Economic Evaluation of Self-Monitoring of Blood Glucose as a Key Component for Type 2 Diabetes Treatment in Mexico Using Stochastic Simulation

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Abstract: - The main purpose of this article is to report the development and application of a simulation model that was used to estimate the effects on the level of glycosylated hemoglobin (HbA1c) and the cumulative costs of four different regimes of self-monitoring of blood glucose (SMBG) plus pharmacologic treatment experienced by patients with type 2 diabetes (T2D) in a typical Mexican public health institution (MPHI). The simulation model was designed to imitate the individual experience of a patient with T2D at a MPHI; the main drivers for cost computation were HbA1c evolution and its effect on the incidence and treatment (or not) of comorbidities, complications and acute events associated with T2D. Simulation runs using this model show that the expected average cumulative cost for a patient with T2D and no SMBG is $60,443 US dollars over a 10-year span, and the use of SMBG will reduce this expected cost in 6.5%, 7.5% and 7.8% for 1, 2 and 3 times daily regimes of SMBG, respectively.

Key-Words: - Type 2 diabetes, economic evaluation, stochastic simulation, self-monitoring, blood glucose

1 Introduction

The American Diabetes Association (ADA) defines diabetes as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. As a result of chronic hyperglycemia, different organs might suffer long-term damage, resulting in significant morbidity and mortality (when compared to healthy individuals) and a heavy clinical and economic burden for society.

According to Shaw et al. [2], the world prevalence of type-2 diabetes (T2D) among adults (aged between 20 and 79 years) was 6.4% in 2010, affecting 285 million adults, and will increase to 7.7%, or 439 million adults, by 2030. Based on predicted demographic changes, the same authors estimate that between 2010 and 2030 there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries.

T2D is a major public-health problem in Mexico. Its prevalence has increased significantly in the last decade: by 2000, the National Health Survey found that 5.8% of adults had been diagnosed with T2D, while for 2006 this number increased to 7.0%, yielding a total prevalence of 14.4% among adult population [3], [4].

Patients with T2D develop micro and macro vascular complications and comorbidities, whose treatment is costly. Current therapies for T2D in a typical Mexican public health institution (MPHI) consist of lifestyle modifications (nutritional and physical activity counseling), pharmacological treatment through oral anti-diabetics (OADs) and insulin provision [5]. Because of the public healthcare system structure, complete treatment for T2D-related complications is provided only in limited MPHIs.

Although not being reimbursed by MPHIs, self-monitoring of blood glucose (SMBG) [6] is included in many glucose control strategies, and has been recommended by medical societies, local clinical guidelines and regulatory mandates as an important part of any integral treatment strategy for patients with T2D, which also include glycosylated hemoglobin (HbA1c) level decrease and control. It has been suggested that the adoption of SMBG is associated to a lower increase (or even decrease) of HbA1c levels (see [6], [7]), thus reducing the

likelihood of developing micro and macro vascular complications and their associated treatment costs. In a country where only 25.4% of treated patients with diagnosed T2D are under control (HbA1c < 7%, see [8]), the evaluation of any cost-effective diabetes-oriented intervention is desirable. However, there is limited local evidence on the clinical and economic impact of SMBG as a component of any therapy strategy for patients with T2D in MPHIs.

The main objective of the research reported in this paper is to estimate the effects on the level of HbA1c and the cumulative cost of available treatment therapies of different SMBG regimes experienced by patients with T2D in a MPHI under an institutional perspective. According to the literature on health economic evaluation (see, e.g., [9]), stochastic simulation has many advantages as a tool to achieve our objective and is becoming a preferred technique for assessing health economic outcomes Although the development and application of a simulation model is, in general, more costly and time-consuming than the application of an analytical model (see e.g., [3]), we decided to develop a simulation model to perform our economic evaluation because the modeling flexibility of a simulation facilitated the consideration of available data and allowed us to develop a flexible tool to imitate the individual experience of a patient with T2D at a MPHI. As we explain in the next sections, our simulation model can be easily modified to incorporate the required data to perform the economic evaluation of different therapies (other than SMBG-related therapies) for T2D patients. The advantages of using a simulation model to assess the impact of screening, prevention, and treatment strategies on chronic degenerative diseases (including T2D) have been reported in the literature (see, e.g., [11], [12], [13]). However, to the best of our knowledge, there are no publications on the medium to long run costs of treatment of T2D, and simulation allows us to estimate these costs.

