for incremental medical costs per person per year in the presence of one chronic complication, in this instance for Mali. It shows that except for retinopathy, the additional cost for treating complications represents at least twice the medical cost of basic diabetes care. Of all chronic complications considered, the most costly was nephropathy in all countries.

Table 3 shows for each study country the estimated cost range in current United States dollars and in percentage of gross national income (GNI) per capita (<http://wdi.worldbank.org/table/1.1>) and of an economic poverty threshold (2\$ per day or 730\$ a year according to the World Bank^[23]) for uncomplicated diabetes, for diabetes with retinopathy, the complication with the lowest incremental cost, and for diabetes with nephropathy which entails the highest additional cost. GNI per capita in current United States dollars 2013 ranged from 460\$ in Guinea to 790\$ in Benin. Uncomplicated diabetes cost amounted to a minimum of 21%-34% of the GNI, with a maximum reaching 238% in Guinea. With chronic complications, the share of the GNI soared. The minimum cost of diabetes with nephropathy represented 73%-176% of the GNI. The medical costs of diabetes without complications ranged from 17.2% to 150% of the annual income corresponding to the poverty line.

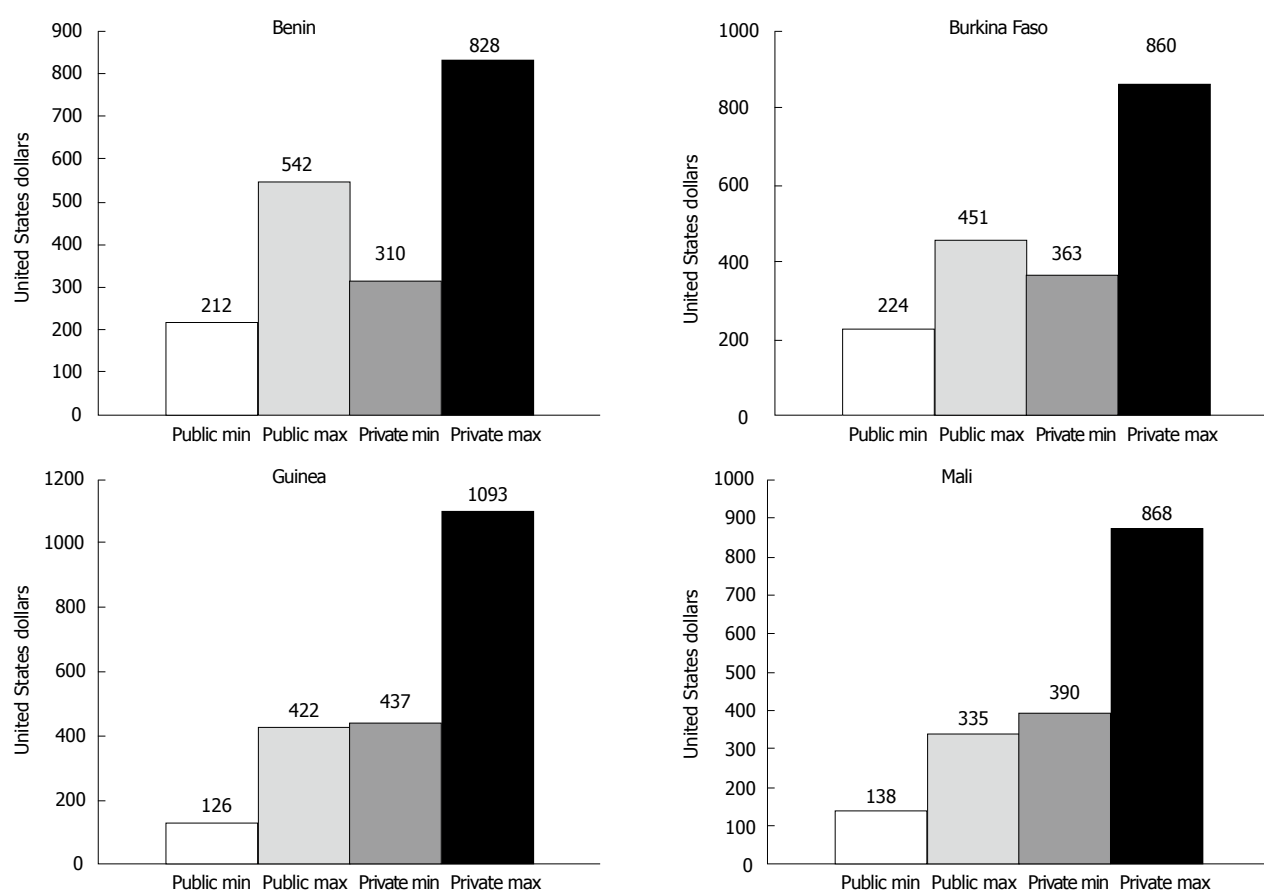


Figure 1 Computed medical costs per individual per year, basic care, no complications.

