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Estimation of Effects of Nationwide Lockdown for Containing Coronavirus Infection on Worsening of Glycosylated Haemoglobin and Increase in Diabetes-Related Complications: A Simulation Model using Multivariate Regression Analysis

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Highlights:

- A lockdown of India in an attempt to preventing the spread of the virus may adversely impact both diabetes control as well as its associated complications by putting a restriction on the available resources and changes in lifestyle.
- This is probably the first study to highlight that there is an increment in both the HBA1c as well as diabetes-related complications with increasing duration of a lockdown.

Abstract:

Introduction and aims:

To prevent the spread of coronavirus disease (COVID19) total lockdown is in place in India from 24th March 2020 for 21 days. In this study, we aim to assess the impact of the duration of the lockdown on glycaemic control and diabetes-related complications.

Materials and methods:

A systematic search was conducted using Cochrane library. A simulation model was created using glycemic data from previous disasters (taken as similar in impact to current lockdown) taking baseline HBA1c and diabetes-related complications data from India-specific database. A multivariate regression analysis was conducted to analyse the relationship between the duration of lockdown and glycaemic targets & diabetes-related complications.

Results:

The predictive model was extremely robust (R2=0.99) and predicted outcomes for period of lockdown upto 90 days. The predicted increment in HBA1c from baseline at the end of 30 days and 45 days lockdown was projected as 2.26% & 3.68% respectively. Similarly, the annual predicted percentage increase in complication rates at the end of 30-day lockdown was 2.8% for non-proliferative diabetic retinopathy, 2.9% for proliferative diabetic retinopathy, 1.5% for retinal photocoagulation, 9.3% for microalbuminuria, 14.2% for proteinuria, 2.9% for peripheral neuropathy, 10.5% for lower extremity amputation, 0.9% for myocardial infarction, 0.5% for stroke and 0.5% for infections.

Conclusion:

The duration of lockdown is directly proportional to the worsening of glycaemic control and diabetes-related complications. Such increase in diabetes-related complications will put additional load on overburdened healthcare system, and also increase COVID19 infections in patients with such uncontrolled glycemia.

Keywords: Diabetes; lockdown; disaster; multivariate regression analysis; complications.

Introduction:

The World is experiencing a viral onslaught of herculean proportion in the form of COVID-19 (Coronavirus disease 2019) caused by SARS-CoV-2 (severe acute 69 respiratory syndrome coronavirus 2).[1] Both the infection rate as well as death from COVID 19 have exhibited an exponential growth.[2] The whole attention now is on prevention and management strategies related to it. However, as the disease evolved, we learned that not all patient population are at equal risk of morbidity and mortality. The elderly and those with additional co-morbidities in the form of diabetes, hypertension and background cardiovascular compromise are at higher risk than those without these co-morbid diseases.[3]

India houses the second largest population of patient with diabetes mellitus after China.[4] Although the pandemic of COVID 19 originated in China, unlike diabetes prevalence, India is, as yet, experienced lesser impact of COVID19.[5] In an attempt to stem the spread of the virus from individuals travelling into India from endemic areas to internal community spread, a feature of the stage 3 of the disease process, a temporary 21 days lockdown(complete restriction on all international and domestic travel, social isolation, and suspension of all non-essential services) as announced by Prime Minister of India on 24th March, 2020. On one hand this could be a vital step in stemming the spread of the virus, however, on the other there are likely to be issues related to the impact of this lockdown on patients with diabetes; the worsening of hyperglycaemia an increase in diabetes-related complications. This could be due to the limitation of free space to exercise, limited resources to implement a healthy lifestyle, restrictions on the availability of anti-hyperglycaemic agents and difficulty in obtainingof physician's guidance. Further, because of limitations of transport of goods and movement of patients, there is likely to be shortage of drugs, insulin, and glucose testing strps and glucose meters. All these factors have the potential to increase the stress level and its associated impact on the pre-existing disease.

What impact will this lockdown have on the glycaemic target and diabetes-related complications? While it is difficult to collect real data, one could use a simulation model created with the aid of a multivariate regression analysis which could predict and answer these questions. We hypothesised that this lockdown of India for period of 21 days and beyond will lead to worsening of glycemia and later, increase in diabetes-related complications.

