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Prediction

High prevalence of post COVID-19 fatigue in patients with type 2 diabetes: A case-control study

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Keywords:
Type 2 diabetes
COVID-19
Fatigue
Sarcopenia
Post COVID-19 syndrome

ABSTRACT

Background: Post COVID-19 syndrome (PCS) has emerged as a major roadblock in the recovery of patients infected with SARS-CoV-2. Amongst many symptoms like myalgia, headache, cough, breathlessness; fatigue is is most prevalent and makes the patient severely debilitated. Research on PCS, in particular fatigue, in patients with diabetes has not been done.

Methodology: In this prospective study, we included patients with type 2 diabetes (T2D) who had COVID-19 (mild to moderate severity), and matched T2D patients who did not suffer from COVID-19. Demography, anthropometry, glycemic measures, treatment, and details of COVID-19 were recorded. Symptoms were scored using Chalder Fatigue Scale (reported as fatigue score, FS) and handgrip strength (in kg) was recorded by Jamar Hydraulic Hand Dynamometer.

Results: A total of 108 patients were included (cases, 52, controls, 56). Both groups were matched for age, duration of diabetes, BMI, TSH, serum albumin and vitamin D levels. T2D patients who had COVID-19 showed significantly more fatigue when compared with patients who did not have COVID-19 but both groups had comparable handgrip strength. Furthermore, patients with T2D with previous COVID-19 infection and who had FS > 4 have had significant higher inflammation markers during acute illness, and post COVID-19, had increased post prandial blood glucose levels, lost more weight, had reduced physical activity and showed significantly lower handgrip strength as compared to those with FS < 4.

Conclusion: Patients with T2D who had COVID-19 infection as compared to those without had significantly more fatigue after the acute illness, and those with higher FS had reduced handgrip strength indicating sarcopenia, even after careful matching for common contributory factors to fatigue at baseline. Rehabilitation of those with FS>4 after acute infection would require careful attention to nutrition, glycemic control and graduated physical activity protocol.

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1. Background

A surge of COVID–19 in India during April–May 2021 has accentuated several health issues during recovery of illness. Post COVID-19 syndrome (PCS, commonly known as “Long COVID”) comprises of myriad symptoms referable to all systems of body and not explained by any alternative diagnosis (1). The symptoms include fatigue, myalgias, cough, sleepiness, headache etc. [2].

Among these, fatigue is predominant, present afterwards in both hospitalized and non-hospitalized patients [3,4]. More specifically, the prevalence of fatigue following hospitalization for COVID-19 ranges from 52 to 72% at 1–6 months after hospital discharge [3,5]. Fatigue and associated symptoms decrease quality of life and interferes with normal working capacity.

Such post-viral fatigue syndrome resembles ‘chronic fatigue syndrome’ when it persists [6]. This has been seen in many other viral illnesses; Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Influenza (H1N1). Such post viral fatigue may persist for long periods and is largely independent of pulmonary function and exercise capacity of patients.
Diabetes complicates course of COVID-19 and results in excess morbidity and mortality [11]. Presence of diabetes also influences PCS via various pathophysiological mechanisms [1]. Further, diabetes poses challenges in recovery of PCS. There have been no studies pertaining to fatigue, as a part of PCS, exclusively in patients with diabetes. We hypothesized that patients with type 2 diabetes (T2D) are at higher risk of suffering from post-COVID-19 fatigue as compared to those who did not suffer from COVID-19. The objective of our study was to determine the prevalence of fatigue using the CFQ-11 and handgrip strength (as a surrogate marker for sarcopenia) in patients with T2D after COVID-19 infection, and to compare with patient with diabetes without history of COVID-19.

2. Methodology

Study design: This was a prospective study of patients with T2D who came to outpatient department of tertiary care diabetes hospital (Fortis CDOC Hospital for Diabetes and Allied Sciences, New Delhi). Cases comprised of a. patients with diabetes who had COVID-19 infection proved with reverse transcriptase polymerase chain reaction, and b. matched patients who did not suffer from COVID-19. Patients with COVID-19 who suffered from mild symptoms and underwent home quarantine or had moderate to severe symptoms and were hospitalized or intensive care unit were included. All patients having history of any other prolonged illness other than COVID-19 and severe complications of diabetes (e.g. end stage organ dysfunction) were excluded from the study. Institutional Review Board approved the study.