Previous work on the economic analysis of SMBG in patients with T2D includes the cost-effectiveness analysis of SMBG in patients on oral anti-diabetes medication in the US [14], and in France, Germany, Italy and Spain [15] by using the CORE model [16] for the estimation of long term outcomes. In addition, this paper extends and actualizes the results initially presented in [17] and our main contribution is the development of a simulation model based on the experience of T2D patients in a MPHI and its corresponding application using cost data from MPHIs.

In order to perform an economic evaluation, our simulation model generates patients with demographic, clinical and epidemiologic characteristics whose distributions are determined by the information in the available literature ([17], [18], [19]). Then, patient evolution through standard medical treatment (including medical consultations and tests) at a typical MPHI (once every quarter) is simulated by following international and regional clinical guidelines ([20, [21]), as well as local mandates ([22]) to determine disease- and complication-specific pharmacologic treatment, resource utilization and therapies. The level of HbA1c was the main driver of disease progression.

The remainder of this article is organized as follows. In Section 2 we present a detailed description of the simulation model that was developed to perform our economic analysis. In Section 3 we present the results from runs of our simulation model to estimate the expected annual cumulative cost per year for patients with T2D at a MPHI. Finally, in Section 4 we provide our conclusions and directions for future work.

2 Conceptual Model

In order to describe the simulation model that was implemented to perform our economic evaluation, we follow the steps suggested in [23].

2.1 Objectives and complexity

The main objective of our simulation model was to estimate the expected annual costs incurred by patients with T2D at a MPHI under four different scenarios related to the daily frequency of self-monitoring of blood glucose: no self-monitoring (SMBG0), once a day (SMBG1), twice a day (SMBG2), and three times a day (SMBG3). Moreover, since SMBG causes an additional cost (mainly because of strips cost), we expect that scenarios SMBG1, SMBG2 and SMBG3 would exhibit larger costs than scenario SMBG0 at the initial years of therapy, and it will be of interest to investigate if break-even occurs (and when) for scenarios SMBG1, SMBG2 and SMBG3, respectively.

The main entity in our simulation model is a patient with (recently diagnosed) T2D that will undergo the following sequential treatment regimes, depending on baseline HbA1c levels and its evolution over time: lifestyle modifications (nutritional and physical activity counseling), pharmacologic treatment (monotherapy and combined therapy) and partial and total insulin use.

For every patient, we simulate the main outcomes through 4 consultations per year (one every quarter) at a MPHI until the patient either dies or reaches a predetermined number of years under treatment (simulation length), with a maximum of 25 years. A patient may die either because of a T2D related complication or any other cause (see Section 2.3 for details). In consultations one and three (of any year) the patient is subject to clinical tests, and the corresponding results are analyzed on consultations two and four, respectively. Based on clinical tests' results, the patient is assigned a therapy for the following six-month period. We assume, in our simulation model, that a specific dose of every prescribed drug is applied for 6 months once the patient is diagnosed on consultations two and four of every year. Treatment success or failure was determined by observed HbA1c levels at the next consultation: success was defined as a HbA1c level $\leq 7\%$, whilst failure as $> 7\%$, as defined by local mandates [23]. If treatment succeeded, previous regime was maintained; otherwise (treatment failure), transition to next regime or pharmacologic dose increase was prescribed. Considered therapies are shown in Table 1, and were randomly assigned to patients both for monotherapy and for combined treatment.

HbA1c level movements among the three different considered treatment regimes and the four SMBG regimes were taken from [6]. All considered drugs (monotherapy, combined treatment) were assumed equally effective in decreasing/increasing HbA1c levels.

