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LETTER TO THE EDITOR

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Craniofacial pain in COVID-19 patients with diabetes mellitus: Clinical and laboratory description of 21 cases

The pandemicity of diabetes mellitus (DM) has always been a challenging concern for oral and maxillofacial practitioners which got aggravated by the coronavirus disease (COVID-19) pandemic.[1–3] DM is an independent risk factor for COVID-19 morbidity and mortality; on the other hand, COVID-19 outbreak has deteriorated the access of diabetic patients to palliative care and limited their outdoor activities and their nutrition. Similar to the severe acute respiratory syndrome (SARS) and the Middle Eastern respiratory syndrome, COVID-19 is strongly associated with altered glycemic levels thus leading in some cases to new-onset diabetes.[4,5] In accordance with the CARE guidelines, we aim to report the characteristics of 21 consecutive diabetic type-2 COVID-19 patients who presented to our department from April to August 2020 with throbbing craniofacial pain.[6] Out of the 5730 diabetic patients with COVID-19 who visited our outpatient clinics or admitted to the inpatient department during the referenced period, those 21 patients (0.37%) sought specialist care due to their new-onset pain (Table 1).

The referenced patients had undergone a polymerase chain reaction (PCR) testing for COVID-19 which confirmed their infection with a mean cycle threshold (C_t) of 28.43 ± 5.64 (15–39), and none of them experienced severe respiratory symptoms that required hospitalization. Their mean age was 51.71 ± 10.62 (38–75) years old with a mean body mass index of 21.76 ± 2.7 (18–26), and the majority (66.7%) were males. On the day of their visit to our department, their mean hemoglobin A1c (HbA1c) was 6.7 ± 9.11 (5–8) indicating that the majority of them had controlled DM (76%).

The patients were on various antidiabetic drugs indicating a wide scale of diseases severity; six patients (28.6%) took thiazolidinediones, four patients (19%) took sulfonylureas, four patients (19%) took sodium–glucose cotransporter 2 inhibitors, three patients (14.3%) took metformin, and four patients (19%) used to take insulin. While six patients (28.6%) had no systemic comorbidities, three patients (14.3%) had cardiac implications, four patients (19%) had renal impairment, and eight patients (38.1%) were asthmatic.

Regarding their COVID-19 symptoms; three patients (14.3%) had a mild fever, four patients (19%) experienced dry coughing, and only two patients (9.5%) had a sore throat. Myalgia (muscles pain) was experienced by only two patients (9.5%). According to the Australian guidelines, 3 patients (14.3%) had a moderate course of illness, and 18 patients (85.7%) had a mild course of illness.[7]

The clinical examination had been carried out systematically by a qualified maxillofacial surgeon beginning with a general assessment of the head and neck, followed by inspection of the ears, nose, oropharynx, and lymph nodes, and neurologic screening.[8] On examining their chief complaint, pain severity was assessed by the patient using an 11-item numerical rating scale when with "0" denoting "no pain" and "10" denoting "pain as bad as you can imagine."[9] The mean pain severity was 7.14 ± 1.15 (5–9), and it had between 3 and 10 episodes every day with a mean of 6.19 ± 1.89 episodes/day. The duration of the pain was estimated from the day of consultation until the day when the patient reported that the pain had completely been relieved; the mean duration was 16.95 ± 8.89 (6–30) days. The pain was related to the masseter region in twelve patients (57.1%), to the temporalis region in four patients (19%), and to both of those regions in five patients (23.8%). While 10 patients experienced pain bilaterally (47.6%), 11 patients reported it on one side (52.4%; Figure 1). In the vast majority of patients, the pain was exacerbated by touching (85.7%) then by chewing (52.4%); on the other hand, hot fomentation was the most common relieving cause (62%) followed by paracetamol (24%), ibuprofen (5%), and diclofenac potassium (5%). All the investigated patients agreed to use their clinical and laboratory results for academic purposes while concealing their identifying personal data.

In addition to the well-known pathophysiologic mechanisms by which the diabetic patients are imposed to a greater risk of viral infections such as impaired neutrophil chemotaxis and phagocytosis; the increased expression of angiotensin-converting enzyme 2 in pancreatic islets and the persistent hyperglycemia in SARS patients indicated transient damage to beta cells.[10] As a consequence of the alterations of lymphocyte phenotype by decreasing T-helper-2 and regulatory T-cells and increasing T-helper-1 and T-helper-17 cells, viral infections can amplify the cytokine response in the adipose tissues.[11] All these factors may be attributed to the inflammatory mechanism by which the craniofacial structure can be affected especially in older patients when tissue susceptibility to pain increases with ageing.[12] Given that our cases' median age was 49-year old, the relationship between diabetes and pain in the orofacial muscles can be related to glutamate's role whose neurotoxicity is mediated by the NMDA receptors found in neuronal tissues and peripheral nonneuronal tissues and cells as β-cells.[13,14]

In contrast to diabetic neuropathies, including focal neuropathy of the face, which are mainly triggered by long-standing hyperglycemia, our cases had meticulous control of their blood glucose levels through medications.[15] Therefore, diabetes-induced neuroinflammation had been ruled out as a pathophysiologic pathway in this series. However, the COVID-19 pandemic had indirectly worsened orofacial pain in

TABLE 1 The demographic, clinical and laboratory characteristics of diabetic COVID-19 patients with craniofacial pain