This analysis was planned to answer above stated hypothesis. In the absence of any previous data, we searched for scenarios very similar to the lockdown situation and zeroed in to several disasters (earthquakes, tsunamis, hurricanes and wars) which closely simulatea lockdown in so far as resource limitations and challenges are concerned.[6,7,8,9,10,11] For baseline glycosylated haemoglobin (HBA1c/A1c) and associated diabetes-related complications for Indian population, data from DiabCare study was taken .[12] Using these parameters as baseline, this analysis was planned aiming at predicting the end-of-lockdown HBA1c as well as the diabetes-related complication rates thereof.

Materials and Methods:

A web-based search was conducted addressing diabetes control during times of disaster, when resources become scarce and lifestyle modification opportunities become constricted. This background was selected to simulate the proposed 21 days lockdown in India facing the menace of coronavirus outbreak. The disaster period was included to closely simulate the resource challenged atmosphere. A search of PubMed, Google Scholar and Cochrane library was conducted using following search terms; "disaster", "diabetes mellitus", "blood glucose targets" and "diabetic complications" as keywords. Subsequently, clubbing "disaster" and "diabetes mellitus" (yielded 7 citations) and then combined with "blood glucose targets" and "diabetes complications" (yielded 546 citations). As per pre-planned inclusion criteria, filters were imposed to include trials only, resulting in 7 studies available for analysis.

There were six citations related to disaster and diabetes mellitus which were included to analyse the predicted HBA1c at the end of the lockdown. The disasters included for analysis were hurricane Katrina (USA,2005, days considered as lockdown period - 8), Kobe earthquake (Japan,1995, days considered as lockdown period - 8), Hanshin-Awashi earthquake (Japan, 1995, days considered as lockdown period - 14), the Gulf war in Iraq (1991, days considered as lockdown period - 60), Murmura earthquake (Turkey, 1999, days considered as lockdown period – 21) and the Great Eastern Japan Earthquake and tsunami (Japan, 2011, days considered as lockdown period - 14). Data was collected in a comma separated-values (CSV) file and uploaded in Jupyter notebook and analysed with the Python 3.8.2 software (Windows 10 64 bit, USA). As a re-validation process and for simplicity of understanding, the data was also analysed using excel with XL-STAT statistical software (Windows 10 64 bit, USA). Once the post-lockdown HBA1c was available, the plan was to include the seventh citation, which was related to the Indian data on the mean HBA1c value of representative Indian population (2014) and the prevalent diabetes-related micro- & macro-vascular complications. This baseline data (DiabCare study) was collected over one year from 330 centres across the country resulting in surveying 6168 diabetic patients (12). Mean HBA1c as well as the annual rates of complications was collected in this cross-sectional study.

The final step planned was to predict the post lockdown complication rates depending on the predicted HBA1c and the duration of lockdown (in days). These data were calculated with the premise that current state of conditions of the patients and constrained resources continue, and that major intervention to control glycemia (introduction of new drugs and insulin, etc) were not carried out.

Results:

The results of this analysis are presented in five steps.

Step 1: The first step was to estimate the HBA1c increment observed during the time period of the respective disasters. (Table 1)

Disaster Name	Number of days*	Baseline A1c	Post-disaster A1c	A1c % increment
KATRINA[6]	8	7.5	7.6	0.01
KOBE[7]	8	7.44	7.64	0.03
Hanshin-Awashi[8]	14	7.74	8.34	0.08
Gulf War[9]	60	10.1	10.9	0.08
Marmara[10]	21	7.4	8.8	0.19
GEJE Tsunami[11]	14	5.9	6.5	0.10

Table 1: Analysis of the HBA1c increment from the pre- and post-disaster HBA1c levels with the number of days as an additional determinant.

*Number of days indicate period where population was mostly resource challenged, facing challenges as enumerated in current lockdown in India.

