

## Review Article

# The impact of lockdowns or severe social restrictions during COVID-19 pandemic on glycaemic control of adults suffering with type 2 diabetes mellitus: a review

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## ABSTRACT

Glycemic control in diabetes has shown to improve insulin sensitivity and reduce both microvascular and macrovascular complications in diabetes mellitus. In 2020, with the globe facing COVID-19 pandemic the governments and authorities resorted to lockdowns to reduce the spread of infection. We aimed to find the impact of lockdowns during COVID-19 pandemic on glycaemic control of adults suffering with type 2 diabetes mellitus. (T2DM). We systematically searched 5 medical databases MEDLINE via PubMed, Embase, CINAHL, web of science and Cochrane library up to 16<sup>th</sup> November 2021 using key terms. Total of 24899 articles were identified by the search, of which 17571 articles were excluded for duplication, 7303 were excluded after screening for title and abstract, and further 16 articles excluded after full text review. We analyzed the final 9 observational studies fulfilling the criteria. There are 2177 participants from final 9 observational studies, 5 studies showed worsening glycemic control during lockdown period, 2 reported improvement and 2 showed no significant change. We noticed that weight was correlating with glycated hemoglobin change. Studies with lockdown period >10weeks reported greater HbA1c deterioration and farther HbA1c when done from start of lockdown, the higher HbA1c values noticed. Glycemic control overall in type 2 diabetes has worsened due to lockdown measures which may be due to reduced physical activity, change in diet or psychosocial changes. There has also been increase in BMI (Body Mass Index) correlating with raise in HbA1c. More in-depth review is required into long term impact of lockdowns on diabetes.

**Keywords:** Glycemic control, COVID-19, Lockdown, Diabetes, Type 2 diabetes

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major cause of morbidity and mortality worldwide affecting both developing and developed countries. According to world health organisation (WHO), it has affected 533 million people worldwide and the prevalence is increasing every year.<sup>1</sup> It also states that Diabetes Mellitus is a major cause of kidney failure, heart disease, stroke, blindness and limb amputation.

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus-

2 (SARS-CoV-2) which was first reported in Wuhan city, China, in December 2019.<sup>2</sup> The infection has affected 618 million people as of March 2023 and caused the death of more than 6.8 million worldwide as of the 6<sup>th</sup> March 2023.<sup>3</sup>

Glycaemic control is strongly related to long term complications. Ousman et al, in their review found that each 1% reduction in HbA1c causes 21% reductions in risk, for any end point related to diabetes.<sup>4</sup> It causes 21% risk reduction for death related to diabetes, 14% for MI and 37% for microvascular complications.

COVID-19 pandemic brought excessive proportion of infection mainly affecting the lungs leading to dyspnoea, hypoxia, and death. The healthcare services could not cope with the situation and were running out of resources. In order to curb the spread of infection and disease in the societies, governments across the globe and authorities enforced lockdowns or social restrictions for greater good. But this would mean that people would spend a lot of time indoors affecting their physical activity, diet, physical and mental health. Standards of care 2022 by American diabetes association (ADA) recommends diet and physical activity, and behavioural change that would bring  $\geq 5\%$  weight loss in people with diabetes mellitus type 2 and obesity or overweight.<sup>5</sup> But this lack of physical activity and change in diet could lead to high blood sugars in people with T2DM.

These is a limited 'review-literature' till November 2021 on 'effect of lockdown on glycaemic control in T2DM'. So, we have undertaken this review of research articles available on 'impact of lockdowns due to COVID-19 pandemic on the glycaemic control in people suffering from T2DM'. The findings will help the clinicians, institutions and the governments in management of diabetes during future lockdowns or severe social restrictions for any reason this could be. This will help the patients to plan their care in advance before the lockdown or social restriction is implemented by their respective governments or authorities.

## PROJECT DESIGN AND METHODS

### Literature search

We conducted literature search on 5 databases-MEDLINE via PubMed, Embase, CINAHL, Web of science and Cochrane library in English from 11<sup>th</sup> February 2020 till 16<sup>th</sup> November 2021. We used 8 search terms in 18 combinations in each search database as below using Boolean operator 'AND' (Table 1). In PubMed, the untagged term in the search box is automatically mapped to the available MeSH terms.

The systematic literature search was done by the co-author SSh of the present article and retrieved articles into a systematic review tool. The same search strategy was used in all the other medical databases. A total of 24,899 articles were retrieved. The systematic review tool 'Rayyan' helped in removing the duplicates.

The predetermined inclusion criteria for studies were-people with T2DM, age above 18 years, any gender, period restricted to COVID-19 pandemic and population not restricted to any geographic region and inclusive of articles from all around the world will be examined.

The included articles should provide information on glycaemic control parameter either HbA1c or glucose levels before COVID-19 pandemic lockdown and during or post lockdown. All the peer reviewed articles in

English, observational, case-control, cohort studies, case reports and conference abstracts considered. Letters, comments, reviews/meta-analysis were not considered.

