Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

Covid-19 Infection is Associated with Diabetes Mellitus in The MASHAD Cohort Study

Maryam Saberi-Karimian[1,2], Hamideh Safarian-Bana[2], Sara Saffar[2], Hamideh Ghazizadeh[2], Ehsan Mousa Farkhani[3], Maryam Mohammadi Bajgiran[2], Alireza Pakar[2], Habibollah Esmaily [4], Ensieh Akbarpour Bahre [4], Gordon A. Ferns[5], Mohsen Mouhebati[6*], Majid Ghayour-Mobarhan[2,6*]

[1] Lung Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[2] International UNESCO Center for Health Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran.
[3] Deputy of Health, Mashhad University of Medical Sciences, Mashhad, Iran.
[4] Department of Biostatistics & Epidemiology, School of Health, Management & Social Determinants of Health Research Center, Mashhad University of Medical sciences, Mashhad, Iran.
[5] Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK.
[6] Cardiovascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLEINFO

Article type:
Original Article

Article history:
Received: 1 June 2021
Revised: 26 December 2021
Accepted: 10 October 2021

Keywords:
COVID-19
Cardiovascular disease
Risk factor

ABSTRACT

Introduction: Previous studies have suggested that diabetes mellitus and obesity are associated with an increased risk of severe complications with COVID. We aimed to investigate whether individuals with obesity and diabetes mellitus are more likely to be infected with COVID19.
Methods: The information related to COVID-19 was extracted from the Sina Health system information of Mashhad Health Deputy among participants in Mashhad cohort study (n=9704 people). Information regarding the cardiac risk factors of the individuals was previously recorded during the recruitment phase of the Mashhad cohort study. The relationship between COVID infection and several CVD risk factors was investigated.
Results: The results showed that obesity (P= 0.001) and diabetes mellitus (DM), (P= 0.01) were positively related to COVID-19. Furthermore, DM augmented the risk of COVID-19 by 1.79 folds (P-value= 0.004; OR: 1.79; CI:1.21-2.67).
Conclusions: The incidence of COVID-19 until 2020.07.19 was 2.36% in Mashhad Study Cohort population. Moreover, DM has increased the risk of COVID-19 by 1.79 folds in the population.

► *Saberi-Karimian, M., Safarian-Bana, H., Saffar, S., Ghazizadeh, H., Mousa Farkhanim, E., Mohammadi Bajgiran, M., Pakar, A., Esmaily, H., Akbarpour Bahre, E., Ferns, G.A., Mouhebati, M., Ghayour-Mobarhan, M. Covid-19 infection is associated with diabetes mellitus in The MASHAD cohort study. J Cardiothorac Med. 2022; 10(1): 913-918.*

* Corresponding author: Majid Ghayour-Mobarhan, International UNESCO center for Health Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran, 99199-91766, Tel: +985138002288, Fax: +985138002287, Email: ghayourm@mums.ac.ir .
Mohsen Mouhebati, Cardiovascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, 99199-91766, Tel: +985138002288, Fax: +985138002287, Email: mouhebatim@mums.ac.ir.

Introduction

In December 2019, acute respiratory syndrome has prevailed in Wuhan city, Hubei province, China, which almost became pandemic in the world according to WHO's a report (1, 2).This novel infectious disease caused by SARS-CoV-2 which is known as coronavirus-2 (1).

According to WHO's a report on 27 May 2020, the prevalence of COVID-19 and its deaths were: 85 815 cases and 2 308 deaths in Africa, 218 523 cases and 6 359 deaths in South-East Asia, 449 590 cases and 11 452 deaths in Eastern Mediterranean, especially 139 511 cases (7 508 deaths) in Iran. Also, the data has shown 2 061 828 cases and 176 226 deaths occur in Europe, especially 370 680 cases (3 968 deaths) in Russian Federation, 265 231 cases (37 048 deaths) in UK, 236 631 cases (29 035 deaths) in Spain and 230 555 cases (32 955 deaths) in Italy. This reports also shown 1 634 010 cases and 97 529 deaths in USA, and 374 898 cases and 23 473 deaths of COVID-19 in Brazil are recorded (3).