We used worksheet that contained background information on demographics, height, weight, duration of diabetes, details of COVID-19 illness, current symptoms, changes in weight, and diet, drugs and insulin before and after COVID-19. For patients without COVID-19 all previously mentioned data except COVID information were recorded.

Assessment of Fatigue: We used a worksheet to analyze the patient’s fatigue using CFQ-11 [10]. This 11-item questionnaire is divided into two components: one that measures physical fatigue (questions 1–7) and the second one that measures mental fatigue (questions 8–11). Each of the 11 items were answered on a 4-point scale ranging from the asymptomatic to maximum symptomology, such as ‘Better than usual’, ‘No worse than usual’, ‘Worse than usual’ and ‘Much worse than usual’. Conventionally, fatigue case-status (fatigued vs. non-fatigued) is defined using this scale with a cut-off <4 vs. ≥4. These have been termed as fatigue score (FS) for further use in this paper.

Assessment of Handgrip Strength: This was performed with standard Jamar Hydraulic Hand Dynamometer (Sammons Preston, IL, USA) which estimates the muscle strength primarily generated by the flexor muscles of the hand and the forearm. This dynamometer displays handgrip force in both pounds and kilograms (maximum of 200 lb. or 90 kg). It has a peak-hold needle that automatically retains the highest reading until reset. This test is isometric, with no perceptible motion of the handle, regardless of the grip strength applied. The participants were encouraged to produce their maximal grip strength. Three trials were recorded, consisting of a 2–4 s maximal contraction, with a 30-s rest period between each trial. The average of the three readings was taken.

Biochemistry: The following investigations were done in patients who suffered from COVID-19: The HbA1C (pre- and post-COVID-19), fasting blood glucose (FBG, pre- and post-COVID-19), post-prandial blood glucose (PPBG, pre- and post-COVID-19), thyroid stimulating hormone (TSH), 25 hydroxy vitamin D [25(OH)D], serum albumin, interluekin-6 (IL-6), ferritin and high sensitivity C-reactive protein (hs-CRP). The following were done for patients with T2D who did not suffer from COVID-19 infection: HbA1C, FBG, PPBG, TSH, 25(OH)D, and serum albumin besides routine investigations.

2.1. Statistical analysis

Data were checked for normality. Continuous variables were summarised as Mean±SD using Student’s t-test or median using Mann Whitney test. Categorical data were summarised as frequency using Person’s Chi square test. The P value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA software (Version 14.2, StataCorp, College Station, Texas USA).

3. Results

A total of 108 patients were included in the study (cases, 52, controls, 56). Both the groups were matched for age, duration of diabetes, and BMI (Table 1). Further matching was done for common factors which may cause fatigue: 25(OH)D, serum albumin and TSH levels. Average time of presentation of patients post-COVID was 92 (range 32–262) days.

Overall, 31 (58.4%) patients with COVID-19 underwent home quarantine, and 22 (41.5%) patients were hospitalized. Out of hospitalized patients 14 (63%) were admitted in ward and 8 (36%) were admitted in intensive care unit. Among latter, 3 patients required ventilator support, 3 required BiPAP and 2 required oxygen support. In T2D and COVID-19 group, 30 patients (57.6%) were given corticosteroids (a combination of oral and injectable corticosteroids) for a variable period of time. On assessment using CFQ-11, 53% of patient who suffered from COVID-19 had significant fatigue whereas 37% of had it in those without COVID-19 (p=0.018). There was no difference in handgrip strength between the two groups.