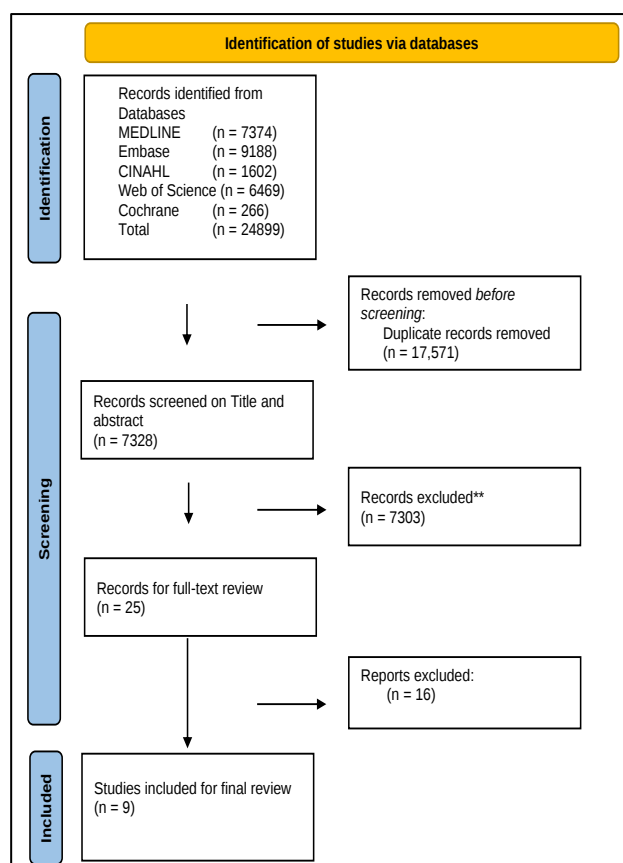
**Table 1: Database search strategy and result.**

| Variables                       | Search strategy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Search databases</b>         | MEDLINE via PubMed, Embase, CINAHL, Web of science and Cochrane library                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Keywords</b>                 | Impact, outcome, pandemic, lockdown, COVID, "glycemic control", HbA1c and diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Search strategy</b>          | Impact and pandemic and HbA1c<br>Impact and pandemic and "glycemic control"<br>Impact and pandemic and diabetes<br>Outcome and pandemic and HbA1c<br>Outcome and pandemic and "glycemic control"<br>Outcome and pandemic and diabetes<br>Impact and COVID and HbA1c<br>Impact and COVID and "glycemic control"<br>Impact AND COVID and diabetes<br>Outcome and COVID and HbA1c<br>Outcome and COVID and "glycemic control"<br>Outcome and COVID and diabetes<br>Impact and lockdown and HbA1c<br>Impact and lockdown and "glycemic control"<br>Impact and lockdown and diabetes<br>Outcome and lockdown and HbA1c<br>Outcome and lockdown and "glycemic control"<br>Outcome and lockdown and diabetes |
| <b>Filters</b>                  | Search up to 16 <sup>th</sup> November 2021, English.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Total number of articles</b> | 24,899.00                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

The exclusion criteria used for the studies involving-gestational diabetes mellitus, T1DM and studies not done during COVID-19 pandemic period.

The articles which did not provide information on lockdown period, type of diabetes or age of participants were also excluded. The articles which have not mentioned the outcome of glycaemic control were removed.

All the retrieved articles were individually screened (abstract screening) independently by all the three reviewers (SSh, SSu, SH). Articles with conflict were resolved by consensus from all the 3 reviewers. Full text reading of screened articles was done by all the reviewers from which 9 were selected in the final review process.



**Figure 1: Prisma flow diagram of literature search for impact of lockdowns or severe social restrictions during COVID-19 pandemic period on glycaemic index in people with diabetes mellitus type 2.<sup>6</sup>**

### Data extraction and analysis

From the 9 final articles, data were extracted into an excel sheet. The data included authors, study design, year of publication, country where the study was conducted, type of diabetes, participant characteristics including age, weight, BMI and male %, lockdown period, pre-lockdown and post-lockdown glycaemic control parameters including HbA1c or glucose levels which could be random or fasting, disease duration and outcomes. The excel sheets were used to analyze the data. The COVID-19 studies were sorted based on the change in outcome-the glycaemic control (HbA1c).

## RESULTS

The initial search using the above strategy on 5 databases collected 24,899 articles. After removing the duplicates, we had 7328 articles which were title and abstract screened resulting in 25 relevant articles. Full text reading of these articles and application of inclusion and exclusion criteria, lead to selection of final 9 studies. Of these, 5 are observational retrospective, 2 are observational prospective, 1 is observational case-control and 1 observational cross-sectional type study design. Data is extracted from these 9 articles into an 'excel

sheet'. A total of 2177 T2DM participants are analyzed. The basic characteristics of the participants and overview of these studies are provided in Table 2.

