Received: 15 February 2024 | Revised: 21 March 2024 | Accepted: 04 April 2024
DOI: 10.48309/JMPCR.2024.448645.1146
Journal of Medicinal and Pharmaceutical Chemistry Research
SAMI

FULL PAPER

Examining the prevalence of COVID-19 patients with diabetes and the relationship between the two diseases in Ghaem Hospital, Mashhad

Behrang Rezvani Kakhki[a] |Shadi Saghafi Khadem[b] |Maryam Ziyaei[c] |Morteza Talebi Doluee[a,*] |Sadegh Ghalenoei[d] |Hasan Hasanie[e] |Zahra Sadaghiani[f] |Zahra Ghalenoee[g] |Mahdi Foroughian[a]

[a]*Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

[b]*Department of Oral and Maxillofacial Pathology, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran*

[c]*Department of Emergency Medicine, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran*

[d]*Department of Dentistry, Faculty of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran*

[e]*Student Research Committee, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran*

[f]*MSC, Faculty of Physical Therapy, Shahid Beheshti University of Medical Science, Tehran, Iran*

[g]*Obstetrics and Gynecology Department, Tehran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:**
Morteza Talebi
Email:Dolueetalebidm@mums.ac.ir
Tel.: +05138525312

On January 30, 2020, the World Health Organization (WHO) announced a global warning due to the rapid spread of the COVID-19 disease. The transmission and pathogenicity of this disease is very high and it rapid global spread. Diabetes Mellitus is one of the most common diseases in the world, the main symptom of which is chronic high blood sugar. In various studies, the possible relationship between diabetes and COVID-19 has been investigated. Corona has been more severe in diabetic patients than in healthy people. Identifying risk factors for COVID-19 is crucial and can play a role in determining treatment priorities; this study was conducted to investigate the frequency of COVID-19 patients with diabetes and the relationship between the two diseases in Ghaem Hospital, Mashhad. In this study, the information available in the medical archive in Ghaem Hospital of Mashhad related to the patients hospitalized due to Coronavirus from April 2019 to September 2021 was used. Demographic information of the patients, including the history of diabetes, blood sugar level, and recovery status was extracted from the files by the project student, and then patients with diabetes were randomly selected with the help of a random number table, by calling the patient or first-degree relatives through the number registered in the file, if possible, information related to have toothache during and after hospitalization, and oral ulcers. During and after hospitalization, the type of diabetes was taken and recorded. In this study, the information of 1370 patients were analyzed. Among the patients, 61.5% had diabetes. 52.9% of cases were related to men and 47.1% were related to women. The mortality rate in patients with diabetes (38.3%) was significantly higher than that in people without diabetes (30.7%). Likewise, the average age of people who died due to Corona was higher than those who were discharged. Oral ulcers during hospitalization were reported in 58.1% of people with type 1 diabetes and 35.3% of people with type II diabetes, and the difference between them was also significant. Oral ulcers after hospitalization were seen in 16.3% of people with type 1 diabetes and 1.5% of people with type II diabetes. In this study, the death rate of patients with diabetes was higher than that of normal people. It was reported that people with type I diabetes have more oral ulcers than people with type II diabetes, which requires more dental attention for these people.

KEYWORDS

Oral ulcer; COVID-19; diabetes mellitus.

Introduction

On January 30, 2020, the World Health Organization (WHO) issued a global alert regarding the widespread transmission of COVID-19 [1-10]. Several risk factors have been identified for this disease, including cardiovascular diseases, male gender, diabetes, chronic respiratory diseases, hypertension, cancers, and age over 60, which are associated with more severe symptoms [11]. Diabetes mellitus is considered a significant and well-known risk factor for infectious diseases, including COVID-19. The pandemic has, directly and indirectly, affected the glycemic control of diabetic patients [12].

