Research Paper

Efficacy and Direct Medical Costs of Metformin-Glibenclamide Treatment in Ecuadorian Population with Type II Diabetes Mellitus during the COVID-19 Pandemic

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Type II diabetes mellitus is one of the most prevalent endocrinological diseases with a high economic impact worldwide. Coronavirus disease 2019 pandemic was declared by the World Health Organization in March 2020 with lockdowns representing an important change in the assessment of type II diabetes mellitus. This study was a retrospective and economic impact analysis of the efficacy and direct costs of type II diabetes mellitus in ambulatory patients treated with metformin plus glibenclamide during the coronavirus disease 2019 pandemic in an Ecuadorian second level hospital. Data collected included demographic characteristics, drug regimen, laboratory tests, diabetes complications, comorbidities and hospitalization stay. Estimates of costs were based on the National Public Procurement Service and the Rate of Benefits for the National Health System. The mean difference in glycated hemoglobin, fasting glucose and weight after 6 and 12 mo of treatment was also analyzed. In total, 39 patients (21 females and 18 males) were enrolled. Medical consultations costs amounted to 8004.00 USD (205.23 USD per patient) with 213 (84.5 %) consultations dedicated to diabetic control (5.5±2.7 consultations per patient/year). All patients required hospitalization and emergency care at least once, which represented a total cost of 77 812.73 USD (1995.20 USD per patient) and 3448.56 USD (88.42 USD per patient), respectively. After 12 mo, fasting glucose [-58.8 mg/dl (95 % confidence interval -19.7 to -97.9 mg/dl; p=0.004)] and glycated hemoglobin levels [-1.05 % (95 % confidence interval -0.16 % to -1.93 %; p=0.02)] significantly decreased. The total annual direct costs were 110 634.81 USD, while the cost per patient was 2836.79 USD. Moreover, metformin plus glibenclamide significantly reduced fasting glucose and glycated hemoglobin levels, but not according to international recommendations. The economic impact of type II diabetes mellitus management during coronavirus disease 2019, however, was considerable mainly due to complications and prolonged stay hospitalizations.

Key words: Diabetes mellitus treatment, drug cost, glycated hemoglobin, diabetes impact budget

Type II Diabetes Mellitus (T2DM) is an endocrinological disease with an important economic burden in public health worldwide[1]. According to the International Diabetes Federation (IDF), an increase of 26.4 % was observed in the global prevalence of T2DM from 2017 (425 million people) to 2021 (573 million people)[2]. In 2017, 462 million people (6.28 % of the world population) were diagnosed with T2DM and the prevalence was 6059 cases per 100 000 inhabitants[3]. However, the prevalence is expected to increase to 7079 cases per 100 000 in 2030[1]. In South and Central America, the IDF reported 32 million people with T2DM in 2021[2]. In Ecuador, a national survey reported a T2DM prevalence of 2.7 % in the population between 10 and 59 y old in 2013[4].

The global burden of T2DM has increased significantly in recent decades and the costs generated by this disease in 2021 reached approximately 966 billion United States Dollar (USD) worldwide[2]. However, by 2030 the absolute global economic burden will increase to 2.1 trillion USD[5]. In South American countries, T2DM accounted for 19.4 % of global health expenditure to reach 65 billion USD in 2021[6]. In Ecuador, the total spending for T2DM

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in 2019 and 2021 was 1 billion USD and 10 billion USD, respectively[2,6].

T2DM pharmacological treatment is based on efficacy, adverse events, cost and patient preferences to improve glycemic control, treatment adherence and quality of life[7]. Metformin plus Glibenclamide (MG) is recommended by the American Diabetes Association (ADA) 2023 guideline as a second line treatment in T2DM patients who were unable to maintain glycemic targets with monotherapy[8]. MG drugs work complementary through different mechanisms and sites of action. Metformin reduces peripheral cell resistance to insulin and improves beta-cell responsiveness to glucose, while glibenclamide stimulates the secretion of insulin in the pancreas[9].

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic was declared by the World Health Organization (WHO) in March 2020[10]. People living with T2DM were associated with a higher risk of adverse outcomes following initial infection[11]. However, restrictions imposed during lockdowns disrupted patients' consultation, drug access and laboratory tests to optimize glycemic control[12]. In this study, we proposed to assess the efficacy and economic impact in terms of direct costs of MG treatment of T2DM Ecuadorian patients hospitalized during the Coronavirus Disease 2019 (COVID-19) pandemic.