Table 1. Different therapies considered in the simulation model.

Therapy	**Main Prescription**
Lifestyle modifications	Nutritional and physical activity counseling
Pharmacologic treatment	Metformine, glibenclamide, acarbose, pioglitazone
Insuline use	NPH insulin, glargine insulin, rapid insulin

Simulation of a patient´s therapy starts by first assigning the level of HbA1C and the presence (or not) of every comorbidity shown in Table 2. In addition, demographic attributes and the presence (or not) of risk factors are also simulated (see Section 2.3 for details). Then, identical copies of the patient are assigned to each of the four SMBG scenarios under study, and the evolution of every copy of the patient (HbA1C level) is simulated for every consultation of every year of treatment, while complication incidence is evaluated once a year, based on years since diagnose (according to data of [18]). Renal failure was not considered in this model, as information on its treatment and evolution was not available.

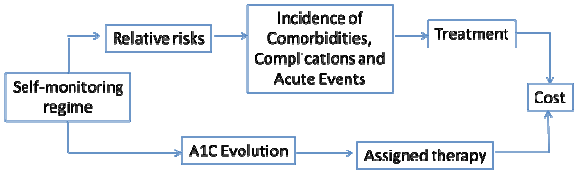
As illustrated in Fig. 1, different scenarios have different relative risks factors for the development of any complication, and also different transition patterns for the level of HbA1C (according to the results of [6]), and this is why they provide different cost patterns (although subject to a random evolution).

Table 2. Comorbidities, complications and acute events considered in the simulation model.

Amputation	Angina	Acute myocardial Infarction
Cataract	Depression	Diabetic Foot
Dyslipidemia	Glaucoma	Erectile dysfunction
Heart failure	Neuropathy	Hypertension
Hypoglycaemia	Ketoacidosis	Congestive heart failure
Micro albuminuria	Nephropathy	Peripheral vascular disease
Renal failure	Stroke	Retinopathy

The main outputs of our simulations are the cumulative costs incurred by a patient in every year of therapy at a MPHI, and the performance measures of interest are the expected cumulative costs per year of therapy. These performance measures can be estimated by using the method of replications and a sufficiently large number of simulated patients (see, e.g., [10]).

Fig. 1: Cost Drivers in the Simulation Model.

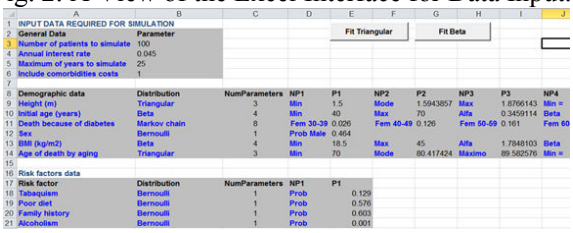


2.2 Process description

As illustrated in Fig. 2, an Excel interface was designed to facilitate the input of data and required parameters into the simulation model; this interface included macros to perform the required parameter fitting from available data. The simulation model was developed using the software Simio [10], and

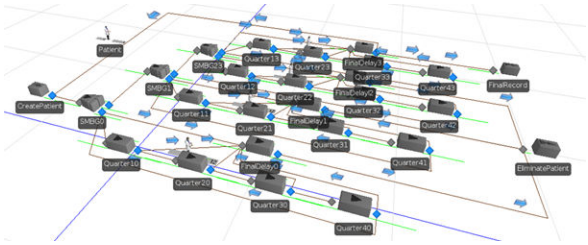
the process flowchart is illustrated from the animation developed in Simio (see Fig. 3).

Fig. 2: A View of the Excel Interface for Data Input.