The participant characteristics show that the two studies (Karatas et al and Farhane et al) have about 70% of women as participants while in most other studies, male participant ratio is higher, being on average above 50%.<sup>7,8</sup> In these two studies, the participants average HbA1c is also high at baseline level. The participants average disease duration is 4.9 years in Tewari et al.<sup>9</sup>

When compared with other 8 studies which have the average participant age of 10 years and above, further analysis yield that seven of the studies have participant sample size between 100-500 while one has below 100 and other above 500. Average age of the participants is between 50-70years in all the 9 studies. The studies from European region have participants average age between 60-70 years while those outside the Europe between 50-60 years.

Five of the studies had lockdown period of 4-8 weeks, 3 studies of 8-12 weeks while one >12 weeks. The results showed that the HbA1c improved in 3 of the reported studies while in 5 other it has worsened and in one it is unchanged.

Karatas et al reported that BMI, Triglyceride level and HbA1c have increased in participants with diabetes at post-lockdown check which was done at 6<sup>th</sup> month from the first lockdown imposition on 20<sup>th</sup> march 2020 and gradual lifting of lockdown after June 2020.<sup>7</sup> Biamonte et al collected data at 12 week from the date of beginning of the 6 weeks of lockdown.<sup>10</sup> They found an increase in weight, BMI, waist circumference, Fasting glucose and HbA1c in the participants. Farhane H et al.<sup>8</sup> when recorded parameters before and after 82days of lockdown, found that after 15wk from start of lockdown, average HbA1c increased in all participants from 8.6% to 9.5% which was nearly similar in both men and women, though there were more women participants in the study (70%) compared to men. In Ludwig L et al's study, where HbA1c was measured between the 6 months preceding and the 6 weeks following the lockdown, post-lockdown HbA1c after 8wk of lockdown in the region, reduced from 7.6% to 7.3%, which was also reported by Rastogi et al where HbA1c after 13wks into lockdown reduced from 7.8% to 7.4%.<sup>11,12</sup>

Falcetta et al outlined that there was no significant difference in fasting plasma glucose (8.6 vs 8.8) and HbA1c (7.1 vs 7.1) before and after the lockdown and similar conclusion was done by D'Onofrio et al that overall, no significant difference in HbA1c was found comparing subjects with stable therapy exposed to lockdown measures.<sup>13,14</sup>

There has been correlation between weight and glycaemic control. Biamonte et al showed that subjects with weight

gain during lockdown period had raised HbA1c as well.<sup>10</sup> This was also measured by other authors Karatas et al, Farhane et al, Tiwari et al and Biancalana et al.<sup>15</sup> The authors Tiwari et al went on to show that Increase in the weight correlated with increase in HbA1c while the decrease in the weight correlated with reduction in HbA1c, both statistically significant. HbA1c reduction was significant in those who lost weight as well. Ludwig et al found that HbA1c reduced from 7.6% to 7.3% in T2DM participants, and they also found HbA1c reduction was significant in those who lost weight as well.<sup>11</sup> But in their study, there were participants from other types of diabetes. The only study which found results to be opposite to what other above studies have found is of Rastogi et al. where average BMI slightly increased from 25.6 to 25.8 while average HbA1c reduced from 7.8% to 7.4%.<sup>12</sup>

The other observation in results is from the percentage of male participants and glycemic control. The two studies, Karatas et al and Farhane et al have male ratio of 31.8% and 30.6% but their post-lockdown HbA1c worsened by 0.84% and 0.95% respectively. Rastogi et al has 71.8% of male participants and their post-lockdown HbA1c improved by 0.51%. This was not reflected in Biamonte et al where the male percentage is 57.8 but still the post-lockdown HbA1c worsened by 0.42%.<sup>10</sup>

From the data in Table 3, the duration of lockdown period shows to have effect on glycemic control. This is reported by Karatas et al, Biamonte et al, Farhane et al and Tewari et al, where the longer the period of lockdown, there is more worsening in glycemic control while the shorter periods of lockdown of 8 weeks or less, seem to have lesser or no effect.<sup>7-10</sup>