MATERIALS AND METHODS

Study settings and design:

The present retrospective, single center, observational study was conducted on hospitalized T2DM patients treated between January and December 2021 in an Ecuadorian second level hospital. T2DM patients included were ≥18 y old, received MG combination regardless of line of treatment, a negative COVID-19 test and were hospitalized due to T2DM complications. Exclusion criteria were patients under 18 y of age and patients who use different antidiabetic drugs. The Institutional Review Board Ethics Committee approved the study.

Data collection:

Chart's information of patients who met the inclusion criteria was collected using a capture report form. Data included demographic, drug regimen, laboratory tests, diabetes complications, comorbidities and hospitalizations. In addition, weight (kg), fasting glucose levels (mg/dl) and glycated Hemoglobin (HbA1c, %) levels were recorded at 6 and 12 mo.

Calculation of direct medical cost of T2DM:

The calculation for direct medical costs of T2DM was performed for 12 mo. The price of drugs was established according to the National public procurement service. The outpatient consultation and hospitalization cost estimations were obtained using the current official information of the Rate of Benefits for the National Health System of 2014 and considering the 2019 update.

Data analysis:

The budget impact model was developed in Microsoft excel to calculate the direct cost of T2DM management. Quantitative data were summarized by the mean and Standard Deviation (SD) while frequency tables (number, percent) were used for categorical variables. The prevalence was estimated with a 95 % Confidence Interval (95 % CI). Treatment differences in HbA1c, fasting glucose and weight after 6 and 12 mo were assessed using a paired t-test. Results were considered significant at the 5 % critical level ($p<0.05$). Data were analyzed using R studio version 4.1.3 and Epi Info version 7.2.5.0.

RESULTS AND DISCUSSION

Demographic characteristics of the participants were shown in Table 1. In total, 39 patients were enrolled in the study, 21 (53.8 %) females and 18 (46.2 %) males, with a mean age of 55.1±14.0 y (range 41-69 y). Among study patients, all were Hispanics, 9 (51.3 %) reported being overweight and 13 (30.8 %) obese. A total of 19 (48.7 %) patients had T2DM for at least 5 y and the baseline diabetic assessment measures were 72.4±11.7 kg of weight, 282±98.7 mg/dl for fasting glucose levels and 11.0 %±2.6 % for HbA1c levels. 14 (35.9 %) patients did not report any comorbidities, while 21 (53.9 %) had arterial hypertension and 14 (35.9 %) dyslipidemia.

A total of 252 outpatient consultations were carried out in 12 mo, of which 213 (84.5 %) were specifically for diabetes control with a mean of 5.5±2.7 consultations per patient. 16 (41.0 %) patients did not have any complication associated with T2DM in 1 y, but 17 (43.6 %) patients presented foot ulcers. All patients required hospitalization, 33 (84.6 %) participants were hospitalized at least once with a mean length stay of 9.5±7.2 d per patient. In addition, 27 (69.2 %) patients had at least one admission to an emergency room, yielding a mean

emergency admission rate of 1.4±0.82 per patient as shown in Table 2.

Changes in glycemic outcomes were shown in Table 3. Regarding treatment efficacy, no significant changes in weight were observed at 6 and 12 mo. Fasting glucose levels significantly decreased at 6 and 12 mo, with a difference of -84.8 mg/dl (95 % CI of -48.1 to -121.5 mg/dl; p<0.0001) and -58.8 mg/dl (95 % CI of -19.7 to -97.9 mg/dl; p=0.004), respectively. In addition, a significant diminution in the HbA1c levels was observed at 6 mo (difference of -1.34 %; 95 % CI of -0.49 % to -2.2 %; p=0.002) and 12 mo (difference of -1.05 %; 95 % of CI -0.16 % to -1.93 %; p=0.02).

The total annual direct costs of patients with type 2 diabetes mellitus were shown in Table 4 and Table 5. The outpatient treatment of T2DM had a total cost of 1817.72 USD for the 39 patients in 1 y (46.61 USD per patient), of which 1335.90 USD were spent in 22 265 doses of metformin 500 mg, 102.20 USD in 2555 doses of metformin 850 mg and 379.62 USD in 11 863 doses of glibenclamide 5 mg. Additionally, the total cost of medical consultations was 8004.00 USD (205.23 USD per patient), among which 6765.25 USD were only for diabetic control consultations.