	A	B	C	D	E	F	G	H	I	J
1	INPUT DATA REQUIRED FOR SIMULATION				Fit Triangular		Fit Beta			
2	General Data	Parameter								
3	Number of patients to simulate	100								
4	Annual interest rate	0.045								
5	Maximum of years to simulate	25								
6	Include comorbidities costs	1								
7										
8	Demographic data	Distribution	NumParameters	NP1	P1	NP2	P2	NP3	P3	NP4
9	Height (m)	Triangular	3	Min	1.5	Mode	1.5943857	Max	1.8766143	Min =
10	Initial age (years)	Beta	4	Min	40	Max	70	Alfa	0.3459114	Beta
11	Death because of diabetes	Markov chain	8	Fem 30-39	0.026	Fem 40-49	0.126	Fem 50-59	0.161	Fem 60
12	Sex	Bernoulli	1	Prob Male	0.464					
13	BMI (kg/m2)	Beta	4	Min	18.5	Max	45	Alfa	1.7848103	Beta
14	Age of death by aging	Triangular	3	Min	70	Mode	80.417424	Máximo	89.582576	Min =
15										
16	Risk factors data									
17	Risk factor	Distribution	NumParameters	NP1	P1					
18	Tabaquism	Bernoulli	1	Prob	0.129					
19	Poor diet	Bernoulli	1	Prob	0.576					
20	Family history	Bernoulli	1	Prob	0.603					
21	Alcoholism	Bernoulli	1	Prob	0.001					

Fig. 3: A View of the Simulation Animation in Simio.



As can be observed from Fig. 3, after a patient is created (by object CreatePatient), three copies are generated (by objects SMBG0, SMB1, SMB23, respectively) and every copy follows their corresponding four consultations per year until patient's death or a predetermined number of years with T2D first occur. The required computations to perform the simulations were implemented by using Simio processes (see [10] for details), and the main processes in the model are: InitialAtributtes, Consultation1, Consultation2, Consultation3 and Consultation4. The process InitialAttributes is performed when a patient exits the object CreatePatient and is designed to initialize the patient's initial attributes and comorbidities. The processes related to the consultations are performed when the patient enters the corresponding consultation object (e.g., Quarter10 or Quarter43) and are designed to simulate the evolution (e.g., HbA1C level and complications incidence) of the patient and to record the corresponding costs.

2.3 Input data

The main input data available to develop our simulation model can be classified in 4 categories: demographic data, risk factors data, clinical data and epidemiologic data. In addition, data on the costs (at a MPHI) of drugs, materials, consultations, clinical tests and clinical events' (complications and acute events) treatment were considered in order to compute the costs incurred by the patients during their therapies. Demographic data consists on parameters for the probability distributions of age, height, body mass index and mortality of patients diagnosed with T2D. Mortality because of other causes was adjusted to occur after T2D diagnosis. Risk factors data correspond to prevalence probabilities of smoking, alcoholism, poor diet and family history of T2D. Both demographic and risk factors data were taken from [3] and [18]. However, because of insufficient information for any of the four SMBG regimes considered, they could not be taken into account to simulate the evolution of HbA1C. All patients are assumed to be diagnosed with T2D at the beginning of the simulation with no previous pharmacologic treatment for glycemic control.

The evolution of the HbA1C level from one consultation to the next was assumed to be Markovian, so that clinical data consisted mainly on parameters for the initial distribution of HbA1C and the transition probability distributions estimated from data available in [18] and [6]. It is worth mentioning that, because the distribution of the HbA1c level is typically asymmetric and bounded, beta distributions were assumed for both initial and transition probability distributions, and the corresponding parameters were estimated using the method of moments (see, e.g., [24]). Similarly, complications evolution is assumed to be Markovian, so that complications data consisted on initial probabilities and transition probabilities estimated from [18] (prevalence data) and [19] (relative risks) for the different scenarios of SMBG. Our study was done under a high-specialty hospital (MPHI) perspective, and only direct medical costs were considered – ie, pharmacologic & insulin treatment (for T2D and associated comorbidities), inpatient hospital care (for complications and acute events) and SMBG. Cost information for drugs was taken from CompraNET (public health institutions bid-tender and price database); data for complication-specific treatment was taken from a micro-costing study in local public institutions, while the price of SMBG material was internally assessed. We used a 4.5% annual discount rate for costs.