**Table 2: Baseline characteristics of participants.**

| Authors, (in year)     | Study design                | Country | N   | Average age (in years) | Diabetes duration | Male (%) | BMI (kg/m <sup>2</sup> ) | HbA1c     |
|------------------------|-----------------------------|---------|-----|------------------------|-------------------|----------|--------------------------|-----------|
| Karatas et al, 2021    | Observational case-control  | Turkey  | 85  | 54.8±10.53             | 11.7              | 31.8     | 33.44±6.48               | 8.52±1.55 |
| Biamonte et al, 2021   | Observational retrospective | Italy   | 128 | 70 (40-91)             | 15                | 57.8     | 29.5±6                   | 7.0±0.8   |
| Farhane et al, 2021    | Observational retrospective | Morocco | 121 | 57.31±0.91             | 9.97              | 30.6     | 27.9±0.68                | 8.67±0.24 |
| Ludwig et al, 2021     | Observational cross-section | France  | 549 | 65                     | NA                | 59.8     | 28.6                     | 7.6       |
| D'Onofrio et al, 2021  | Observational retrospective | Italy   | 141 | 68                     | 13                | 61       | 28.2                     | 7.4       |
| Tewari et al, 2021     | Observational retrospective | India   | 313 | 50.8                   | 4.9               | 45.4     | Not mentioned*           | 7.9       |
| Rastogi et al, 2020    | Observational prospective   | India   | 422 | 58                     | 11                | 71.8     | 25.6                     | 7.8       |
| Falcetta et al, 2021   | Observational retrospective | Italy   | 304 | 69.1±9.2               | 16                | 65       | 29.2±5                   | 7.1±0.9   |
| Biancalana et al, 2021 | Observational prospective   | Italy   | 114 | 69.4±10.3              | 8.4               | 62.3     | 28.8±5.3                 | 6.7±0.7   |

\*Author has used weight instead of BMI in the study.

**Table 3: Extracted data and analysis.**

| Authors          | Average age (in years) | Male participant (%) | Lockdown period (weeks) | Timing of HbA1c measurement (from start of lockdown) (weeks) | Pre-BMI (Kg/m <sup>2</sup> ) | Post-BMI (Kg/m <sup>2</sup> ) | Pre-HbA1c | Post-HbA1c | Change in HbA1c (%) |
|------------------|------------------------|----------------------|-------------------------|--------------------------------------------------------------|------------------------------|-------------------------------|-----------|------------|---------------------|
| Karatas et al    | 54.8                   | 31.8                 | 14                      | 23-27                                                        | 33.44                        | 34.15                         | 8.54      | 9.26       | 0.84                |
| Biamonte et al   | 70                     | 57.8                 | 10                      | 12-18                                                        | 29.5                         | 30.1                          | 7.0       | 7.3        | 0.42                |
| Farhane et al    | 57.31                  | 30.6                 | 11                      | 15-37                                                        | 27.9                         | 28.9                          | 8.67      | 9.5        | 0.95                |
| Ludwig et al     | 65                     | 59.8                 | 8                       | 8-14                                                         | 28.6                         | NA                            | 7.6       | 7.3        | -0.39               |
| D'Onofrio et al  | 68                     | 61                   | 8                       | 12.5-17.5                                                    | 28.2                         | 28.2                          | 7.4       | 7.3        | -0.13               |
| Tewari et al     | 50.8                   | 45.4                 | 10                      | 8-12                                                         | NA                           | NA                            | 7.9       | 8          | 0.12                |
| Rastogi et al    | 58                     | 71.8                 | 5                       | 13                                                           | 25.6                         | 25.8                          | 7.8       | 7.4        | -0.51               |
| Falcetta et al   | 69.1                   | 65                   | 8                       | 13-17                                                        | 29.2                         | 29.3                          | 7.1       | 7.1        | 0.0                 |
| Biancalana et al | 69.4                   | 62.3                 | 8                       | 8-9                                                          | 28.8                         | 29.2                          | 6.7       | 6.8        | 0.14                |