With global prevalence of 2019-nCoV, many patients have been detected with metabolic syndrome or cardiovascular disease and COVID-19 comorbidity (1, 3-5).

Recent investigations has recommended that people with old age and people with enduring health conditions, including cardiovascular disease (CVD), are at greater risk for morbidity and mortality caused by COVID-19 than the healthy population (2, 6). However, new study showed that COVID-19 can leads in heart injury, even in individuals without underlying heart disease (7)

In some cohort studies on outpatients and hospitalized patients with COVID-19 revealed that many of patients had underlying diseases including hypertension, diabetes mellitus (DM) and cardiovascular disease (8-13). In one of these studies in this field, meta-analysis of 8 studies in China on 46248 patients with COVID_19 showed that the most common underlying diseases in these patients were, respectively: high blood pressure, diabetes, cardiovascular disease, and finally pulmonary diseases (14).

Angiotensin-converting enzyme 2 (ACE2) is a functional receptor for coronaviruses family, including SARS-CoV and SARS-CoV-2. These investigations provide the clues about indirect association of ACE2 with cardiovascular pathology. ACE2 receptor is abundantly found in myocytes and bind with SARS-CoV-2 (6, 15). Patients with CVD might develop more severe kind of COVID-19, which may be related to increased secretion of ACE2 in these patients compared with healthy population (6). Also, Preceding studies have reported an association between cardiovascular metabolic diseases and SARS and MERS (16).

Dyslipidemia has long been recognized as one of the risk factors for CVD(17, 18). One study reported that the severe consequences of COVID-19 is more likely to happen in individuals with dyslipidemia (17).

Therefore, it seems that pre-existing cardiovascular disease is related to worse consequences and increased risk of death in patients with COVID-19, while COVID-19 itself can also cause arrhythmia, myocardial injury, acute coronary syndrome, venous thromboembolism and acute coronary syndrome (15).

In this study, we aim to determine prevalence of COVID-19 in Mashhad city, Khorasan province in Iran, and its relationship with cardiovascular risk factors.

Material and Methods

The participants in Mashhad cohort study (n=9704 people) had been examined for COVID-19 during the epidemic. Information related to the disease had been extracted from Sina Health system information of Mashhad Health Deputy.

The Covid-19 infection is confirmed by laboratory tests of all samples in Mashhad cohort study undertaken in the medical centers affiliated with Mashhad University of Medical Sciences. Information regarding the cardiac risk factors of the participants had been extracted from the records of patients in the second phase of the Mashhad cohort study. Finally, the incidence of this disease and its relationship with cardiovascular risk factors had investigated. It should be noted that cardiac risk factors included blood lipids, blood pressure, blood sugar and obesity.

The entire population of the Mashhad cohort study (which compromised about 10,000 men and women aged 35-65 years) included in the study. Patients whose confirmed quantitative PCR diagnostic test has been registered in the Sinai system are considered as Covid-19 patients and suspects are excluded from the study. For subjects

whose Covid-19 infection/non-infection information has not been registered in Sina system, the result of quantitative PCR detection test had been checked via phone by an expert colleague.

Statistical analysis

Data analysis is conducted using SPSS statistical software. Frequency tables and graphs as well as averages, medians and standard deviations are used for data description. Statistical analyses of the differences in the frequency of variables between patient and healthy groups are performed by Chi-square test. Using logistic regression, the association between cardiovascular risk factors and disease is determined by estimating the odds ratio (OR) at a 95% confidence interval and controlling the intervening variables. The statistical analysis is performed at a significant level of 0.05.