2.4 Verification and animation

Verification of the model developed in Simio was performed by testing that the main outcomes (demographic and risk factor data, comorbidities' and complications' prevalence and incidence, mean and variance of HbA1C levels) provided by the model were consistent with data reported in the existing literature.

Fig. 4: Animation of Simulation Output in Simio.

Also, as discussed in the simulation literature (e.g., [10]), animation is a powerful tool for verification and, besides the simple animation shown in Fig. 3, animations (graphs) for the main outputs (e.g., evolution of HbA1C levels, complications and comorbidities) were included in the dashboard window of Simio in order to facilitate validation of the model (see Fig. 4).

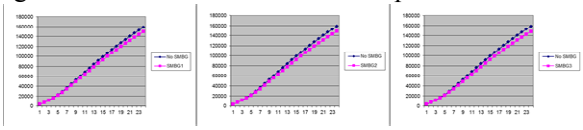
3 Experimental Results

In this section we report the results from our simulation experiments in order to estimate the expected cumulative costs for patients with T2D at a MPHI. At the end of this section we also comment on the limitations and assumptions of our simulation model.

3.1 Main results

In Table 3 we report the expected, (present value) cumulative cost (in US dollars) and the corresponding estimation error (half-width of a 90% confidence interval) by different years of therapy for patients with T2D at a MPHI. Our results were obtained from running our simulation model with 250,000 replications (of patients) to ensure small estimation errors.

Fig. 4: Animation of Simulation Output in Simio.



As can be observed from Table 3, our simulation runs show that the expected cost per patient after 10 years of T2D treatment (at a MPHI) are smaller for patients under SMBG compared to patients with no SMBG, although at the initial years the corresponding cumulative expected costs are larger. Note also that the estimation error (half width of a 90% confidence interval) increases with more years of therapy. As illustrated in Fig. 5, cost break-even (or return of investment) occurs at year 3 for all three scenarios SMBG1, SMBG2 and SMBG3. As shown in Table 3, the expected cumulative cost for patients with T2D and no SMBG is around US $60,443 over a 10-year therapy, and the use of SMBG will reduce this expected cost in 6.5%, 7.5% and 7.8% for 1, 2 and 3 times daily regimes of SMBG, respectively.

Table 3. Expected cumulative cost (US $[1]) per patient with T2D under different SMBG scenarios.

	SMBG0		SMBG1		SMBG2		SMBG3	
Year	Cost	HW	Cost	HW	Cost	HW	Cost	HW
1	3371	16	3420	16	3484	19	3548	19
2	6944	31	6967	31	7048	37	7136	37
3	11675	47	11470	47	11421	56	11486	56
4	16931	63	16352	63	16197	76	16225	76
5	22712	81	21537	81	21308	97	21284	97
6	29449	99	27662	100	27337	119	27274	119
7	36772	117	34419	118	34020	141	33932	140
8	44487	135	41615	136	41126	162	40992	162
9	52426	153	49014	154	48456	184	48304	183
10	60443	171	56507	172	55886	206	55712	206
15	99282	272	93083	273	92300	327	91945	326
20	133983	384	126082	388	125252	463	124649	461

[1]Exchange rate was 13 Mexican pesos per dollar (Banco de Mexico's december 2013 average rate).

3.1 Assumptions and limitations of the simulation model

The main limitations of our simulation model in its actual version are derived from the lack of experimental data to estimate the main parameters for the probability distributions that drive the simulations. As mentioned before, both the initial and transition probability distributions for the HbA1c levels were assumed to be beta and the method of moments was applied to estimate the corresponding parameters. Input analysis (see, e.g., [10]) to select the probability distributions that best fit the observed data could not be applied since the main information published in the existing literature are only the corresponding mean and variance, and this is also why the method of moments was feasible for parameter estimation. Further input analysis to incorporate parameter uncertainty induced by the estimation procedure (as suggested, e.g., in [25]) could not be accomplished because of lack of experimental data as well.