**Table 4: Extracted information from the included studies.**

| Author(s)                     | Country | Aim of study/research                                                                                                                        | Key findings / outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Research theme                                                                                                                         |
|-------------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Karatas et al <sup>7</sup>    | Turkey  | To evaluate change in body weight and metabolic control in T2D and non-diabetic healthy subjects during prolonged lockdown                   | <p>BMI, Triglyceride level and HbA1c have increased in participants with diabetes at post-lockdown check.</p> <p>HbA1c was checked at 6 months into lockdown when the lockdown restrictions were less stringent</p> <p>Duration of diabetes was independent predictor of change in HbA1c</p> <p>Metabolic parameters maintained stable despite weight gain in non-diabetic subjects after prolonged lockdown.</p>                                                                                                                                                                                                                                                                                 | COVID-19 pandemic lockdown effect: Diabetes management, lifestyle during pandemic, glycemic control, body mass index, lockdown effect. |
| Biamonte et al <sup>10</sup>  | Italy   | To evaluate the changes of anthropometric parameters and glycemic control in a homogeneous population of T2DM                                | <p>The baseline variable showed disease duration, HbA1c, FPG, BMI, waist circumference was high in insulin treated than non-insulin treated group.</p> <p>There is increase in weight, BMI, waist circumference, fasting glucose and HbA1c at post-lockdown period check.</p> <p>The study showed the significant linear correlation between weight gain and HbA1c variation</p> <p>Author signs that lack of proper insulin dose adjustment during lockdown may certainly have had a role in worsened glycemic control so need for structured educational program dedicated to T2DM patients.</p>                                                                                                | COVID-19 pandemic lockdown effect: Glycemic control, diabetes management, lifestyle effect,                                            |
| Farhane et al <sup>8</sup>    | Morocco | To analyze impact of the COVID-19 pandemic's lockdown on monitoring and care of T2DM patients in Doukkala region                             | <p>Male % of participants was 30.6%. women in study gained more average weight 78.1-81.8 kg while men 79-80.2 kg.</p> <p>Baseline parameters found 70% women as illiterate while only 27% of men. Also 56% of women answered 'no' to physical activity of 30 min/day while men were 32%.</p> <p>Average HbA1c increased in all participants from 8.6% to 9.5% which was nearly similar in both men and women.</p>                                                                                                                                                                                                                                                                                 | COVID-19 pandemic lockdown effect: Gender differences in diabetes management, lockdown effect, glycemic control, physical activity.    |
| Ludwig et al <sup>11</sup>    | France  | Describe the impact of the COVID-19 lockdown on metabolic control and access to healthcare in a population sample of patients with diabetes. | <p>Lockdown impact was studied in 549 participants of all types of diabetes but for the purpose of our work, only T2DM data was considered</p> <p>HbA1c reduced from 7.6% to 7.3% in T2DM participants. HbA1c reduction was significant in those who lost weight as well. 32.1% patients gained weight while 15.9% lost weight.</p> <p>During lockdown, 49.4% and 92.3% of patients did not consult their GP and diabetologists respectively. Only 32% used teleconsultation services, 78.3% patients refilled their prescription</p> <p>Detailed assessment of other relevant factors (lifestyle, stress, mental health etc.) that might influence glycemic measures has not been performed.</p> | COVID-19 pandemic lockdown effect: diabetes management, glycemic control, lockdown effect, weight impact on DM,                        |
| D'Onofrio et al <sup>14</sup> | Italy   | To assess the effect of the COVID-19 lockdown on glycemic control in subjects with T2D                                                       | <p>This is age, sex and HbA1c matched controls retrospective study which raises chances of bias.</p> <p>A validated PGWBS was used to assess well-being. Subjects with poorest psychological well-being score showed a worsening in their HbA1c and BMI compared with highest well-being score.</p> <p>Overall, no significant difference in HbA1c was found comparing subjects with stable therapy exposed to lockdown measures.</p>                                                                                                                                                                                                                                                             | COVID-19 pandemic lockdown effect: glycemic control, psychological health, diabetes management,                                        |
| Tewari et al <sup>9</sup>     | India   | To assess the effect of lockdown on the glycemic status and weight of people with type 2 diabetes                                            | <p>Increase in the weight correlated with increase in HbA1c while the decrease in the weight correlated with reduction in HbA1c, both statistically significant.</p> <p>Weight had increased in 151 participants while HbA1c in 195 from the total of 313 participants.</p> <p>Average age=50.8 year and disease duration was 4.9 years which is low compared to other studies in this review.</p> <p>All tertiary care hospitals in public sector were converted to COVID care centers, people had little or no access to their physicians, non-availability of drugs due to lack of means of transportation and strict restrictions on mobility.</p>                                            | COVID-19 pandemic lockdown effect: weight management and HbA1c, diabetes care, lockdown effect, lockdown planning and arrangements.    |

Continued.

| Author(s)                            | Country | Aim of study/research                                                                                                        | Key findings / outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Research theme                                                                                             |
|--------------------------------------|---------|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Rastogi et al<sup>12</sup></b>    | India   | To evaluate the effect of lockdown on physical activity and glycemic control in people with pre-existing T2DM                | 71.8% of 422 participants were male, average BMI slightly increased from 25.6-25.8 while average HbA1c reduced from 7.8-7.4%, post-prandial glucose from 200-158 mg. Glucose levels done at home using home glucometers and HbA1c is done from nearest available laboratory facility. Pre-lockdown weight was from patient electronic database while during lockdown weight was from home-based weighing scales/ nearest available health facility.<br>Physical activity increased during lockdown from GPAQ score 140-840 MetS. But author concluded that there was improvement in glycemic control independent of gender/increase in physical activity.<br>The partial COVID-19 lockdown was still in place when the data was collected from the participants. | COVID-19 pandemic lockdown effect: glycemic control, physical activity,                                    |
| <b>Falcetta et al<sup>13</sup></b>   | Italy   | To evaluate the effect of home confinement related to COVID-19 lockdown on metabolic control in subjects with T2DM in Italy. | There was no significant difference in fasting plasma glucose (8.6 vs 8.8) and HbA1c (7.1 vs 7.1) before and after lockdown.<br>There was no significant difference in mean weight (81.5 vs 81.8 kg) and BMI (29.2 vs 29.3) before and after lockdown.<br>Worsening of glycemic control occurred more frequently in older patients (32.2% in >80 years vs 21.3% in 61-80yrs vs 9.3% in <60yrs) and insulin users (28.8% vs 16.5%)                                                                                                                                                                                                                                                                                                                                | COVID-19 pandemic lockdown effect: diabetes management in old, insulin therapy, lockdown effect, COVID-19. |
| <b>Biancalana et al<sup>15</sup></b> | Italy   | To evaluate immediate impact of lockdown rules on metabolic profile of cohort of patients with T2D and good glucose control  | Lockdown induced relevant short term HbA1c and fasting glucose worsening in approximately 1/4 <sup>th</sup> of previously well-controlled individuals. Levels were stable in pre-lockdown 2 years duration.<br>Fasting triglyceride level was slightly but significantly higher in patients who worsened glucose control, so is predictable parameter.<br>Lockdown period was for 8 weeks, post lockdown parameters were collected within 1 week of end of lockdown.                                                                                                                                                                                                                                                                                             | COVID-19 pandemic lockdown effect: glycemic control, fasting triglycerides, diabetes management.           |