Results

According to the available data related to MASHAD cohort study among 6920 residents of Mashhad city, the second largest city in Iran, the prevalence of laboratory-confirmed COVID-19 until 2020.07.19 was 2.36% that 55.2% of them were women and 44.8% of them were men (Table 1). Moreover, obesity (P-value= 0.001) and DM (P-value= 0.01) was positively related to COVID-19 (Table 1).

Furthermore, after multivariate regression analysis the association between DM and COVID-19 remained significant, in a way that DM increased the risk of COVID-19 by 1.79 folds (CI 95%= 1.21-2.67, P-Value= 0.004), (Table 2).

Discussion

According to the available data related to MASHAD cohort study among 6920 residents of Mashhad city, the second largest city in Iran, the prevalence of laboratory-confirmed COVID-19 until 2020.07.19 was 2.36%. Moreover, our primary analysis revealed that obesity (BMI>30 kg/m2) and DM was positively associated with COVID-19. Furthermore, after multivariate regression analysis the association between DM and COVID-19 remained significant, in a way that DM increased the risk of COVID-19 by 1.79 folds.

Most of the studies in this context are retrospective and about the risk factors of COVID-19 outcomes including intensive care unit admission (ICU), mechanical ventilation and death. In one of the earliest studies published in February 2020 on 41 hospital admitted patients, comorbidities including DM, HTN and CVD were not associated with to ICU admission among hospitalized patients while increase systolic blood pressure was significantly associated with ICU admission (19). In another study in China on 1099 patients confirmed for COVID-19 by real-time PCR test form 552 hospitals, the presence of any comorbidities was more common among patients with severe disease and more probability of ICU admission, mechanical ventilation and death (20). Another retrospective study in China on 137 discharged and 54 died laboratory-confirmed patients, respectively death due to COVID-19 was associated with CVD, HTN and DM but it was associated with systolic blood pressure (1). Moreover, a nationwide analysis in China on 1590 laboratory-confirmed hospitalized patients, after adjustment for age and sex, DM and HTN were the risk factors of ICU admission, mechanical ventilation and death due to COVID-19 (21). Furthermore, A meta-analysis on seven Chinese studies was confirmed that HTN, DM and CVD were the most prevalent comorbidities among hospitalized laboratory-confirmed COVID-19 patients, in a way that CVD and HTN increased the risk the severity of COVID-19 by 2.46 and 3.42 folds compare non-severe patients (22). While the most prevalent comorbidities in 5700 hospitalized patient due to COVID-19 were HTN, Obesity and DM in New York City area (23). Also in single center retrospective study in Iran DM is the most prevalent comorbidity among 2968 hospitalized patients due to COVID-19 (24).

Only one prospective study was available investigating the associations between preexisting diagnoses and hospitalized COVID-19 with or without mortality. This cohort study on UK Biobank among 502,506 community volunteers at baseline (2006-2010) revealed that diabetes and HTN respectively associated with the risk of COVID-19 by 1.73 and 1.38 folds (25). Although the findings of these cohort study

was comparable to our findings on the relation between COVID-19 and DM but unlike our study they excluded non-inpatients and only included COVID-19 positive inpatients in their analysis.

Furthermore, a simple comparison indicated that , the prevalence of diabetes between patients infected with COVID-19 and general population in both China and Italy were the same (26) which is in contrast with finding from our prospective study. This similarity of DM prevalence between patients infected with COVID-19 and general population may due to underreporting of DM in general population.

Several mechanisms could be suggested in relation with DM and higher susceptibility to COVID-19 infection. DM as an inflammatory condition could affect the body response to pathogens due to several metabolic and vascular disorders (27). Insulin resistance and hyperglycemia as two dominant phenomena in DM that could affect tissue inflammation by increasing the production of glycosylation end products, cytokines and oxidative stress which increase adhesion molecules (27, 28).