In 1 y, emergency room admissions and hospitalizations reported a total cost of 3448.56 USD (88.42 USD per patient) and 77 812.73 USD (1995.20 USD per patient), respectively. T2DM additional treatment during hospitalization required a total cost of 85.18 USD (2.18 USD per patient). However, 1781.86 USD (45.69 USD per patient) were spent in other drugs used during hospitalizations, of which 1250.86 USD were for antibiotics, 219.77 USD for analgesics/anti-inflammatories and 120.98 USD for prophylactic anticoagulants.

TABLE 1: BASELINE CHARACTERISTICS OF THE PARTICIPANTS (n=39)

Trebuchet MS	Category	Mean±SD, Number (%)
Age (years)		55.1±14.0
Gender	Male	18 (46.2)
	Female	21 (53.8)
Race	Hispanic	39 (100)
	Other	0 (0.0)
Body mass index (kg/m^2)	<18.5	0 (0.0)
	18.5-24.9	6 (15.4)
	25-29.9	20 (51.3)
	30-34.9	9 (23.1)
	35-39.9	3 (7.7)
	>40	1 (2.6)
Duration of T2DM	1-5 y	19 (48.7)
	5-10 y	13 (33.3)
	>10 y	7 (18.0)
Diabetic assessment measures	Weight (kg)	72.4±11.7
	Fasting glucose (mg/dl)	282±98.7
	HbA1c (%)	11.0±2.6
Comorbidities	Arterial hypertension	21 (53.9)
	Dyslipidemia	14 (35.9)
	Obesity	12 (30.8)
	Renal impairment	8 (20.5)
	Other	2 (5.1)
	None	14 (35.9)

Note: T2DM-Type 2 Diabetes Mellitus; HbA1c-Glycated Hemoglobin and SD-Standard Deviation

TABLE 2: T2DM PATIENT CONSULTATIONS, COMPLICATIONS, HOSPITALIZATIONS AND EMERGENCY ATTENTIONS IN 12 mo

Variable	Category	Mean±SD, Number (%)
Outpatient consultations	Total	252 (100)
	Diabetic consultations	213 (84.5)
	Dentistry	9 (3.6)
	Cardiology	6 (2.4)
	Psychology	5 (2.0)
	Pneumology	4 (1.6)
	Rheumatology	4 (1.6)
	Neurology	3 (1.2)
	Vascular Surgery	3 (1.2)
	Others	5 (2.0)
Diabetic consultations	Total number	213
	Number per patient	5.5±2.7
Complications of diabetes	Diabetic foot ulcers	17 (43.6)
	Diabetic nephropathy	2 (5.1)
	Cardiovascular complications	2 (5.1)
	Diabetic ketoacidosis	2 (5.1)
	Diabetic retinopathy	0 (0.0)
	None	16 (41.0)
Frequency of hospitalization	1	33 (84.6)
	2	3 (7.7)
	3	3 (7.7)
Length of hospitalization (days)	Total no. of days	372
	No. of days/patient	9.5±7.2
Number of times attended in emergency	1	27 (69.2)
	2	9 (23.1)
	≥3	3 (7.7)
Emergency admissions	Total no. of entries	56
	No. of entries/patient	1.4±0.82

Note: T2DM-Type 2 Diabetes Mellitus and SD-Standard Deviation

TABLE 3: EFFECT OF MG TREATMENT IN GLYCEMIC CONTROL AND WEIGHT

Variable	Baseline (Mean±SD)	Duration	Mean±SD	Difference (95 % CI)	p-value
Weight (kg)	72.4±11.7	6 mo	71.9±10.3	0.57 (-1.29 to 2.45)	p=0.53
		12 mo	71.4±12.2	1.08 (-2.03 to 4.19)	p=0.48
Fasting glucose (mg/dl)	282±98.7	6 mo	197±63.0	-84.8 (-48.1 to -121.5)	p<0.0001
		12 mo	233±84.8	-58.81 (-19.7 to -97.91)	p=0.004
HbA1c (%)	11.0±2.59	6 mo	9.63±2.33	-1.34 (-0.49 to -2.2)	p=0.002
		12 mo	9.96±2.55	-1.05 (-0.16 to -1.93)	p=0.02