## DISCUSSION

The results have been very mixed and heterogenous. Out of 9 studies, 2 have shown improvement in glycemic control in T2DM with respect to lockdown period while other 5 have shown worsening and two studies showed no significant change. We have tried to focus on each of the finding and discuss individually as below.

### HbA1c and BMI during lockdown

From the above review of the studies, we found that 5 studies (Karatas et al, Biamonte et al, Farhane et al, Tewari et al, and Biancalana et al) showed raised BMI (weight in Tewari et al) correlated with raise in HbA1c.<sup>7-10</sup> There is a strong relationship between BMI and HbA1c as increase in BMI will increase the HbA1c levels as well. This is proved in a brief report by Boye et al follow up of T2DM individuals from 2012 to 2019 showed that the overweight and obese category of people rose from 89.5% in 2012 to 93.4% in 2019 respectively and during the same period, the mean HbA1c increased from 7.29% in 2012 to 7.32% in 2019.<sup>16</sup> This was also reported by Sisodia et al the authors in their cross-sectional study found that all the participants with BMI >30 had HbA1c >8%.<sup>17</sup> We can observe this in the famous diabetes prevention program (DPP) study by Knowler et al as well

where after the average 2.8 years follow-up, the incidence of diabetes was 11.0, 7.8 and 4.8 cases per 100 person-years in the placebo, metformin and lifestyle modification which included weight-loss of at least 7% body weight and 150-minute weekly physical activity.<sup>18</sup>

### Lockdown and studies with HbA1c improvement: the psychological effect

D'Onofrio et al comments in results that no absolute difference in HbA1c was found between lockdown and control groups. But they also acknowledge that those with worse psychological general well-being index (PGWBS) showed a worsening of  $\Delta$ HbA1c (0.2% [-0.3%-0.6%] vs. -0.2% [-0.9%--0.1%];  $p=0.014$ ) and  $\Delta$ BMI.

COVID-19 pandemic has brought significant disease to the communities physically but also mentally due to social restrictions/ lockdowns, which force people stay indoors for longer durations, sometimes alone. These would raise the highly significant level of psychological distress as reported by Xiong et al.<sup>19</sup> They have reported that different percentages of anxiety, depression, post-traumatic stress disorder, psychological stress, and stress in the general population during COVID-19 pandemic. Meta-analysis of 94 RCTs by Winkley et al reported that there was statistically significant improvement in

glycemic control in pooled mean difference with absolute reduction in HbA1c of -0.19 (equivalent to 3.7 mmol/mol) in those randomized for psychological intervention.<sup>20</sup>

Rastogi et al study has reported improvement in hba1c (From 7.8-7.4%) and post prandial glucose (from 200-158 mg) while the fasting glucose has worsened (from 135-150 mg) during the lockdown period. The authors report that >20% of participants took insulin, 58.3% participants had neuropathy, 59.7% had foot complications, 30.1% retinopathy and 27% nephropathy. In discussion, the author writes that the reason for improvement in glycemic control could be due to reduced work-related stress, adequate time for self-care, better compliance with medications, adherence to dietary recommendations and increase in indoor physical activity. The post-lockdown information has been collected by telephone consultation and the hba1c was done by participants in any laboratory near to their home due to lockdown restrictions. This could cause a bias in the hba1c result as the pre-lockdown test was done in one laboratory while the post-lockdown test done in another laboratory. Though the improvement in glycemic control has been observed in many types 1 diabetes studies including where an observation of 307 patients study reported improvement in estimated HbA1c from 7.4-7.1%, mean glucose decreased from 166.8-158.0 mg/dl and Time in Range increased from 57.8-62.4%.<sup>21</sup> A similar result seen in a meta-analysis carried out by Garofolo et al including 17 studies with 3441 participants of type 1 diabetes mellitus showing time in range increasing by 3.05%, estimated HbA1c and GMI (Glucose management indicator) decreasing by 0.18%.<sup>22</sup> The author attributes that “telehealth strategy, telemedicine and remote access to sensor data have been proved as effective and efficient tools in the management of T1DM during COVID-19”.