The increased expression of ACE2 in lung alveolar cells, myocardium, kidney, and pancreas in diabetic patients enhances the virus's binding affinity, leading to an increased risk of COVID-19 [13]. It has been confirmed in the literature that diabetes is a major risk factor for COVID-19, with a high mortality rate and poor prognosis [14,15]. Diabetic individuals exhibit more severe symptoms of COVID-19 and require additional care [16,17]. Some COVID-19 patients have experienced acute diabetes mellitus due to viral targeting of the Langerhans islets and ACE2 receptors [18]. Poor prognosis in diabetic patients with COVID-19 is attributed to higher body temperature, decreased oxygen concentration, and increased blood urea levels [19].

Since identifying the risk factors of COVID-19 disease is crucial and is significant in determining treatment priorities, this study aimed to determine the relationship between diabetes and COVID-19 disease and the severity of the disease.

Methods

Ethical consideration and participants

This cross-sectional study examined the medical records of patients who were hospitalized for COVID-19 and underwent FBS testing at Ghaem Hospital in Mashhad between April 2019 and September 2020. The study follows the Helsinki declaration and approved by the Ethics Committee of Mashhad University of Medical Scienceswith the ethic code of IR.MUMS.DENTISTRY.REC.1400.140.

Data collection

The inclusion criteria included complete medical records and a definite diagnosis of COVID-19 based on the PCR test. Demographic information, including age, sex, history of diabetes, blood sugar level, and recovery status, was extracted from the files. The study team contacted patients who met two conditions: 1) fasting blood sugar above 126 at the time of hospitalization and a diagnosis of diabetes in the patient's file and 2) discharge from the hospital.

Patients with diabetes were randomly selected for further investigation and information regarding type of diabetes, toothache, and oral ulcers during and after hospitalization, were collected and recorded. If patients did not respond, they were randomly selected again from the list. Calls were made from within the faculty, and verbal consent was obtained before proceeding with the questionnaire.

Statistical analysis

Descriptive and frequency statistical tests were used to obtain the mean and standard deviation and frequency of quantitative and qualitative data. Other chi-square and independent T-tests were also used to measure the relationship of study variables. The significance level was considered with an error of 5% less than 0.05 (P-value < 0.05).

Results

Out of the 1370 patients meeting the criteria, 725 cases (52.9%) were male and 645 cases (47.1%) were female. Among these patients, 843 (61.5%) had diabetes. A total of 323

individuals (38.3%) died as a result of both corona disease and diabetes. The association between gender and mortality rate was examined specifically among diabetic patients. Among the deceased, 164 were women (40.9%) and 159 were men (36.0%) who had corona. The statistical analysis did not reveal a significant relationship between gender and mortality in patients (*P*-value=0.08) (Table 1).

TABLE 1 Demographics of the patients included in the study

Variable	Demographics	Frequency
Gender	Male	725 (52.9%)
	Female	645 (47.1%)
Diabetes Status	Healthy	527 (38.5%)
	Diabetics	843 (61.5%)
Patient Status	Deceased	485 (35.4%)
	Discharge	885 (64.6%)

Also a telephone survey was conducted with 244 individuals. Calls were made from within the faculty by a single person, and verbal consent was obtained before providing full explanations. The death rate was 162 (30.7%) in healthy individuals and 323 (38.3%) in diabetic individuals. The results of the chi-square test indicated a significant relationship between these variables *(P*-value<0.01*)*. The age range of the patients was 9 to 98 years. The average fasting blood sugar level at the time of hospitalization was 164, with a standard deviation of 80.

The average age of those who died due to corona was 67.58 years, while the average age of those discharged was 57.50 years. The results of the independent t-test demonstrated a significant relationship between age and mortality (*P*-value<0.01) (Table2).