Patients with COVID-19 and FS>4 had more symptoms of shortness of breath and weakness and had more weight loss than those with FS <4. These patients also had significantly higher TSH, lower serum albumin, higher PPBG, IL-6, and ferritin levels when compared with patients with COVID-19 having FS <4. Handgrip strength was also significantly reduced in patients with COVID-19 with high vs low FS (Table 2). Those with higher FS also had significantly reduced physical activity as compared to those with lower FS. Specifically, exercise capacity (level walk) was significantly reduced in patients with COVID-19 irrespective of hospitalization and home quarantine treatment. In hospitalized patients it reduced from 37.63 ± 16.23 to 21.31 ± 11.23 min/day (p 0.05) and in patients who were home quarantined it reduced from 28.78 ± 4.15 to 24.39 ± 12.32 min/day (p 0.04).

4. Discussion

This research shows that patients with T2D who had COVID-19 have higher fatigue than those who did not have COVID-19. There was no difference in the two groups in handgrip strength, suggesting significant sarcopenia had not occurred. Further, among patients who suffered from COVID-19, those who had higher FS, as compared to lower FS score, had more symptoms, weight loss, lower handgrip strength post infection and higher levels of inflammatory markers during infection. These data become more important since these patients were matched for age, BMI, duration of diabetes, and factors that could contribute to fatigue and morbidities i.e., TSH, 25(OH)D [12] and serum albumin levels.
Limitation of our study were non-inclusion of autonomic function tests and muscle enzyme levels. We also did not evaluate psychological factors. It is important to note that while many studies have looked at PCS and fatigue, this question on exclusive cohort of logical factors. It is important to note that while many studies have tests and muscle enzyme levels. We also did not evaluate psychological factors. It is important to note that while many studies have

While fatigue has been seen in considerable number of patients after COVID-19, its pathogenesis is largely unknown [1]. One of the key factors is inflammation induced by COVID-19, which can cause 'accelerated ageing' of the muscles [13] leading to sarcopenia. In our study, those patients who had high levels of inflammatory markers during COVID-19 had high FS and reduced handgrip strength. In a previous study, 35% of the hospitalized patients who suffered from COVID-19 was characterised as malnourished, mainly caused by considerable weight loss and 73% had high risk of sarcopenia [14]. Immobility during hospital stay is further detrimental to skeletal muscles. This could be further prolonged because of secondary infection.

Table 1
Demographic, clinical and biochemical profiles of patients with type 2 diabetes who had COVID-19 vs. those without.

| Variables                                | COVID-19 (n, 52) | Non-COVID-19 (n, 56) | P value |
|------------------------------------------|------------------|----------------------|---------|
| Age (y)                                  | 55.21 ± 11.30    | 58.33 ± 9.85         | 0.12    |
| Sex, n (%) Males                         | 32 (47.76)       | 35 (52.24)           | 0.010   |
| Duration of diabetes (y)                | 10.20 ± 1.28     | 11.87 ± 0.91         | 0.06    |
| Weight (Kg)                              | 76.06 ± 12.14    | 74.74 ± 16.30        | 0.63    |
| Body mass index (Kg/m²)                  | 27.77 ± 3.73     | 27.25 ± 5.31         | 0.56    |
| HbA1C (%)                                | 8.08 ± 1.77      | 8.21 ± 1.76          | 0.70    |
| Thyroid stimulating hormone (m IU/l)    | 4.16 ± 7.71      | 3.14 ± 1.55          | 0.39    |
| 25-hydroxyvitamin D (ng/ml)             | 55.01 ± 33.33    | 39.57 ± 24.3         | 0.09    |
| Serum albumin (g/dl)                     | 4.13 ± 0.59      | 4.10 ± 0.47          | 0.82    |
| Handgrip strength (Kg)                  | 27.86 ± 10.47    | 26.15 ± 9.45         | 0.37    |
| Fatigues score on CFQ                    |                  |                      |
| Mean fatigue score                       |                  |                      |
| ≤4                                       | 3.90 ± 3.52      | 2.98 ± 3.58          | 0.018   |
| >4                                       | 24 (46.15)       | 35 (63.50)           | 0.08    |
| Sex, n (%) Female                        | 16 (30.8)        | 12 [23]              |         |
| Age (y)                                  | 54.12 ± 11.36    | 56.14 ± 11.37        | 0.52    |
| Sex, n (%) Female                        | 16 (30.8)        | 8 (15.4)             | 0.06    |
| Duration of diabetes (y)                | 12.10 ± 7.56     | 8.57 ± 3.21          | 0.04    |
| Weight (Kg)                              | 78.39 ± 14.55    | 74.06 ± 9.44         | 0.20    |
| Body mass index (Kg/m²)                  | 28.43 ± 4.50     | 27.20 ± 2.88         | 0.24    |