### **Timing of post-lockdown HbA1c measurement**

Timing of hba1c plays an important role and different studies have done it differently. Diabetes standards of care guidelines, 2022 recommends assessing the glycemic status by HbA1c or other glycemic measurement indicator.<sup>23</sup> HbA1c reflects the average glycemia over approximately 3months. This is a reliable method and convenient in people with stable diabetes control. HbA1c best correlates with the mean blood glucose of past 8 to 12 weeks and is not affected by recent glucose level fluctuations.<sup>24</sup> The selected studies in our review have done HbA1c at different periods from the start of the lockdown as shown in the Table 3. Karatas S et al. have done between 23-27 weeks and Farhana et al at 15-17 weeks, Biamonte et al at 12-18 weeks. This could impact on the result of the HbA1c and may not exactly reflect the lockdown effects due to delay in the collection of hba1c sample beyond 12 weeks from start of lockdown. Though the lockdowns in most of the countries have been different to the level of restrictions and were imposed at different months of the year depending on the number of

COVID-19 cases of in their countries. Many countries started with pandemic lockdowns which involved closing of schools, non-essential shops, non-essential production, cancellation of recreational venues, curfews and stay at home orders. All the above studies have mentioned the lockdown period in their articles. But the impact of the pandemic restrictions was not just limited to the lockdown period but beyond as well, to a lesser extent. These also could affect the level of glycated hemoglobin.

### **Lockdown and physical activity**

ADA recommends aerobic (at least 150min/week) and resistance (at least 2 times a week) exercise for people with T2DM.<sup>5</sup> Exercise volume, intensity and frequency are associated with reductions in HbA1c as reviewed by Kirwan et al diabetes is due to combination of reduced production of insulin and reduced insulin sensitivity (peripheral insulin resistance) in the tissues.<sup>25</sup> Way et al in their meta-analysis looked at the effect of regular exercise on insulin sensitivity in participants with diabetes mellitus.<sup>26</sup> They found that there was significant pooled Size effect for the impact of exercise on insulin sensitivity. In their meta-analysis, there was significant improvement in insulin sensitivity in favor of exercise versus control between 48 to 72 hours and this persisted when measured >72 hours after the last exercise session. So, insulin sensitivity can be improved by exercise which in turn will improve the glycemic control.

McCarthy et al in their longitudinal smartphone-tracking study of adults found that covid -19 lockdown caused significant reduction in physical activity.<sup>27</sup> They found that physical activity reduced from baseline 152 minutes/week to 57 minutes/week when lockdown started and even further down to 21 minutes/week after 8wks of lockdown. At 12 weeks it further dropped to 17 minutes/week, though lockdown was further relaxed, and shops were reopened. In another similar study by To et al the investigators monitored the number of ‘steps’ in the participants.<sup>28</sup> They found that the number of steps reduced by 3.4% at the beginning of the lockdown. About a month into lockdown, further reduction in number of steps by 5% was noted. So, we can see that the physical activity has been affected by the lockdown. There has been Impact of home-based exercise regimes during covid 19 lockdowns. Samuel et al conclude in their review of exercise and diabetes that regular physical exercise can reduce the CV risk factors such as DM and high blood pressure.<sup>29</sup> They also mention that home-based exercise may influence anthropometric parameters associated with diabetes. They also suggest that home-based exercise could be an important element of future physical activity guideline.

In their review, Marcal et al report that Physical activity and exercise are important tools in preventing and treating diabetes.<sup>30</sup> They go on to say that home-based exercises are useful, safe, and effective in management of diabetes, especially during outbreak. Rastogi et al also

reports in their observational study that there was improvement in HbA1c during the lockdown period in people with T2DM while during the same period their global physical activity questionnaire (GPAQ) results increased from 140-840 MetS on telephone questionnaire.

### **Lockdown, diabetes, and dietary habits**

COVID-19 pandemic lockdowns have forced millions of people to stay indoors and in most places, authorities allowed only essential movements. This has caused changes in the eating habits and physical activity as reported by Ruiz-roso et al after their study in which participants were asked food frequency questionnaire, physical activity questionnaire and food craving questionnaire.<sup>31</sup> The study results showed an increase in intake of vegetable, sugary food and snack consumption and high percentage of physical inactivity. Similar results were noted by Ghosh A et al.'s study where the group telephonically interviewed 150 participants who reported that carbohydrate consumption and frequency increased by 21-23% respectively, physical activity duration reduced by 42%, mental stress was reported by 87% of participants and medicines / insulin was interrupted in 9% of participants.<sup>32</sup> While in comparison some authors like Grabia et al reported from an online questionnaire study on improvement in dietary habits, that 60% of participants reported eating regular and nutritious meals during the COVID-19 pandemic.<sup>33</sup> So, the different studies have reported different eating habits of the people during the lockdown. ADA consensus recommendations on goals of nutrition therapy is to promote healthy eating patterns which improve HbA1c, BP and cholesterol levels, achieve body weight goals and delay or prevent diabetes complications.<sup>34</sup>