TABLE 2 Diabetes types and existence of oral ulcer and toothache

Variables		Frequency	Percentage
Diabetes Type	Diabetes Type I	43	17.6
	Diabetes Type II	201	72.4
Oral ulcer Existence during hospitalization	Positive	96	39.3
	Negative	148	60.7
Oral ulcer Existence after hospitalization	Positive	10	4.1
	Negative	234	95.9
Toothache present during hospitalization	Positive	18	7.4
	Negative	226	92.6
Toothache present after hospitalization	Positive	17	7
	Negative	227	93

TABLE 3 The relationship between oral ulcers/toothache with hospitalization time and the type of diabetes

Diabetes	Oral ulcer During hospitalization			Oral ulcer After hospitalization			Toothache During hospitalization			Toothache After hospitalization		
	Positive (%)	Negative (%)	P-value*	Positive (%)	Negative (%)	P-value	Positive (%)	Negative (%)	P-value	Positive (%)	Negative (%)	P-value
Type I	25 (58.1)	18 (41.9)	<0.01	7 (16.3)	36 (83.7)	<0.01	3 (7)	40 (93)	1	6 (14)	37 (86)	0.089
Type II	71 (35.3)	130 (64.7)		3 (1.5)	198 (98.5)		15 (7.5)	186 (92.5)		11 (5.5)	190 (94.5)	

*:Chi square, P-Value< .05 significant

Patients with type 1 diabetes exhibited a significantly higher prevalence of oral ulcers.

The association between age and oral ulcers during hospitalization was examined. The average age of individuals with oral ulcers was 60.87 years, while those without oral ulcers had an average age of 57.04 years. However, the results of the independent T-test did not indicate a significant relationship between age and oral ulcers during hospitalization (*P*-value=0.43). Similarly, the relationship between age and toothache after discharge was investigated. The average age of individuals experiencing toothache after hospitalization was 48.23 years, compared to 59.32 years in those without toothache. The independent T-test did not reveal a significant relationship between age and toothache. It is important to note that the analysis of the relationship between age and ulcers after hospitalization and pain during hospitalization was not conducted due to the limited number of participants (10 and 15, respectively) (Table3).

Discussion

The SARS-Cov-2 virus has been observed to bind to the ACE2 receptor in various tissues, including kidney epithelium tissue, pancreas, endothelial cells, lungs, and heart, via the spike protein [20] and Immunostaining tests have demonstrated that the pancreas is a prominent site of infection in SARS-Cov-2 cases [21]. Consequently, the destruction of pancreatic cells may contribute to disruptions in glucose metabolism and the development of hyperglycemic complications in individuals with diabetes. Furthermore, individuals with diabetes exhibit a higher susceptibility to infection due to the functional decline of neutrophils and macrophages [12]. The present study revealed a higher mortality rate among individuals with diabetes compared to healthy individuals. In addition, individuals with diabetes experienced elevated body temperature, reduced oxygen concentration during hospitalization, and a higher frequency of admission to the intensive care unit [19].Complications arising from COVID-19 are also more severe in individuals with diabetes, necessitating specialized care [16]. A comprehensive review of 83 studies indicated that individuals with diabetes have an increased risk of mortality and are more likely to experience severe forms of the disease [23]. Moreover, hospitalized diabetics with COVID-19 commonly present with comorbidities such

as hypertension, cardiovascular disease, and neurological disorders [24]. The management of diabetes directly influences the mortality rate and complications associated with COVID-19 [25]. The higher mortality rate observed in individuals with diabetes may be attributed to a compromised immune system [26]. Age has been identified as a significant factor in the mortality of COVID-19 patients, with older individuals facing a higher risk of death [27]. Notably, the ACE2 receptor is prominently expressed in the oral cavity, and substantial amounts of the virus have been detected in the saliva of individuals with COVID-19 [28,29]. People with diabetes are more susceptible to viral entry through the oral route due to oral wounds and delayed wound healing. Hyperglycemic conditions can further lead to damage in the connective tissue of the oral environment, resulting in oral ulcers and periodontal diseases. The impact of COVID-19 on the oral environment is further exacerbated in individuals with diabetes due to pancreatic tissue damage and disrupted glucose metabolism, leading to an increased incidence of oral ulcers. Furthermore, the SARS-CoV-2 virus can directly affect oral ACE2 receptors [30]. This study reported a higher occurrence of oral ulcers in people with diabetes during hospitalization compared to healthy individuals.