Table 3 Diabetes medical costs and national income in the study countries (United States dollars)

Countries		Mali	Benin	Burkina Faso	Guinea
GNI per capita (2013)		670	790	670	460
% of population with < \$2/d (= \$730/yr)		78.7	74.3	72.6	72.7
Uncomplicated diabetes	Minimum cost	137.21	211.63	224.42	125.58
	Maximum cost	868.60	827.91	859.30	1093.02
% of GNI (% of poverty threshold ¹)	Minimum	20.5 (18.7)	26.8 (28.9)	33.5 (30.7)	27.3 (17.2)
	Maximum	129.6 (118.9)	104.8 (113.4)	128.3 (117.6)	237.6 (149.7)
Diabetes + retinopathy	Minimum cost	176.74	320.93	305.81	187.21
	Maximum cost	1002.33	987.21	983.84	1243.02
% of GNI (% of poverty threshold)	Minimum	26.4 (24.2)	40.6 (43.9)	45.6 (41.9)	46.8 (25.6)
	Maximum	149.6 (137.3)	125.0 (135.2)	141.6 (134.7)	270.2 (170.3)
Diabetes + nephropathy	Minimum cost	490.70	850.00	782.56	808.14
	Maximum cost	4068.60	3197.67	3411.63	4256.98
% of GNI (% of poverty threshold)	Minimum	73.2 (67.2)	107.6 (116.4)	116.8 (107.2)	175.7 (110.7)
	Maximum	607.3 (557.3)	404.8 (438.0)	509.2 (467.3)	925.4 (583.1)

¹Threshold of 2 dollars/d (\$ 730/year) as set by the World Bank. GNI: Gross national income.

With retinopathy, the least costly complication, medical costs varied from 24.2% in Mali to 170% in Guinea. For nephropathy, the most costly complication, medical costs amounted to at least 67% of the annual poverty line.

DISCUSSION

The aim of this study was to develop and test a simple medical cost calculator for diabetes to be used primarily for