### **Studies with low male ratio**

The significant worsening of glycemic control was seen in Karatas et al, Farhane et al studies. We also note that the participant has more female ratio of nearly 70% in these studies. Though COVID-19 restrictions have affected both men and women, Nienhuis et al found that women were significant less active compared to men during the lockdown period and women reported more barriers and fewer facilitators for physical activity.<sup>35</sup> The author measured physical activity in men and women using Godin measure score and vigorous-moderate physical activity score. Women scored 416 min/week while men scored 539 min/week. Score was given to each minute of activity done during the week.

In our data analysis, longer lockdown period studies have shown more worsening of glycemic control compared to shorter lockdown period studies. We found that studies with lockdown period 8 week or less have better outcome in glycemic control compared to studies with 10wk or above period. We could not explain the reason for this. We may think that people were able to maintain healthy lifestyle, indoor exercise, stable mental health, and good

medication compliance but as the duration dragged more than 8 weeks, the diabetes distress/ psychological effect or lack of well-being feeling might have affected the glycemic control.

### **COVID-19 and diabetes strategies**

Patients with Diabetes are at high risk for COVID-19 infection. Georgino et al hypothesises that an immunocompromised status of diabetes and an exacerbated inflammatory state, its frequent coagulation response, as well as reduction of insulin secretion and inducing a significant production of cytokines, causing insulin resistance-are likely to play a role in the disease and its outcome.<sup>36</sup> D'Onofrio et al found that those with good pre-lockdown glycemic control not requiring changes in antidiabetic therapy, had no difference in glycemic control during lockdown period. Diabetes predisposes them to severe covid infection as reported by Peric et al in a review increasing their mortality risk.<sup>37</sup> Often the patients with diabetes also have other comorbidities which does not help the recovery. In a meta-analysis of 6007 articles, Li et al found that 22.9% of the people had severe disease, underlying immunosuppression, diabetes, and malignancy were the most strongly associated with severe COVID-19.<sup>38</sup> Ciardullo et al reported that 23% of the people who died of COVID-19 had diabetes in a study from northern Italy.<sup>39</sup>

As people with diabetes carrying high risk, glycemic control in these subjects becomes very important as otherwise the risk of COVID-19 increases and the outcome is not favourable. Peric et al review suggests implementation of novel telemedicine strategies.<sup>37</sup> Girogino et al report that telemedicine, predominantly in the form of virtual clinics and online/phone consultations, has played critical role in diabetes management during COVID-19 pandemic.<sup>36</sup> Some countries like Romania even had online mobile application to educate people with diabetes monitoring and comorbidities during COVID-19.

### **Limitations**

We have done the medical databases search mainly in English and had only 10 foreign language articles in our initial search but there could be many more from other language databases which have not been explored in our review. We have not investigated the long-term effects of the lockdown as well. We focused only on glycemic control mainly as the review was not extensive. There is also an opportunity to look at the impact on other parameters like blood pressure, waist circumference etc. Our review has taken the articles published from March 2020 to November 2021 only due to time constraints but there have been many articles having published after this period. It would have been a better to include these articles.

## CONCLUSION

Summarizing from the above review, as practicing physicians in diabetes, we expected that lockdown and its effects would worsen the glycemic control in people with diabetes before doing the review. We found 55% of the studies to be as we thought worsened the glycemic control. We also have 22% of the studies which showed improvement and 22% which showed no significant change in the in glycemic control. We found that the Improvement in physical activity has shown improvement in HbA1c. we also found that the lockdown had affected the mental health but those with Stable mental state have good glycemic control / disease control. Those who are retired / those who are taking insulin had stable hba1c during lockdown or improvement because they could take better care of themselves. People with good pre-lockdown glycemic control and who do not need the change in antidiabetic medication had no difference in hba1c. The review reinforces the need for diabetes education, telephone consultations, home based exercise programs, mental health support, diabetes distress management, medication management including change, if necessary, after discussion with the patients and the weight management. Fortunately, the studies have not found the post-lockdown HbA1c to be in critical levels.

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After the pandemic was declared in March 2020, the worldwide scientific community came together and shared the research information wholeheartedly and the publishers offered free availability of this material on their platforms like journals. The information was pouring in and was getting quickly published compared to non-pandemic situations where the article would take longer for publishing. We are thankful for this gesture, and this has made it easy for us to write this review.

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