Table 1: Summary demographics for subjects with COVID-19 in MASHAD study population

Variables		Cov + (163)	Cov – (6757)	P value
Age (year)(Mean±SD)		49.0±8.0	48.1±7.6	0.140
Gender; n(%)	*Female*	85(55.2%)	3653(57.2%)	0.620
	Male	69(44.8%)	2732(42.8%)	
Marriage status; n(%)	*Single/divorced/widow*	6(3.9%)	373(5.8%)	0.310
	Married	148(96.1%)	6016(94.2%)	
Physical activity level		1.6±0.3	1.6±0.3	0.180
Smoking status n(%)	*Non smoker*	105(68.2%)	4431(69.4%)	0.880
	Ex – smoker	17(11.0%)	629(9.8%)	
	Current smoker	32(20.8%)	1327(20.8%)	
Blood group type n (%)	*A*	33(27.5%)	1380(29.2%)	0.810
	B	33(27.5%)	1316(27.9%)	
	AB	13(10.8%)	397(8.4%)	
	O	41(34.2%)	1626(34.5%)	
Hypertention; n(%)		52(33.8%)	1949(30.9%)	0.440
Metabolic syndrome; n(%)		66(42.9%)	2416(37.9%)	0.200
Diabetes mellitus; n(%)		34(22.4%)	819(13.1%)	0.001
Obesity (BMI > 30 kg/m2); n(%)		60(39.0%)	1906(29.9%)	0.010
Dyslipidemia; n%		136(88.3%)	5444(85.7%)	0.350
Systolic blood pressure (mmHg)		123.0 ±18.8	121.4±17.7	0.420
Diastolic blood pressure (mmHg)		79.7±10.3	79.1±10.9	0.820
Fasting blood glucose (mg/dl)		102.3±53.1	91.4±36.8	0.130
Cholesterol (mg/dl)		190.3±37.9	191.2±38.6	0.660
Triglyceride (mg/dl)		125.5(90.8-192.3)	121.0(85.0-171.0)	0.070
LDL-C (mg/dl)		114.4±33.7	116.6±35.3	0.510
HDL-C (mg/dl)		41.3±9.2	42.8±9.9	0.060
Hs-CRP (mg/l)		1.5(0.9-3.8)	1.6(0.9-3.4)	0.640
Hematologic parameters	**WBC**	6.1±1.4	6.0±1.5	0.390
	RBC 106/M	4.9±0.5	4.9±0.5	0.150
	HGB (g/dL)	13.8±1.5	13.8±1.6	0.660
	HCT %	41.6±3.5	41.4±3.9	0.540
	MCV (fl)	84.4±5.3	84.8±6.0	0.110
	MCH (pg)	28.1±2.4	28.4±2.7	0.250
	MCHC (g/dL)	33.2±1.7	33.3±1.7	0.730
	RDW-CV (%)	13.9±1.2	13.8±2.3	0.100
	PLT (103 /UL)	227.3±61.4	230.3±60.4	0.610
	PDW (fl)	41.8±3.4	41.6±3.2	0.360
	MPV (fl)	10.1±0.9	10.1±1.9	0.730

Table 2: Association between CVD risk factors and COVID-19 in MASHAD study population

Variables		Odds ratio	0.95.CI for odds ratio	P-value
Diabetes mellitus		1.79	1.21-2.67	0.004
BMI (mg/kg2)	**≤ 24.99**	Ref.	Ref.	Ref.
	25-29.99	0.92	0.60-1.40	0.69
	≥ 30	1.29	0.84-1.98	0.24
Triglyceride (mg/dl)		1.00	1.000-1.003	0.10
HDL-C (mg/dl)		0.99	0.97-1.01	0.17

Also some abnormalities in immune system has been proposed to be associated with hyperglycemia including, inhibited response of lymphocytes to proliferation (29), failure in monocyte/macrophage and neutrophil functions (27), defect in type 4 hypersensitivity reaction (30) and impaired complement activation (31). Furthermore, previous studies has been indicated that hyperglycemia could facilitate viral replication (32). Moreover, structural and functional lung changes due to hyperglycemia may responsible for higher propensity to lung infections including COVID-19 (33, 34).