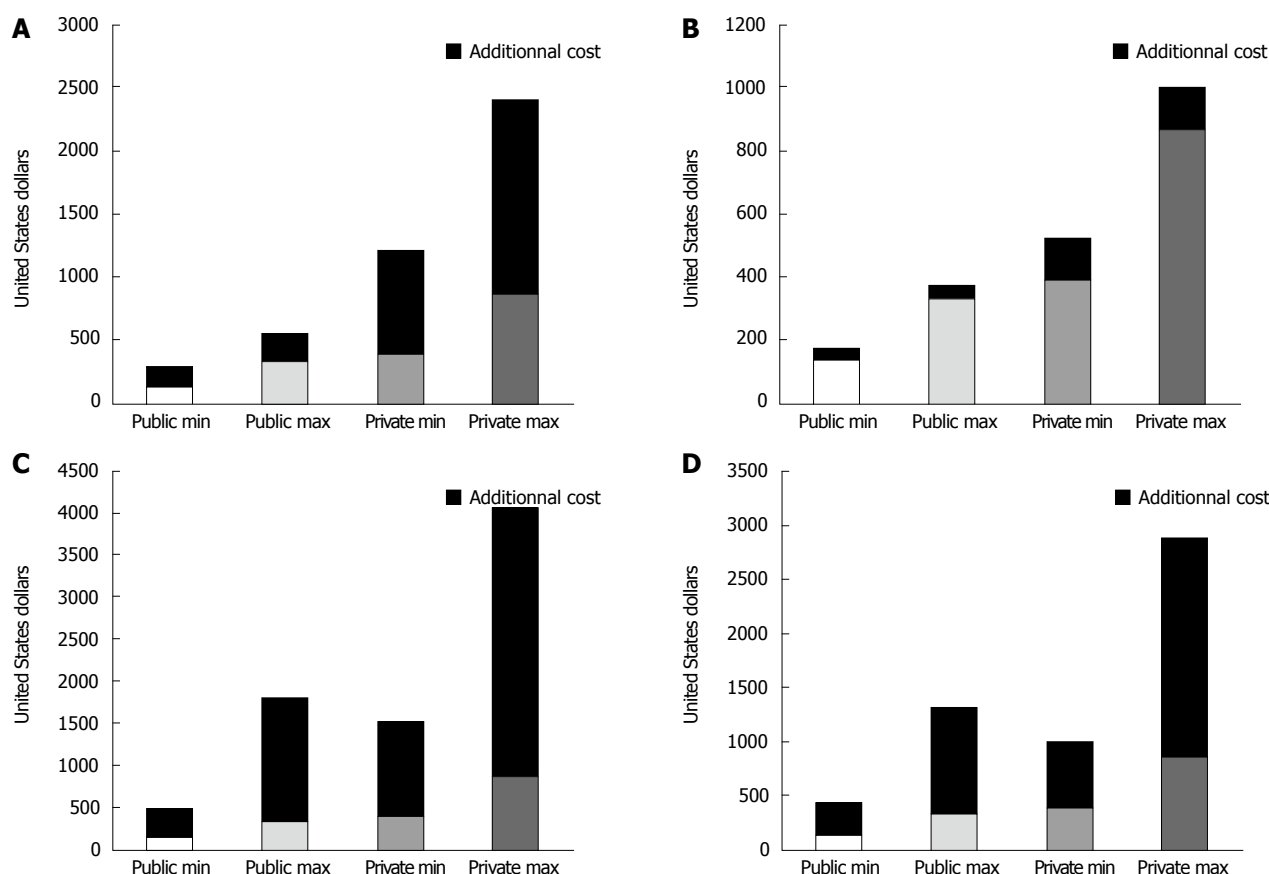


Figure 2 Computed annual medical costs per individual, basic care plus complications (Mali). A: Annual medical costs per individual, basic diabetes care plus hypertension; B: Annual medical costs per individual, basic diabetes care plus retinopathy; C: Annual medical costs per individual, basic diabetes care plus nephropathy; D: Annual medical costs per individual, basic diabetes care plus cardiopathy.

advocacy purposes. Research evidence is not consistently used for policy formulation^[24], even by international organizations^[25]. Demonstration of unbearable economic and human costs of a chronic disease such as diabetes may be regarded as concrete and therefore more promising as a means to influencing decision makers. While considerations other than financial, whether political or other, are at play, economic arguments are important even if not sufficient by themselves to induce changes in public policy and programmes^[26]. Furthermore, figures are compelling for decision-makers who have to address competing priorities. Cost indeed plays a critical role in decision making regarding health, in any country.

What the study showed is that the medical cost calculator was quite user-friendly and that collecting country-specific price data was highly relevant, considering the wide differences observed across countries in estimated medical costs of uncomplicated and complicated diabetes. The country-specific cost data collected using this instrument could actually be used to update regional estimates that are needed for macroeconomic models. The diabetes cost calculator is certainly not intended as a substitute for highly technical and validated models such as CORE^[7] and WHO-CHOICE^[8]. However, their use is constrained by their complexity, the global scale of the figures, and the numerous assumptions underlying

the calculations. Expertise is required to manipulate and adjust the models. Furthermore, since data on local effectiveness of interventions are scanty, particularly in Africa, assumptions have to be made. The costing tool was designed so as to remain simple in order to encourage its use at country level. The participants of the advocacy training workshop during which the calculator was presented indeed felt that the instrument was transparent and easy to use, but at the present time, we have no feedback on the effective use of the calculator for advocacy purposes.

The results confirmed that medical costs vary considerably between the private and public healthcare systems and even within each sector. Similarly, in India, direct costs were nearly four times higher in Chennai than in Delhi, illustrating wide variations within a country^[6]. Providing ranges of medical costs was considered more representative than means. Medical costs in other hospitals, clinics and pharmacies of the country would most likely fall within the computed range. Additionally, in order to compute means that would be representative of a whole country's medical costs, the process would be much heavier and expensive, with the need for a large number of randomly selected health facilities to include in the study. The cost calculator also allows to better size up the medical cost discrepancies between the private and public

sector. Public subsidies on drugs, hospitalization and other treatment components were not taken into account and likely contribute to these discrepancies among countries and between the private and public sector, for example in Benin, where the government gives subsidies for dialysis and for hospitalization. Additionally, costs for drugs will depend on the type of molecules and on whether or not generic formulations are available. The specific guidelines provided with the cost calculator regarding the type of drugs to consider (available on demand) contribute to standardize as much as possible cost data compilation.