Step 2: A linear regression analysis was performed between the number of days and the HBA1c increment. (Fig 1)

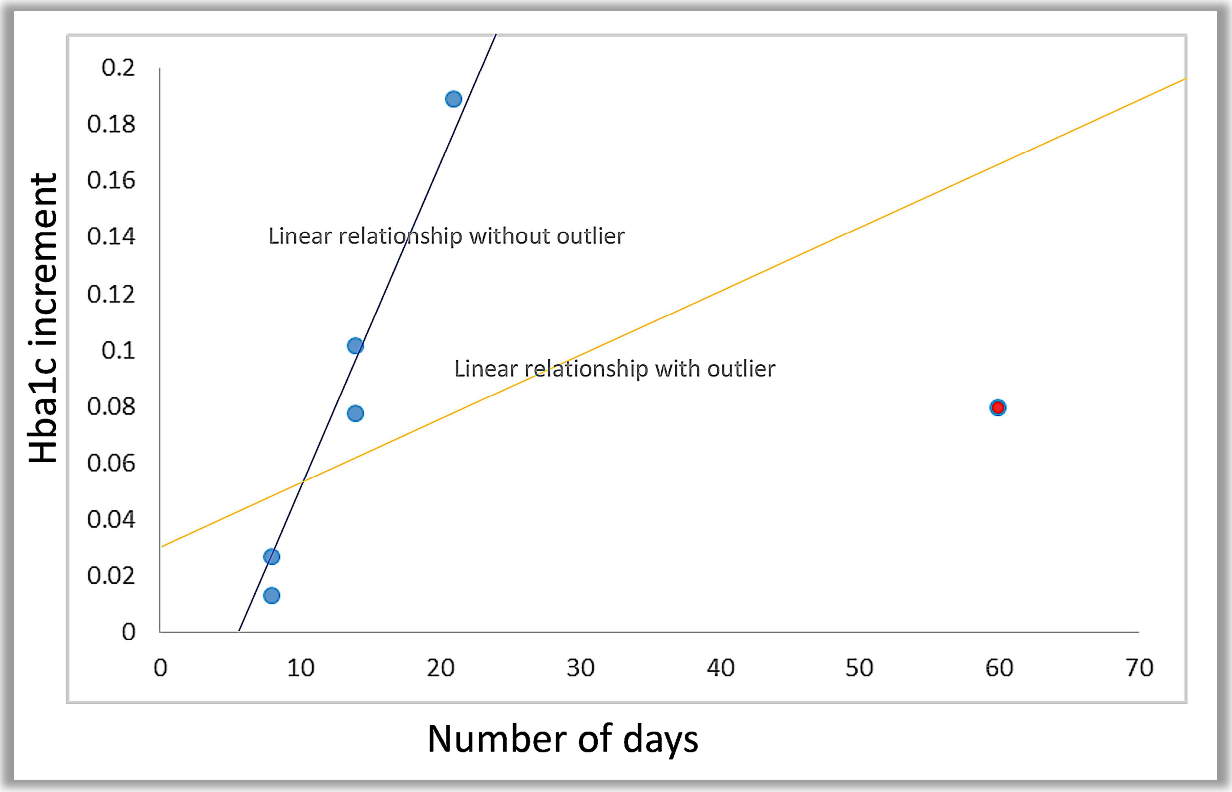

Fig 1: Linear regression analysis between number of days and HBA1c increment with and without the significant outlier (Gulf war-●).

The correlation analysis revealed a moderately good correlation between the post-disaster HBA1c & the duration of the disaster (r=0.48) and a strong correlation with baseline HBA1C (r=0.81).

Step 3:

A multivariate regression analysis was done revealing a very strong association between the inputs (days count and the baseline HBA1c) and the output (post-disaster HBA1c). The relationship between days count and post-disaster HBA1c was statistically significant (P=0.009), as was the relationship between the baseline HBA1c and the post-disaster HBA1c (P=0.004). The multivariate linear model was robust with a R^2=0.99 and an adjusted R^2=0.98. (Table 2)
The formula generated by the multivariate regression analysis was: Post-disaster A1c = b0+ (b1* number of days of lock-down) + (b2*Baseline A1c). Inserting all the intercepts, the equation turns out to be: Post-disaster A1c = 0.95+ (0.09* number of days of lock-down) + (1.04*Baseline A1c).