Note: HbA1c-Glycated Hemoglobin; SD-Standard Deviation and CI-Confidence Interval

TABLE 4: TOTAL ANNUAL DIRECT COSTS OF PATIENTS WITH T2DM BY OUTPATIENT TREATMENT (n=39)

Variable	Category	n	Unit cost (USD)	Total cost (USD)
Outpatient treatment of T2DM				1817.72
	Metformin 500 mg	22 265	$ 0.06	1335.90
	Metformin 850 mg	2555	$ 0.04	102.2
	Glibenclamide 5 mg	11 863	$ 0.032	379.62
Medical consultations				8004.00
	Diabetic consultations	213	31.76	6765.25
	Dentistry	9	31.76	285.84
	Cardiology	6	31.76	190.56
	Psychology	5	31.76	158.8
	Pneumology	4	31.76	127.04
	Rheumatology	4	31.76	127.04
	Neurology	3	31.76	95.28
	Vascular surgery	3	31.76	95.28
	Others	5	31.76	158.8
Emergency care	Total of attentions	57	457.77	3448.56
Hospitalization	Total days	372	327.02	77 812.73
T2DM treatment during hospitalization				85.18
	Glargine insulin 100 IU/ml	2	35.7	55.87
	NPH insulin 100 IU/ml	11	2.67	29.05
	Metformin 500 mg	1	0.06	0.06
	Metformin 850 mg	5	0.04	0.2
Other drugs used during hospitalizations				1781.86
	Antibiotics	956	1.31*	1250.86
	Analgesics	219	1.01*	219.77
	Prophylactic anticoagulants	29	4.17*	120.98
	Gastric acid secretion inhibitors	34	1.37*	46,58
	Electrolytes	90	0.45*	40.8
	Hydration	37	1.07*	39.5
	Antihypertensives	173	0.21*	36.23
	Vitamins	9	0.25*	2.25
	Others	31	0.83*	24,89
Laboratory tests				10 940.63
	T2DM control	1653	3.07*	5071.09
	Arterial blood gas	116	10	1159.78
	Hepatic panel	337	3.11*	1047.53
	Microbiology culture tests	41	24.40*	1000.56
	Renal panel	259	3.47*	899.55
	Complete blood count	243	35.02	663.97
	Lipids panel	169	2.85*	482.39

	Urinalysis	95	3.04	289.08
	Serum electrolytes (sodium, potassium, chlorine)	114	2.23	254.22
	Thyroid panel	4	14.38*	57.5
	Quantitative C-reactive protein	1	10.49	10.49
	Coagulation test	2	2.24	4.48
Imaging tests				354.91
	Chest radiography	9	14.9	134.1
	Chest CT scan	2	60.48	120.96
	Abdominal CT scan	2	17.38	34.76
	Head CT scan	2	15.33	30.66
	Abdominal ultrasound	1	21.7	21.7
	Soft tissue ultrasound	1	12.73	12.73
Special test				2516.12
	Electrocardiogram	66	10.98	724.68
	Colonoscopy	1	1791.44*	1791.44
Procedures				3873.10
	Infracondylar amputation	5	457.77	2288.85
	Phalange amputation	4	210.37	841.48
	Wound healing	63	11.79	742.77
Total cost				110 634.81
Total cost per patient				2836.79

Note: T2DM-Type 2 Diabetes Mellitus; CT-Computed Tomography; USD-United States Dollar; * indicates average cost; NPH: Neutral Protamine Hagedorn and IU: International Units

TABLE 5: TOTAL ANNUAL DIRECT COST PER PATIENT OF T2DM (n=39)

Variable	Total cost (USD)	Cost per patient (USD)
Outpatient treatment of T2DM	1817.72	46.61
Medical consultations	8004.00	205.23
Emergency care	3448.56	88.42
Hospitalization	77 812.73	1995.20
Additional T2DM treatment during hospitalization	85.18	2.18
Other drugs used during hospitalizations	1781.86	45.69
Laboratory tests	10 940.63	280.53
Imaging tests	354.91	9.10
Special tests	2516.12	64.52
Procedures	3873.10	99.31
Total cost	110 634.81	2836.79