The costing tool that we developed is the first of its kind and there is no equivalent in the published literature, where only out-of-pocket expenditures based on patients' surveys are to be found. The cost calculator refers to a standardized medical care protocol so that costs can be compared across countries. The tool is flexible in that prices can be updated as required in the Excel file, with automatic adjustment of the outputs (tables and graphs). This allows for the tool to be updated whenever new data become available. However the treatment components cannot be modified in the software in order to allow comparisons.

The estimated total medical cost for the basic treatment of diabetes at the individual level in a given country using this standard procedure may be of value to health professionals, governments and other potential payers such as insurance companies in many ways. Firstly and of foremost importance, the burden of the expenses that households or individuals would have to incur for basic care of uncomplicated diabetes can be appraised based on income levels and income distribution in the country, where such data are available. In the absence of recent household budget surveys, a basis for comparison could be the country's minimum wage, the GNI per capita, or else an economic poverty threshold, as was done in the present study. This may allow to clearly show that several patients are not minimally treated because they simply cannot afford the medical follow-ups and even the drugs, in the absence of government subsidies or insurance (or even when these are available). These cost data may therefore represent in themselves powerful advocacy arguments. In Cameroon, a study on out-of-pocket expenditures of more than 350 diabetes patients revealed that monthly medical costs reached 148\$ United States in 2009-2011 (89.40\$ for medicines, 10.40\$ for consultations, 35.0\$ for tests, and 13.20\$ for glycemia monitoring), which amounted to more than twice the minimum wage^[27]. According to the present study, basic treatment cost range of uncomplicated diabetes would represent 27%-105% of GNI per capita in Benin, 21%-130% of GNI in Mali, 27%-238% in Guinea, and in Burkina, where the minimum estimated cost was the highest of the four countries, from 34% to 138%. Actual expenditures of patients probably lie somewhere in-between the minimum and the maximum. Analysis of data from a survey of several hundred individuals living with diabetes in Mali showed that annual medical expenditures of

subjects free from complications were within the range of estimated costs using the calculator, at least in the public sector (unpublished data). A study on the economic burden of diabetes in Africa^[5] showed that average medical costs (including the same components as the present study) represented 36% of GNI for countries with a GNI lower than 2000\$ United States, which includes all four countries of the present study. Furthermore, this is the basic cost only. Treatment costs soared when diabetes complications are present, which is the case for a majority of persons living with diabetes -70% according to the survey in Mali^[28]. In India, the cost-ratio for those having complications vs those without was around 2.0^[6]. In our study, for instance, the treatment of nephropathy, considering only the minimum cost in the public sector, would more than treble the yearly basic cost, ranging from a factor of 3.5 in Burkina Faso to 6 in Guinea. A few studies have shown that the cost of diabetes is indeed beyond reach of a sizeable proportion of the population. In Côte d'Ivoire, for instance, 35% to 55% of the household income would have to be spent for diabetes care^[29]. In Mali, it was estimated that for insulin only, households with a diabetic member spent 38% of their total income^[30]. This confirms that acceptable diabetes care is likely unaffordable to most. In our study, we used the GNI per capita as a proxy of income, as well as the World Bank poverty threshold of 2\$/d (or 730\$/year). It is noteworthy that the GNI per capita itself is below this poverty threshold in three of the four study countries. Roughly 75% of the population of these countries lives with less than 2\$/d, which betrays rampant poverty. It is therefore likely that a good majority of the people would not afford even the most basic medical treatment of type-2 diabetes. The diabetes cost calculator provides for an estimation of minimum incurred medical expenses as a percentage of income proxy without having to conduct lengthy and expensive surveys for that purpose. Furthermore, demonstrating the cost increment associated with complications related to a late diagnosis may help convince decision-makers to make the screening more efficient at primary health care level. Comparing the medical costs of diabetes in neighbouring countries may also be of interest for policy purposes, even if only the cost of the disease is computed at this stage.

There are obviously several limitations to this costing tool. Only direct medical costs are estimated, on the basis of diabetes treatment component price data collected locally in public and private care institutions. Other direct costs incurred by families, such as transportation, traditional medicine, time of the care-provider and extra-expenditures for the diet are not taken into account and besides, these can hardly be standardized. However, according to other studies on actual expenditures, direct costs tend to be higher than indirect costs^[6].