Table 2
Clinical profile and investigation in patients with type 2 diabetes who had COVID-19 infection categorised according to fatigue score.

| Variables                                | Fatigue score (≤4) | Fatigue score (>4) | P value |
|------------------------------------------|--------------------|--------------------|---------|
| n (%)                                    | 24 (46.15)         | 28 (53.85)         |         |
| Age (Years)                              | 54.12 ± 11.36      | 56.14 ± 11.37      | 0.52    |
| Sex, n (%) Male                          | 16 (30.8)          | 8 (15.4)           | 0.06    |
| Duration of diabetes (y)                | 12.10 ± 7.56       | 8.57 ± 3.21        | 0.04    |
| Weight (Kg)                              | 78.39 ± 14.55      | 74.06 ± 9.44       | 0.20    |
| Body mass index (Kg/m²)                  | 28.43 ± 4.50       | 27.20 ± 2.88       | 0.24    |

Fasting blood glucose (mg/dL)             | 132.01 ± 33.80     | 134.81 ± 38.92     | 0.80    |
Post prandial blood glucose (mg/dL)       | 180.66 ± 52.17     | 184.76 ± 55.4      | 0.82    |
HBA1C (%)                                 | 7.41 ± 1.50        | 7.52 ± 1.31        | 0.81    |

Clinical profile and investigations during COVID-19

Fever                                     | 14 (58.3)          | 23 (82.1)          | 0.05    |
Weakness                                  | 5 (20.8)           | 10 (35.7)          | 0.23    |
Shortness of breath                        | 0                  | 4 (14.2)           | 0.05    |
Gastrointestinal symptoms                 | 1 (4.1)            | 1 (3.5)            | 0.9     |
Loss of smell/taste                        | 3 (12.5)           | 2 (7.1)            | 0.5     |
Severity score on CT scan                 | 13.81 ± 4.76       | 12.38 ± 6.24       | 0.65    |
Thyroid stimulating hormone (m IU/l)      | 2.55 ± 1.28        | 5.53 ± 1.65        | 0.04    |
25-hydroxyvitamin D (ng/ml)               | 55.03 ± 4.56       | 54.09 ± 6.56       | 0.99    |
Serum albumin (g/dl)                      | 4.33 ± 0.44        | 3.97 ± 0.64        | 0.07    |
Interleukin-6 (pg/ml)                     | 22.83 ± 10.23      | 96.38 ± 16.32      | 0.0001  |
Serum ferritin (ng/ml)                    | 236.22 ± 26.56     | 318.59 ± 28.62     | 0.007   |
High sensitivity C-reactive protein (mg/dl)| 12.87 ± 15.23     | 16.67 ± 13.25      | 0.5     |

Glycemic parameters after COVID-19

Fasting blood glucose (mg/dL)             | 157.37 ± 81.1      | 155.8 ± 55.32      | 0.93    |
Post prandial blood glucose (mg/dL)       | 208.91 ± 54.75     | 226.12 ± 67.57     | 0.05    |
HBA1C (%)                                 | 7.79 ± 1.78        | 8.37 ± 1.74        | 0.28    |

Clinical profile after COVID-19

No symptom                                | 11 (45.8)          | 3 (10.7)           | 0.004   |
Weakness/symptom of fatigue               | 10 (41.6)          | 22 (78.8)          | 0.006   |
Gastrointestinal symptoms                 | 3 (12.5)           | 2 (7.1)            | 0.51    |
History of weight change (Kg)             | 0.95 ± 0.21        | −1.96 ± 0.42       | 0.04    |
Handgrip strength (Kg)**                  | 30.42 ± 10.81      | 25.67 ± 9.83       | 0.04    |
Physical activity before COVID-19 (mins/day)| 30.23 ± 12.32    | 33.75 ± 11.23      | 0.09    |
Physical activity after COVID-19 (mins/day)| 28.54 ± 11.23    | 18.75 ± 9.56       | 0.004   |

* As measured by Jamar Hydraulic Hand Dynamometer, CFQ: Chalder Fatigue Scale.