ID	Gender	Age	BMI	HbA1c	Anti-DM drugs	Systemic comorbidities	C_t	Pain location	Relieving	Aggravating	Intensity	Episodes	Duration
1	Male	42	19	5	Metformin	Cardiac Implication	34	Left and right masseter	Hot pack	Touch, chewing	8	4	10
2	Female	57	22	8	Sulfonylureas	None	35	Right masseter	Hot pack	Touch	7	5	30
3	Female	41	25	6	Insulin	Renal impairment	21	Left masseter	N/A	Chewing	8	7	7
4	Male	39	18	8	Thiazolidinediones	None	15	Left temporalis	Hot pack	Touch	7	8	23
5	Female	67	20	7	Sulfonylureas	Asthma	31	Right masseter	Paracetamol	Touch, chewing	9	6	29
6	Male	71	26	6	Insulin	Asthma	25	Left temporalis	Ibuprofen	Touch	7	9	8
7	Female	47	21	8	SGLT2 inhibitors	None	26	Right masseter	Hot pack	Chewing	6	4	8
8	Male	50	20	7	Sulfonylureas	Asthma	27	Left and right masseter + left and right temporalis	Hot pack	Touch, chewing	9	10	23
9	Female	49	18	8	Thiazolidinediones	Asthma	39	Left and right masseter + left and right temporalis	Paracetamol	Touch, chewing	8	4	28
10	Female	53	22	6	Insulin	Renal Impairment	30	Right temporalis	Hot pack	Touch	7	7	8
11	Male	48	26	8	Thiazolidinediones	Asthma	31	Left temporalis	Hot pack	Touch	6	8	21
12	Female	41	22	6	Thiazolidinediones	Asthma	32	Right masseter	Hot pack	Chewing	8	6	19
13	Female	38	19	7	Metformin	Cardiac Implication	26	Left and right masseter	Hot pack	Touch	9	5	13
14	Female	46	20	6	Thiazolidinediones	Asthma	30	Right masseter	Hot pack	Touch	6	6	29
15	Female	53	24	7	SGLT2 inhibitors	None	18	Left and right masseter	Hot pack	Touch	7	4	9
16	Male	47	26	6	Thiazolidinediones	Renal Impairment	30	Left and right masseter	Hot pack	Touch	6	3	24
17	Female	61	19	6	Sulfonylureas	Asthma	32	Left and right masseter	Paracetamol	Touch, chewing	5	5	29
18	Female	42	23	6	SGLT2 inhibitors	Renal impairment	24	Left and right masseter + left and right temporalis	Paracetamol	Touch, chewing	6	7	9
19	Female	60	22	6	Insulin	Cardiac Implication	29	Left and right masseter	Hot pack	Touch	7	8	6
20	Female	75	25	7	SGLT2 inhibitors	None	30	Right masseter	Paracetamol	Touch, chewing	6	6	11
21	Male	59	20	7	Metformin	None	32	Left and right masseter + left and right temporalis	Diclofenac potassium	Touch, chewing	8	8	12

Abbreviations: BMI, body mass index; DM, diabetes mellitus; SGLT2, sodium–glucose cotransporter 2.

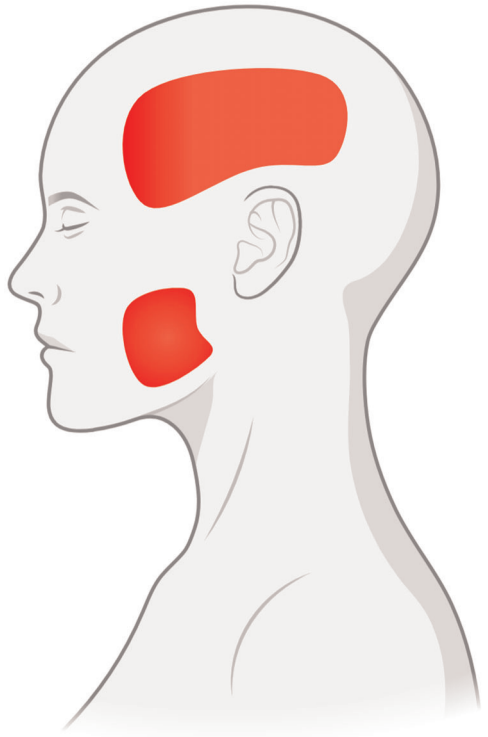

FIGURE 1 The craniofacial pain experienced by COVID-19 patients with diabetes mellitus type-2 was related to masseter muscle region, temporalis muscle region, or both masseter and temporalis muscles regions

various populations due to the significant increase in psychoemotional stress that aggravates bruxism and temporomandibular disorders, all the cases in this series reported that they had no history of bruxism nor prior experience with orofacial pain.[16,17]

In conclusion, this case series provides the first clinical evidence on a possible interference of COVID-19 with craniofacial tissues leading to an inflammatory-mediated pain that warrants further investigation for the pathophysiologic mechanisms of pain perception in diabetic patients infected by SARS-COV-2.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Mai Badrah: Writing-original draft and formal analysis. Abanoub Riad: Writing-original draft. Islam Kassem: Data curation and investigation. Michela Boccuzzi: Writing-review and editing. Miloslav Klugar: Supervision and writing-review and editing.

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