Note: T2DM-Type 2 Diabetes Mellitus and USD-United States Dollar

In the 39 participants, laboratory tests reported a total cost of 10 940.63 USD (280.53 USD per patient), of which 5071.09 USD were spent for T2DM control tests, 1159.78 USD for arterial blood gas, 1047.53 USD for hepatic panel and 1000.56 USD for microbiology culture tests. Additionally, imaging tests led to a total cost of 354.91 USD (9.10 USD per patient), of which radiographic studies amounted 134.1 USD, Computed Tomography (CT) scans 186.38 USD, and ultrasounds 34.43 USD. Patients also required special tests and procedures for a total cost of 2516.12 USD (64.52 USD per patient) and 3873.1 USD (99.31 USD per patient), respectively. Total direct costs per patient were 2836.79 USD.

This study assessed the efficacy and direct costs of T2DM patients treated with MG combination, the most common treatment administered in the hospital in second line, during the COVID-19 pandemic in Ecuador. The patients were mainly Hispanics with a 1 to 5 y history of diabetes and with hypertension and dyslipidemia as comorbidities. Most enrolled patients were overweight or obese, one plausible reason may be due to the cultural and socioeconomic context of the population studied or COVID-19 restrictions impact on physical activity, which was not evaluated in this project. However, a study reported that during the COVID-19 lockdown there was an increased physical inactivity (Odds Ratio (OR) 1.67; 95 % CI, 1.099-2.524, $p<0.016$) with a mean increase in weight of 3.61±2.35 kg[13].

The main medical consultations in the study population were for diabetes control, but an insufficient follow-up of only 5.5 consultations per patient per year instead of 12 was clearly evidenced. Some reasons may be due to the confinement measures that interrupted the follow-up of patients and our institution was unable to implement teleconsultations during the COVID-19 pandemic. In addition, all patients were hospitalized and treated in the emergency room at least once, probably due to complications related to the disease and the impact of COVID-19. The three most common additional drugs during hospitalizations were antibiotics, analgesics, and antihypertensives, while the laboratory tests most requested were for T2DM control, arterial blood gas, hepatic panel and microbiology culture. The study participants were hospitalized due to diabetic complications and they needed antibiotics, analgesics and anti-inflammatories as recommended by ADA guideline 2023[8]. Prophylactic anticoagulants were used to prevent venous thromboembolism after limbs amputations in critically ill medical inpatients[14]. Moreover, most patients had arterial hypertension as comorbidity, requiring antihypertensives during hospitalization. The hepatic panel was investigated several times during hospitalization because the association of T2DM and non-alcoholic fatty liver disease[15]. The most prescribed imaging test was chest radiography, while electrocardiograms were also highly requested. An electrocardiogram was performed at least once during hospitalization as a cardiovascular screening for all patients[16]. Also, in ambulatory setting, cardiology consultations and electrocardiograms were limited during COVID-19 pandemic. Some patients needed special procedures like amputations and wound healing, highly associated with severe complications and poor glycemic control.

In terms of efficacy, we observed a significant decrease in glycemic and HbAc1 levels in comparison with the baseline values. However, these T2DM glycemic results did not reach international recommendations, i.e., HbAc1 less than 7 % and fasting glucose between 80-130 mg/dl according to the ADA 2023, thus showing a lack of efficacy of the treatment[17]. Additionally, there was a considerable decrease in fasting glucose levels at 6 mo compared to that at 12 mo. However, no such significant change in HbAc1 level was noted either after 6 or 12 mo. One reason could be that patients changed their behavior before being tested, so acute markers like fasting glucose could be reduced, while HbAc1 showed the accurate glycemic control of the last 3 mo[9]. Some trials had reported that MG combination (2.5/500 mg) reduced mean HbA1c levels by 1.7 % to 1.9 % ($p<0.001$) and fasting glucose by -2.62 mmol/l ($p<0.05$) in comparison with monotherapy; in the present study, a less marked reduction of -48.1 % to -121.5 % ($p=0.002$) was reported for HbA1c and -0.49 to -2.2 mg/dl ($p<0.0001$) for fasting glucose at 6 mo[18,19]. These results were not evaluated in the context of a pandemic, but some systematic reviews and meta analyses reported that during the COVID-19 pandemic, a significant increase in the levels of HbAc1, fasting glucose and body mass index ($p<0.05$) in patients with T2DM was observed, and that the lockdown was associated with poor glycemic control[20-22].