Conclusions

The prevalence of COVID-19 until 2020.07.19 was 2.36% in Mashhad Study Cohort population. Besides, DM has increased the risk of COVID-19 by 1.79 folds in the population.

Conflict of Interest

The authors confirm no conflict of interest.

Funding

This study has been supported financially by Mashhad University of Medical Sciences (ID: 990172).

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020.
2. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM ,Masoumi A, et al. COVID-19 and Cardiovascular Disease. Circulation. 2020;141(20):1648-55.
3. Organization WH. Coronavirus disease (COVID-19), Situation Report–115, Data as received by WHO from national authorities by 10: 00 CEST, 14 May 2020.
4. Wang D ,Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
5. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. Journal of the American College of Cardiology. 2020;75(18):2352-71.
6. Paramasivam A, Priyadharsini JV, Raghunandhakumar S, Elumalai P. A novel COVID-19 and its effects on cardiovascular disease. Hypertension Research. 2020:1-2.
7. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA cardiology. 2020.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet. 2020;395(10223):507-13.
9. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. International Journal of Infectious Diseases. 2020;91:264-6.
10. Yang J, Feng Y, Yuan M, Yuan S, Fu H, Wu B, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabetic medicine. 2006;23(6):623-8.
11. Yu C, Wong RS, Wu E, Kong S, Wong J, Yip GW, et al. Cardiovascular complications of severe acute respiratory syndrome. Postgraduate medical journal. 2006;82(964):140-4.
12. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. International Journal of Infectious Diseases. 2016;49:129-33.
13. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708-20.
14. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a

systematic review and meta-analysis. International Journal of Infectious Diseases. 2020.
15. Nishiga M, Wang DW, Han Y, Lewis DB ,Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nature Reviews Cardiology. 2020:1-16.
16. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical Research in Cardiology. 2020;109(5):531-8.
17. Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020.
18. Hedayatnia M, Asadi Z, Zare-Feyzabadi R, Yaghooti-Khorasani M, Ghazizadeh H, Ghaffarian-Zirak R, et al. Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids in Health and Disease. 2020;19(1):1-11.
19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al .Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
20. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020.
21. Guan W-j, Liang W-h, Zhao Y, Liang H-r, Chen Z-s, Li Y-m, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European Respiratory Journal. 2020;55(5).
22. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. International Journal of Infectious Diseases. 2020;94:91-5.
23. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area .Jama. 2020.
24. Nikpouraghdam M, Farahani AJ, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. Journal of Clinical Virology. 2020.
25. Atkins JL, Masoli JA, Delgado J, Pilling LC, Kuo C-L, Kuchel GA, et al. Preexisting Comorbidities Predicting COVID-19 and Mortality in the UK Biobank Community Cohort. The Journals of Gerontology: Series A. 2020.
26. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes research and clinical practice. 2020:108142.
27. Knapp S. Diabetes and infection: Is there a link?-A mini-review. Gerontology. 2013;59(2):99-104.
28. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Canadian Journal of Cardiology. 2018;34(5):575-84.
29. Moutschen M, Scheen A, Lefebvre P. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete & metabolisme. 1992;18(3):187.
30. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunology & Medical Microbiology. 1999;26(3-4):259-65.
31. Ilyas R, Wallis R, Soilleux EJ, Townsend P, Zehnder D, Tan BK, et al. High glucose disrupts oligosaccharide recognition function via competitive inhibition: a potential mechanism for immune dysregulation in diabetes mellitus. Immunobiology. 2011;216(1-2):126-31.
32. Kohio HP, Adamson AL. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. Virology. 2013;444(1-2):301-9.
33. Lange P, Groth S, Kastrup J, Mortensen J , Appleyard M, Nyboe J, et al. Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. European Respiratory Journal. 1989;2(1):14-9.
34. Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. European Respiratory Journal. 1997;10(8):1850-8.