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.996689185
R Square	0.993389331
Adjusted R Square	0.986778662
Standard Error	0.100311991
Observations	5

ANOVA

	df	SS	MS	F	Significance F
Regression	2	3.024195009	1.512097504	150.2706253	0.006610669
Residual	2	0.020124991	0.010062496		
Total	4	3.04432			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	-0.947434847	0.523979061	-1.808154022	0.212312463	-3.201934786	1.307065091
Days count	0.094627913	0.009378432	10.08995067	0.009680104	0.054275779	0.134980048
Baseline A1c	1.041310725	0.06858315	15.18318611	0.004309824	0.746221249	1.336400201

Table 2: Summary output of the multivariate regression analysis done between the inputs (days count and the baseline HBA1c) and the output (post-disaster HBA1c).

Step 4: The DiabCare India study (12) was taken as the reference for all baseline characteristics (baseline mean HBA1c in India as well as the diabetes-related complication rates prevalent at that HBA1c). Hence inserting the mean baseline HBA1c from the DiabCare study i.e. 8.9%, we calculated the post-disaster predicted HBA1c. (Table 3) These predicted data should be accepted only if no major intervention (major changes in treatment by physician, initiation of insulin therapy etc.) is done.

Step 5: Having established the relationship between the days of lockdown and the predicted end-of-lockdown HBA1c, the posterior diabetes-related complication rates were calculated, taking the baseline data from the DiabCare study (12) at a baseline HBA1c of 8.9%. (Table 3)

Number of days of lock-down	Baseline A1c	Post-disaster A1c	Non-proliferative diabetic retinopathy	Proliferative diabetic retinopathy	Photocoagulation	Microalbuminuria	Overt proteinuria	DPN	Amputation risk	MI	CVA	Infections
*	8.9		11.0%	11.6%	5.8%	36.5%	11.3%	41.4%	11.6%	3.4%	1.9%	2.1%
30	8.9	11.16	13.8%	14.5%	7.3%	45.8%	14.2%	51.9%	14.5%	4.3%	2.4%	2.6%
45	8.9	12.58	15.5%	16.4%	8.2%	51.6%	16.0%	58.5%	16.4%	4.8%	2.7%	3.0%
60	8.9	14.00	17.3%	18.2%	9.1%	57.4%	17.8%	65.1%	18.2%	5.3%	3.0%	3.3%
75	8.9	15.42	19.1%	20.1%	10.0%	63.2%	19.6%	71.7%	20.1%	5.9%	3.3%	3.6%
90	8.9	16.84	20.8%	21.9%	11.0%	69.0%	21.4%	78.3%	21.9%	6.4%	3.6%	4.0%

Table 3: Predicted diabetes-related complication rates in proportion to the increasing duration of lockdown (30-90 days) and associated increase in HBA1C.

With increasing duration of the lockdown, the increment in HBA1c from baseline continues to increase and carries along with it the increasing annual complication rates. The annual predicted percentage increment in complication rates from baseline at the end of 30-day lockdown due to COVID19 pandemic was 2.8% for non-proliferative diabetic retinopathy, 2.9% for proliferative diabetic retinopathy, 1.5% for retinal photocoagulation, 9.3% for microalbuminuria, 14.2% for overt proteinuria, 2.9% for peripheral neuropathy, 10.5% for amputation, 0.9% for myocardial infarction, 0.5% for stroke and 0.5% for infections. The annual predicted percentage increment in complication rates from baseline at the end of 45-day lockdown due to COVID19 pandemic was 4.5% for non-proliferative diabetic retinopathy, 4.8% for proliferative diabetic retinopathy, 2.4% for retinal photocoagulation, 15.1% for microalbuminuria, 4.7% for overt proteinuria, 17.1% for peripheral neuropathy, 4.8% for amputation, 1.4% for myocardial infarction, 0.8% for stroke and 0.9% for infections.