Conclusion

The findings of this study revealed a significant association between diabetes and increased mortality rates among individuals diagnosed with COVID-19. During hospitalization, oral ulcers were observed in over one-third of patients with comorbid diabetes and COVID-19. However, reports of toothache during and after hospitalization were limited to approximately seven percent of the patient population. Notably, the incidence of oral ulcers during hospitalization was significantly higher in individuals with type I diabetes compared to those with type II diabetes. Similarly, the occurrence of oral ulcers after hospitalization was significantly more prevalent in individuals with type I diabetes compared to those with type II diabetes.

Acknowledgements

The authors would like to thank the Clinical Research Development Unit of Ghaem Educational and Research and Therapeutic Center of Mashhad University of Medical Sciences for providing facilities to this work.

Funding

This study was supported by Mashhad University of Medical Sciences

Authors' Contributions

All authors contributed toward data analysis, drafting, and revising the manuscript and agreed to be responsible for all the aspects of this work

Conflict of Interest

The authors declare that there is no conflict of interest.

Orcid:

Behrang Rezvani Kakhki:
https://orcid.org/0000-0003-3715-6618
Shadi Saghafi Khadem:
https://orcid.org/0000-0002-4910-1895
Maryam Ziyaei:
https://orcid.org/0000-0003-1693-6818
Morteza Talebi Doluee:
https://orcid.org/0000-0003-2570-3733
Sadegh Ghalenoei:
https://orcid.org/0009-0000-5811-1465
Hasan Hasani:
https://orcid.org/0009-0008-3727-7392
Zahra Sadaghiani:
https://orcid.org/0009-0008-8903-4202
Zahra Ghalenoee:
https://orcid.org/0009-0003-4069-5521
Mahdi Foroughian:*
https://orcid.org/0000-0002-3944-9361

References

[1] K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 pathophysiology: A review, *Clinical Immunology*, **2020**, *215*, 108427. [Crossref], [Google Scholar], [Publisher]

[2] R. Amirkhani, A. Zarei, M. Gholampour, H. Tavakoli, A. Ramazani, Computational study on inhibitory potential of natural compounds against SARS-CoV-2 main protease, *Chemical Methodologies*, **2024**, *8*, 85-95. [Crossref], [Publisher], [Pdf]

[3] N. Askari, S. Shafieipour, F. Noormand, E. Karami Raviz, S. Khanamani Falahatipour, TNF-alpha 308G/A polymorphism and serum level of TNF-α associated with Covid-19 severity, *International Journal of Advanced Biological and Biomedical Research*, **2023**, *11*, 221-231.[Crossref], [Publisher] ,[Pdf]

[4] N. Kalani, N. Hatami, M. Haghbeen, U. Yaqoob, E. Raeyat Doost, COVID-19 health care for Afghan refugees as a minor ethnicity in Iran: Clinical differences and racial equality in health, *Acta Medica Iranica*, **2021, 59,**466-471. [Crossref**],** [Google Scholar], [Publisher]

[5] E. Erdag, A Molecular Docking Study: Benzoxazolone Derivatives against SARS-CoV-2 Omicron Subvariant EG.5.1, *Chemical Methodologies*, **2023**, 7, 825-836. [Crossref], [Publisher], [Pdf]

[6] K. R. Surana, L.V. Savale, J.S. Aher, S.N. Aher, D.D. Sonawane, D.M. Patil, Nutraceuticals for the COVID-19 prevention and treatment, *International Journal of Advanced Biological and Biomedical Research*, **2023**, *11*, 247-260. [Crossref], [Publisher], [Pdf]

[7] A. Saedi, S. Saedi, M.M. Ghaemi, M. Milani Fard, A Review of epidemiological study of Covid-19 and risk factors, *Eurasian Journal of Science and Technology*, **2022**, *2*, 218-226. [Crossref], [Publisher], [Pdf]

[8] N. Tadayon, A. Ramazani, Molecular docking and dynamics analysis of COVID-19 main protease interactions with alkaloids from hyoscyamus niger and datura stramonium, *Chemical Methodologies*, **2023**, *7*, 883-903.[Crossref], [Publisher], [Pdf]