Although the treatment protocol was considered realistic for Africa, all included elements of care may not be absolutely necessarily in spite of their relevance. For instance, some could argue that care may be acceptable

even if some costly tests are not performed. Moreover, although consensus was required in the working group to define the treatment components, some arbitrariness was unavoidable, whether in the frequency of medical visits or in medicine posology.

The cost calculator does not include either the indirect costs to the health system (salaries and training of health personnel; health facilities; subsidies, etc.), the families and the society as a whole (loss of productivity, of income, of healthy life years...). The medical costs estimated with the calculator represent only a fraction of the total economic burden of the disease.

A useful addition to the costing tool would be to estimate cost-effectiveness of interventions for primary prevention among high-risk individuals, combined with secondary prevention among diagnosed individuals, in order to demonstrate the savings that may accrue from earlier detection and treatment of diabetes, using the costing tool. However, there are no cost-effectiveness data that are relevant for Africa and the only controlled interventions in low- and middle-income countries were conducted in India^[31] and China^[32]. Additionally, cost-effectiveness analyses do not take into account non-health benefits, such as income gains, which may be important^[33].

In conclusion, the study confirms in an objective and standardized fashion that the basic medical cost of diabetes is likely beyond reach of a majority of people in West-African countries considering that no medical insurance is available in most of them. In spite of its limitations, the medical cost calculator, which can be used in different countries, is deemed important in Africa, considering the paucity of data on diabetes cost in the whole region. It is also flexible enough since cost data can easily be changed. No study had so far designed a simple costing tool which would take into account the various components of medical care of diabetes and its complications in sub-Saharan Africa.

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COMMENTS

Background

Non-communicable chronic diseases such as diabetes are taking a heavy social and economic toll in low income countries already overburdened by acute diseases. However, diabetes remains far from the top of health priorities in most of sub-Saharan Africa. In addition to global calls for action, specific advocacy strategies and instruments are therefore timely. The study describes a standardized calculator that was developed to estimate the medical costs of diabetes in sub-Saharan Africa. Showing the exorbitant cost of inaction is regarded as potentially convincing for decision makers.

Research frontiers

Economic models of diabetes and other chronic diseases exist but their complexity is a serious barrier to their wider use notably for advocacy purposes. The development and testing of simple yet standardized estimators of medical costs of diabetes (and other chronic diseases) is a relevant research area for low- and middle-income countries who now face a staggering escalation of chronic diseases.

Innovations and breakthroughs

Previous studies on this topic in Africa focused on medical costs of acute complications in the hospital or of specific care components such as insulin treatment, whereas this study included all direct medical costs for basic treatment and for the treatment of chronic and acute complications. To develop the medical cost calculator, a detailed protocol for the basic treatment of type-2 diabetes and for the treatment of main complications was first developed by a working group consisting of medical and public health specialists from the four West African study countries. Care components for minimally adequate treatment included physicians and allied health professionals' services, hospital care, lab tests and controls, and drugs and medical supplies. Price data for the care components were then collected in the public and private health sectors of the study countries. The user-friendly software designed on Excel 2010 for Windows allows to compute ranges of total medical costs for patients. Total yearly medical costs for a person with diabetes convincingly show that the treatment is unaffordable for many, particularly when taking into account local incomes and if complications are present, which is the case for a majority of patients.

Applications

The medical costs calculator developed in the study can be used in other African countries since the treatment protocol is standardized; only local prices vary. This tool can be used by health professionals or other stakeholders for advocacy so that action is taken for type 2 diabetes prevention and control. The calculator allows to show the prohibitive cost of inaction vis-à-vis type 2 diabetes, whether at the individual or country level. The tool would have to be complemented with data on alternative interventions in order to show the cost of action.

Terminology

Direct medical costs of diabetes: The calculator provides an estimate of out-of-pocket expenditures of patients with diabetes for their treatment in the study countries of West Africa. Other direct costs (transportation, diet...) are not included. Gross national income (GNI) per capita: This figure is often used as a proxy for income, as done in the study countries. The GNI is converted to international dollars using purchasing power parity rates. An international dollar has the same purchasing power as a United States dollar in the United States.

Peer-review

The authors describe a tool that is a simple medical cost calculator; they report and discuss the results of this tool. The manuscript is well written and well organized.

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