Discussion:

In this first of the kind analysis, we show substantial increase in HbA1C and diabetes-related complications in people with diabetes. While these data are estimates based on some assumptions, numbers generated are good enough to alert us to strengthen already challenged healthcare resources toward this high-risk population.

Achieving and maintaining good glycemic control (defined as an HBA1c <7.0%) is one of the primary requirements to reduce diabetes related complications. [13,14]. It is also important to take into consideration that while the whole world is struggling to contain this deadly viral illness, focus on the co-morbidities facilitating the viral-related morbidities and mortality cannot be compromised. There is sufficient evidence to indicate that poor glycemic control and presence of organ dysfunction predisposes an individual infected with COVID19 to far greater risk of mortality than those without. Hence, it is of paramount importance to achieve as well as maintain good glycemic control for short as well as long term benefits during this pandemic.

One of the most worrisome factors is restriction to routine physician consultations. As a result, patients suffering from chronic diseases, although stable, are not offered the usual standards of care. Not only physicians, but also the para-medical staff numbers are reduced and channelized toward dedicated COVID19-related care. As a result, non-COVID related complications rate are expected to rise, which independently predispose these patients to acquire COVID19 infection.

This analysis was therefore designed to deduce the adverse impact of a total lockdown on glycemic targets and associated complications. This is likely to be the first study to make such a deduction. In the absence of any prior data on the same, a simulation model was created from the natural and unnatural disasters we faced in the past. Based on the simulation, a model was created to predict the adverse impact of COVID19 related lockdown on diabetes and related complications. There was a moderate correlation between the post-disaster HBA1c and the duration of the disaster (r=0.48) and a strong correlation with the baseline HBA1c (r=0.81). Based on this result a multivariate regression analysis was done revealing a very strong model to predict the post-lockdown HBA1c depending on the duration (in days) of the lockdown. Assuming a uniform baseline HBA1c derived from the DiabCare study which is the latest epidemiological database on diabetes and its complications in India, the post-lockdown HBA1c increases from baseline as the duration of lockdown got extended (example- HBA1c of +2.26% with a 30 days lockdown to +3.68% with 90 days lockdown). In addition, this increment in HBA1c permitted us to calculate the annual proportional increase in diabetes-related complications rate, which increased as the duration of lockdown increased.

To prevent the increase in HBA1c and associateddiabetes-related complications, a system must be put in place to facilitate patent doctor interface through telecommunication, online consultations, use of social media platforms which can bring the whole medical care at home in a virtual sense. Dedicated campaigns can be launched utilizing the audio-visual media encouraging lifestyle modifications at home. Further, government must put required mechanism to prevent shortages of medicines and insulins.

Limitations of this study:

One of the main limitations of this study is the non-availability of diabetes-related outcomes in a lockdown. This was replicated by bringing in a scenario (natural & non- natural disasters) which is similar to, but not the same to as may occur in a lockdown. Clearly, there are a lot of differences, between a lockdown and a hurricane, earthquake or a tsunami. The disasters that we have taken for analysis have occurred several years before (Gulf war was 29 years ago). Since then information flow and modes of virtual consultations have increased, and may help patients control their diabetes better. Further, information flow, availability of physicians, and drugs and resources varied in different countries, and may be, in general, better now than previously. These factors may lead to overestimation of risk in our model. However, the limited availability of resources needed to manage diabetes, being a bridging factor made us choose disasters as a prior for the analysis. Finally, any model-based prediction has its problem related to over-estimating the risk profile.

Strengths of this analysis:

The principle strength of this analysis is the robustness of the multivariate regression model. It was both robust and statistically significant. Secondly, in the absence of any previous data available on a lockdown related situation, this was the case best scenario which could have been created in spite of all the limitations.

Conclusion:

This is probably the first analysis to predict the adverse effect of a total lockdown on glycemic targets as well as diabetes-related complications. We demonstrated an incremental increase in both HBA1c as well as diabetes-related complications, with the increase in the duration of lockdown days. A pre-planned strategy must be put in place to prevent such a scenario as poorly controlled diabetes is an independent risk factor of mortality from COVID19.

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Conflict of Interest: None to declare

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Conflicts of Interest Statement

Manuscript title:

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