[9] M. Deylami, M, Vatankhah, T. Zarei, E. Rahmanian, F. Javdani, S.H. Shafa, Systematic review and meta-analysis of narcolepsy management during the covid-19 pandemic, *Journal of Medicinal and Pharmaceutical Chemistry Research*, **2024**, *6*, 292-301. [Crossref], [Google Scholar], [Publisher]

[10] G. Motazedian, P. Aryanpoor, E. Rahmanian, S. Abiri, N. Kalani, N. Hatami, Incidence of Pediatric Perforated Appendicitis during the COVID-19 Pandemic; a Systematic Review and Meta-Analysis, *Archives of Academic Emergency Medicine*, **2021**, *10*, 3. [Crossref], [Google Scholar], [Publisher]

[11] Y. Wang, Y. Wang, Y. Chen, Q. Qin, Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures, *Journal of Medical Virology*, **2020**, *92*, 568-576. [Crossref], [Google Scholar], [Publisher]

[12] S. Elamari, I. Motaib, S. Zbiri, K. Elaidaoui, A. Chadli, C. Elkettani, Characteristics and outcomes of diabetic patients infected by the SARS-CoV-2, *Pan African Medical Journal*, **2020**, *37*. [Google Scholar], [Publisher]

[13] R. Muniyappa, S. Gubbi, COVID-19 pandemic, coronaviruses, and diabetes mellitus, *American Journal of Physiology-Endocrinology and Metabolism*, **2020**, *318*, 36-41. [Crossref], [Google Scholar], [Publisher]

[14] A. Abdi, M. Jalilian, P.A. Sarbarzeh, Z. Vlaisavljevic, Diabetes and COVID-19: A systematic review on the current evidences, *Diabetes Research and Clinical Practice*, **2020**, *166*, 108347. [Crossref], [Google Scholar], [Publisher]

[15] A.M. Alguwaihes, M.E. Al-Sofiani, M. Megdad, S.S. Albader, M.H. Alsari, A. Alelayan, S.H. Alzahrani, S. Sabico, N.M. Al-Daghri, A.A. Jammah, Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study, *Cardiovascular Diabetology*, **2020**, *19*, 1-12. [Crossref], [Google Scholar], [Publisher]

[16] M. Akbariqomi, M.S. Hosseini, J. Rashidiani, H. Sedighian, H. Biganeh, R. Heidari,

M.M. Moghaddam, G. Farnoosh, H. Kooshki, Clinical characteristics and outcome of hospitalized COVID-19 patients with diabetes: A single-center, retrospective study in Iran, *Diabetes Research and Clinical Practice*, **2020**, *169*, 108467. [Crossref], [Google Scholar], [Publisher]

[17] M. Nassar, A. Daoud, N. Nso, L. Medina, V. Ghernautan, H. Bhangoo, A. Nyein, M. Mohamed, A. Alqassieh, K. Soliman, M. Alfishawy, Diabetes mellitus and COVID-19. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **2021**, *15*, 102268. [Crossref], [Google Scholar], [Publisher]

[18] M. Nassar, N. Nso, C. Gonzalez, S. Lakhdar, M. Alshamam, M. Elshafey, Y. Abdalazeem, A. Nyein, B. Punzalan, R.J. Durrance, M. Alfishawy, COVID-19 vaccine-induced myocarditis: case report with literature review, *Diabetes & Metabolic Syndrome*, **2021**, *15*, 102205. [Crossref], [Google Scholar], [Publisher]

[19] M. Pazoki, M. Keykhaei, S. Kafan, M. Montazeri, M. Mirabdolhagh Hazaveh, M. Sotoodehnia, S. Kazemian, M. Talebpour, H. Ashraf, R. Shariat Moharari, F. Majidi, Risk indicators associated with in-hospital mortality and severity in patients with diabetes mellitus and confirmed or clinically suspected COVID-19, *Journal of Diabetes & Metabolic Disorders*, **2021**, *20*, 59-69. [Google Scholar], [Publisher]