We also mention that, although our simulation model considers the evolution of all the comorbidities, complications and acute events reported in Table 2, the simulation runs reported in Section 3.1 have incorporated only the costs of

amputation, angina, cataracts, congestive heart failure, hypoglycaemia, infarct, ketoacidosis, peripheral vascular disease and stroke. Further, because of the lack of experimental data, the evolution of all complications has been assumed to be independent, except for some clinical dependences as, for example, nephropathy after micro albuminuria and amputation after diabetic foot.

Our model and estimations rely on several clinical and patient-based assumptions, such as similar efficacy among considered pharmacologic treatment options and regimes, perfect adherence and compliance to drugs by patients, no a priori (pre-diagnosis) treatment and no patient- nor group-based education programs, among others. We were not able to establish a differentiated effectiveness of each of the former for the considered SMBG regimes over a long-run time frame as there is no available information. However, because of how the model was built and structured, any treatment additions (such as telemetry, education programs or new drugs) could be easily incorporated by knowing its individual impact on HbA1c levels for different SMBG regimes.

Our study adds valuable information to the available economic literature on the long term costs associated to T2D treatment. To the best of our knowledge, no such study is available for the Mexican context. Our results lie between the cost estimates shown by Rodriguez Bolaños [26] and Arredondo and De Icaza [27]; and the cost trend seems exponential between years 1 and 10 of simulation. After the tenth year, our cost estimations might be volatile due to the loss of patients during simulation, either because of T2D-related complications, or of natural death.

4 Concluding Remarks

We report the development and application of a simulation model that was designed to imitate the individual experience of a patient with type-2 diabetes at a Mexican public health institution, and performed simulation runs to estimate the expected annual costs incurred by patients with type-2 diabetes under four different scenarios related to the frequency of self-monitoring of blood glucose: no self-monitoring, once a day, twice a day, and three times a day. Although there is some controversy on the impact of SMBG on the evolution of patients with T2D (for a report on a non-significant impact see, e.g., [28]), our simulation experiments are in agreement with the literature that report a positive impact of SMBG and, in particular, with reports (e.g., [7]) on a significant reduction in HbA1c for patients using SMBG (once a day), with no significant further reduction with more intensive SMBG (in our case, twice or three times a day). Our simulation runs show that, compared to the non-SMBG scenario, the expected cumulative cost incurred by patients with T2D break evens at year 3 for all three scenarios of SMBG (one, twice and three times a day). In addition, the expected (present value) cumulative cost for patients with T2D and no SMBG is around US $60,443 over a 10-year span, and the use of SMBG will reduce this expected cost in 6.5%, 7.5% and 7.8% for 1, 2 and 3 times daily regimes of SMBG, respectively.

The simulation model reported in this paper incorporates input data in 4 categories: demographic data, risk factors data, clinical data and epidemiologic data, and the main drivers for cost computation are the evolution of glycosylated hemoglobin, and the incidence (or not) of the main comorbidities, complications and acute events associated with T2D. For the application reported in this paper, economic evaluation of four different scenarios of SMBG has been performed. However, simple modifications on the appropriate transition probabilities for the evolution of HbA1c and the corresponding complications' relative risks can be implemented to perform economic analysis of other therapies for T2D.

The main limitations of the results reported in this paper are associated to the lack of experimental data to support the estimation of the main parameters for the probability distributions that drive the simulations, and in particular, we are aware that data (from individual diabetic patients) on the evolution of HbA1c may allow us to apply appropriate input analysis techniques to drive our simulations. We expect that this application may help Latin-American healthcare decision makers to understand the importance of recording the appropriate information to support important healthcare policy-decisions. For instance, if implementation of SMBG may provide a 7% reduction in the cumulative per-patient cost over a 10-year period, the expected total savings from this policy on a population of 6.5 million patients with T2D in Mexico (see [8]) will be around 27 billion US dollars over a 10-year period.

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