As far as economic aspects are concerned, the study reported a total direct cost of T2DM management

of 110 634.81 USD during COVID-19 pandemic. However, a health care cost model in Europe among people with T2DM during the first wave of COVID-19 reported an estimated cost per hospital admission ranging between 25 018 Euros (EUR) among T2DM people in good glycemic control and 46 130 EUR in case of poor glycemic control. In the same study, the average weighted cost per diem (24 h) for admission to general hospital was 883 EUR, while here only 327.02 USD were reported[23].

Other studies that evaluated the economic impact of diabetes before COVID-19 pandemic reported lower expenses in comparison with our study, for example an Ethiopian economic evaluation reported a total cost of 2836.79 USD per patient while an eastern India study reported an annually total cost of 136.57 USD per patient[24,25]. In our study, 71 % of the total medical direct cost were due to hospitalizations, but a pharmacoeconomic Ecuadorian analysis of T2DM before COVID-19 pandemic reported that drugs costs were the most important, between 63.9 % to 84.7 % of total cost[26].

T2DM complications can generate important financial resources because of hospitalizations, consultations, drugs, special tests and procedures. A Brazilian trial reported that microvascular complications in T2DM had an annual cost per patient of 176.30 USD, while we calculated an approximate cost of 2584.95 USD per patient (sum of hospitalization, emergency care, drugs used during hospitalizations laboratory, imaging tests, special test and other procedures)[27].

The main limitation of the present cross-sectional retrospective study was the lack of efficacy and economic assessment before and after the COVID-19 pandemic. Additionally, it was based on a limited sample of hospitalized patients from a single second-level hospital, hence making extrapolations difficult and with unknown T2DM costs in non-hospitalized patients. Another limitation was the poor follow-up consultation and inadequate glycemic implementation in our population that could be a confounding factor at the efficacy analysis. According to the international guidelines, HbAc1 should be monitored every 3 mo. Unfortunately, COVID-19 pandemic limited our health services access and the laboratory reagents were scarce in our hospital. During hospitalization, patients received insulin as recommended by ADA 2023[8], but due to the lack of supply of drugs to hospitals nationwide, some younger hospitalized patients received only metformin[28]. Finally, MG is not considered the best combination therapy because of the increased risk of hypoglycemia and cardiovascular mortality associated[8]. Also, patient education and treatment adherence in T2DM was not evaluated to confirm the lack of treatment reasons of our patients and justified the complications and long stay hospitalization of patients. Our results revealed the need to improve T2DM control to reduce unnecessary and preventable costs for the healthcare system. More economic analyses should be conducted in the Latin American region to compare the real impact of COVID-19 pandemic in diabetic populations. Behavioral changes before testing can have an impact on results; hence we recommend further research on the differences between fasting glucose and HbAc1 changes with ambulatory treatments for T2DM.

In conclusion, this study showed that MG decreased fasting glucose and HbA1c levels, but not according to the international recommendations and important costs were related with complications and long stay hospitalizations in T2DM management. Finally, the present study highlights the significant costs in T2DM patients and the importance of appropriate follow up and adequate treatment.

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Conflict of interests:

The authors have no conflict of interest to disclose.

REFERENCES

1. Khan MA, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes-global burden of disease and forecasted trends. J Epidemiol Glob Health 2020;10(1):107-11.
2. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: International Diabetes Federation; 2021.
3. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet 2017;389(10085):2239-51.
4. Freire W, Ramírez Luzuriaga MJ, Belmont P, Mendieta MJ, Silva Jaramillo K, Romero N, *et al.* Encuesta Nacional de Salud y Nutrición. 1st ed. Ensanut-Ecu 2012; 2014. p. 722.
5. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, *et al.* Global economic burden of diabetes in adults: Projections from 2015 to 2030. Diabetes Care 2018;41(5):963-70.

6. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.
7. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174(8):1227-34.
8. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* 9. Pharmacologic approaches to glycemic treatment: Standards of care in diabetes-2023. Diabetes Care 2023;46(1):140-57.
9. Upadhyay J, Polyzos SA, Perakakis N, Thakkar B, Paschou SA, Katsiki N, *et al.* Pharmacotherapy of type 2 diabetes: An update. Metabolism 2018;78:13-42.
10. CDC COVID-19 response team, Bialek S, Boundy E, Bowen V, Chow N, Cohn A, *et al.* Severe outcomes among patients with coronavirus disease 2019 (COVID-19)-United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69(12):343-6.
11. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, *et al.* Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: A whole-population study. Lancet Diabetes Endocrinol 2020;8(10):813-22.
12. Scott ES, Jenkins AJ, Fulcher GR. Challenges of diabetes management during the COVID-19 pandemic. Med J Aust 2020;213(2):56-7.
13. Sooriyaarachchi P, Francis TV, King N, Jayawardena R. Increased physical inactivity and weight gain during the COVID-19 pandemic in Sri Lanka: An online cross-sectional survey. Diabetes Metab Syndr 2021;15(4):102185.
14. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, *et al.* American Society of Hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and non-hospitalized medical patients. Blood Adv 2018;2(22):3198-225.
15. Dewidar B, Kahl S, Pafili K, Roden M. Metabolic liver disease in diabetes-from mechanisms to clinical trials. Metabolism 2020;111:154299.
16. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Medical care in diabetes-2020. Diabetes Care 2020;43(1):37-47.
17. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* 6. Glycemic targets: Standards of care in diabetes-2023. Diabetes Care 2023;46(1):97-110.
18. Blonde L, Rosenstock J, Mooradian AD, Piper BA, Henry D. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. Diabetes Obes Metab 2002;4(6):368-75.
19. Marre M, Howlett H, Lehert P, Allavoine T. Improved glycaemic control with metformin–glibenclamide combined tablet therapy (Glucovance®) in Type 2 diabetic patients inadequately controlled on metformin. Diabet Med 2002;19(8):673-80.
20. Wafa IA, Pratama NR, Sofia NF, Anastasia ES, Konstantin T, Wijaya MA, *et al.* Impact of COVID-19 lockdown on the metabolic control parameters in patients with diabetes mellitus: A systematic review and meta-analysis. Diabetes Metab J 2022;46(2):260-72.
21. Ojo O, Wang XH, Ojo OO, Orjih E, Pavithran N, Adegboye AR, *et al.* The effects of COVID-19 lockdown on glycaemic control and lipid profile in patients with type 2 diabetes: A systematic review and meta-analysis. Int J Environ Res Public Health 2022;19(3):1095.
22. O'Mahoney LL, Highton PJ, Kudlek L, Morgan J, Lynch R, Schofield E, *et al.* The impact of the COVID-19 pandemic on glycaemic control in people with diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2022;24(9):1850-60.
23. Bain SC, Czernichow S, Bøgelund M, Madsen ME, Yssing C, McMillan AC, *et al.* Costs of COVID-19 pandemic associated with diabetes in Europe: A health care cost model. Curr Med Res Opin 2021;37(1):27-36.
24. Patro BK, Taywade M, Mohapatra D, Mohanty RR, Behera KK, Sahoo SS, *et al.* Cost of ambulatory care in diabetes: Findings from a non-communicable disease clinic of a tertiary care institute in Eastern India. Cureus 2022;14(1):e21206.
25. Bekele M, Norheim OF, Hailu A. Cost-effectiveness of saxagliptin compared with glibenclamide as a second-line therapy added to metformin for type 2 diabetes mellitus in Ethiopia. MDM Policy Pract 2021;6(1):1-2.
26. Rojas G, Nunes A. Pharmacoeconomic analysis of sitagliptin/metformin for the treatment of type 2 diabetes mellitus: A cost-effectiveness study. Value Health Reg Issues 2021;26:33-9.
27. Julian GS, Accetturi Pititto LM, Miresashvili N, Broe Honoré J, Lopes Assis Coelho RC, Campos D. Cost of microvascular complications in people with diabetes from a public healthcare perspective: A retrospective database study in Brazil. J Med Econ 2021;24(1):1002-10.
28. Pasquel FJ, Lansang MC, Dhatariya K, Umpierrez GE. Management of diabetes and hyperglycaemia in the hospital. Lancet Diabetes Endocrinol 2021;9(3):174-88.

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