[20] A. Hussain, B. Bhowmik, N.C. do Vale Moreira, COVID-19 and diabetes: Knowledge in progress, *Diabetes Research and Clinical Practice*, **2020**, *162*, 108142. [Crossref], [Google Scholar], [Publisher]

[21] J.K. Yang, S.S. Lin, X.J. Ji, L.M. Guo, Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes, *Acta Diabetologica*, **2010**, *47*, 193-199. [Google Scholar], [Publisher]

[22] Y.J. Chee, S.K. Tan, E. Yeoh, Dissecting the interaction between COVID-19 and diabetes mellitus, *Journal of Diabetes Investigation*, **2020**, *11*, 1104-1114. [Crossref], [Google Scholar], [Publisher]

[23] A. Mantovani, C.D. Byrne, M.H. Zheng, G. Targher, Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies, *Nutrition, Metabolism and Cardiovascular Diseases*, **2020**, *30*, 1236-1248. [Crossref], [Google Scholar], [Publisher]

[24] Q. Shi, X. Zhang, F. Jiang, X. Zhang, N. Hu, C. Bimu, J. Feng, S. Yan, Y. Guan, D. Xu, G. He, Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study, *Diabetes Care*, **2020**, *43*, 1382-1391. [Crossref], [Google Scholar], [Publisher]

[25] M. Raoufi, S. Khalili, M. Mansouri, A. Mahdavi, N. Khalili, Well-controlled vs poorly-controlled diabetes in patients with COVID-19: Are there any differences in outcomes and imaging findings?, *Diabetes Research and Clinical Practice*, **2020**, *166*, 108286. [Crossref], [Google Scholar], [Publisher]

[26] H. Rastad, H. Karim, H.S. Ejtahed, R. Tajbakhsh, M. Noorisepehr, M. Babaei, M. Azimzadeh, A. Soleimani, S.H. Inanloo, N. Shafiabadi Hassani, F. Rasanezhad, Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease, *Diabetology & Metabolic Syndrome*, **2020**, *12*, 1-11. [Google Scholar], [Publisher]

[27] N. Rezaei, F. Montazeri, M.R. Malekpour, A. Ghanbari, S. Azadnajafabad, E. Mohammadi, N. Rezaei, S. Naderimagham, E. Ghasemi, M. Abbasi-Kangevari, S.H. Ghamari, COVID-19 in patients with diabetes: factors associated with worse outcomes, *Journal of Diabetes & Metabolic Disorders*, **2021**, *20*, 1605-1614. [Crossref], [Google Scholar], [Publisher]

[28] H. Xu, L. Zhong, J. Deng, J. Peng, H. Dan, X. Zeng, T. Li, Q. Chen, High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa, *International Journal of Oral Science*, **2020**, *12*, 1-5. [Crossref], [Google Scholar], [Publisher]

[29] L. Chen, J. Zhao, J. Peng, X. Li, X. Deng, Z. Geng, Z. Shen, F. Guo, Q. Zhang, Y. Jin, L. Wang, Detection of SARS-CoV-2 in saliva and

characterization of oral symptoms in COVID-19 patients, *Cell Proliferation*, **2020**, *53*, 12923. [Crossref], [Google Scholar], [Publisher]

[30] A. Pfützner, M. Lazzara, J. Jantz, Why do people with diabetes have a high risk for severe COVID-19 disease?—A dental hypothesis and possible prevention strategy, *Journal of Diabetes Science and Technology*, **2020**, *14*, 769-771. [Crossref], [Google Scholar], [Publisher]

How to cite this article: Behrang Rezvani Kakhki, Shadi Saghafi Khadem, Maryam Ziyaei, Morteza Talebi Doluee, Sadegh Ghalenoei, Hasan Hasani, Zahra Sadaghiani, Zahra Ghalenoee, Mahdi Foroughian, Examining the prevalence of COVID-19 patients with diabetes and the relationship between the two diseases in Ghaem Hospital, Mashhad. *Journal of Medicinal and Pharmaceutical Chemistry Research*, 2024, 6(9), 1360-1367. **Link:** https://jmpcr.samipubco.com/article_194412.html