* Measure by Chalder Fatigue Scale **As measured by Jamar Hydraulic Hand Dynamometer.

[1] Mittal, A. Ghosh, S.P. Bhatt et al. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 102302
electrolyte disorders (e.g., hypokalaemia) could exacerbate muscle weakness. Uncontrolled glycemic status of our patients post COVID-19 could have also contributed to fatigue (Table 2).

Nutritional deficiencies could be a major concern after discharge in COVID-19 patients. Patients may have poor oral intake due to disease, drugs or lack of taste and smell, which may lead to decreased protein levels and other nutrients essential to muscle metabolism. About 61% had weight loss, and 14.6% were undernourished in a small cohort of COVID-19 patients at discharge [17]. Among these the following deficiencies were noted; 19.5% hypalbuminemia, 19.5% hypocalcemia, 34.1% anemia, 12.2% hypomagnesemia and 51.2% deficiency in vitamin D (17). Despite these problems, nutrition advice has not been given adequately to the patients [14]. It is important to mention that both groups in our study were matched for serum albumin levels at baseline, and these levels were adequate, thus excluding this factor as a cause of fatigue. However, those patients with T2D and previous COVID-19, and high FS, showed decreased serum albumin levels.

All the above discussed factors are operative to a larger extent in elderly, and those with chronic diseases, including diabetes. Sarcopenia is common in patients with diabetes and increases with age. It is more common in Asians vs. non-Asians, and Indians may be more predisposed to it [18]. Other contributing factors to sarcopenia include gender (more in females), BMI (higher with low BMI), disease duration (increase with duration of diabetes), glycemic control (greater with poorer control), presence of microvascular or macrovascular complications, nutritional status, etc. [19]. Occurrence of severe COVID-19 should be added as another factor, and resulting sarcopenia would lead to fatigue. In our study, those who had COVID-19, and had FS >4 also lost more weight and had decrease in physical activity. These patients also had reduced handgrip strength indicating functional sarcopenia.

One of the causes of PCS has been hypothesized as ‘dysautonomia’, It has been shown that participants with PCS and fatigue had dysregulation of heart rate variability [20]. The authors stated that such dysautonomia could lead to fatigue and hypoxia. It is to be noted that autonomic dysfunction is common in longstanding and uncontrolled diabetes, and post COVID-19 dysautonomia may augment it. In our study, we did not perform autonomic function tests.

Management of post COVID-19 fatigue should be multidisciplinary including physician, psychological counsellor, nutritionist, and physical therapy expert (1). Blood glucose and blood pressure should be optimally controlled [21,22]. In our study, PPBG after COVID-19 showed increase, and at this time point more agressive glycemic management is required. Special care must be taken regarding nutrition; protein and vitamin supplements should be used as per requirement [23]. Vitamin D, calcium, iron, magnesium and C supplementation may help. In a review, data from nine clinical studies showed significant decrease in fatigue scores in the group receiving vitamin C vs. control group [24]. Exercise and physiotherapy should be started early after COVID-19 as it may benefit not only fatigue but cardiovascular, pulmonary and mental fitness [1]. In cases of marked weight loss, it may be advisable to withhold SGLT2 and GLP-1 receptor analogs.

**Funding**

There is no source of funding for this study.

**Author contribution**

AM conceived the study, reviewed, and edited the manuscript. AG conducted the study and wrote the manuscript. JM, IA conducted the study, SA and SP analysed, interpreted the data, and contributed to discussion. AM is the guarantor for this manuscript.

**Declaration of competing interest**

Authors declare no conflict of interests.

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