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ORIGINAL ARTICLE

The gender differences as a risk factor in diabetic patients with COVID-19

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ABSTRACT

Background and Objectives: In a Turkish cohort study, we revealed first time in literature the gender differences in admission to hospital and rates of mortality for diabetic patients with COVID-19.

Materials and Methods: The demographics, length of stay, mortality rates and concomitant chronic metabolic diseases of 152 patients diagnosed with COVID-19 were found in our hospital electronic document system (Probel) and recorded in excel files for further statistical analysis.

Results: In the mortality group (n:22), the numbers of men and women were 9 (40.9%) and 4 (18.2%), respectively. Comparing gender rates in diabetic group, the mortality risk of diabetic men was higher and statistically significant (p<0.05, Pearson Chi-square value:7.246).

Conclusion: We hope that the findings of this research will give scientists an idea of gender differences in viral pandemics for further studies.

Keywords: COVID-19; Diabetes mellitus type 2; Sex factors

INTRODUCTION

For the first time, towards the end of 2019, acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China. It reached many countries within months and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. As an important part of the effort for patients with COVID-19, we should provide care to the diabetic patients in time and in place as soon as possible despite the disadvantages of the conditions. Because of the high prevalence of diabetic patients with COVID-19, for anyone during the pandemic, the being diabetic was recognized as a determinant of severity and mortality (1). For the virus, the entrance might be easy in patients with diabetes mellitus (DM) due to certain reasons including the inhibition of lymphocyte proliferative response to virus, impaired monocyte, macrophage and neutrophil functions, or complement activation dysfunctions (2, 3). Influenza-associated mortality rates in older patients with diabetes after pneumonia currently are over mortality rates from both cardiovascular disease and cancer (4). As like in other infections, COVID-19 is also related to an increase in the blood level of glucocorticoids and catecholamines, leading to blood glucose fluctuation (5).

Not only hyperglycemia but also from a retrospective study from Wuhan, we know that diabetic patients with COVID-19 also have a possibility for hypoglycemia (6). After a hypoglycemic event, the mobilization of pro-inflammatory monocytes beside an increase in platelet reactivity may cause subjects to have a risk of cardiovascular mortality (7). Patients with diabetes mellitus due to the underlying mechanism from the inflammatory state are likely to have COVID-19 (8). During hyperglycemia, influenza can replicate quickly *in vitro*, which was shown in a study, and the study indicates it might be seen

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as the same pattern *in vivo* (9). As we know, being diabetic is associated with endothelial dysfunction and a tendency to platelet aggregation and activation. These abnormalities favor the possibility of of developing a hypercoagulable pro-thrombotic state in a patient with DM concomitant with COVID-19, which enhance the pathology easily (10). Diabetics also should be evaluated with their medications by physicians because medications could be inappropriate when they are used during the pandemic. It might worsen the pathophysiological mechanism of COVID-19. For example, pioglitazone was proven to increase the ACE2 expression in liver tissues, and it was proposed to avoid in patients with COVID-19 (11). But pandemic's relation to anti-diabetic drugs has not been fully understood yet.

In the present study, we aimed at revealing that whether demographics and the type of chronic diseases make any differences in mortality rates and length of stay in the patients with COVID-19.

MATERIALS AND METHODS

Between the dates of 01.03.2020 and 30.04.2020, the length of stay, mortality rates, and concomitant chronic metabolic diseases of patients from a city (Izmir) in Turkey with demographics were found in a hospital electronic document system (Probel) and recorded in excel files. The study was approved by the Bozyaka Training and Research Hospital Ethics Committee (Date:21.05.2020, Number:15345988-193-2020).

Statistical analysis. All statistical analyses of the frequency rates, percentages, proportions, means, correlations and standard deviations were performed using IBM SPSS Statistics v26. In the continuous variables that were normally distributed, independent T-tests were used for the comparison of means. Proportions for categorical variables were compared using the $\chi 2$ test, and a two-sided P-value less than 0.05 was considered statistically significant.

RESULTS

Patients. A total of 152 patients charged in the hospital diagnosed with Covid-19 from 01.03.2020 to 30.04.2020 were compared by age, gender, and length of the stay, mortality and chronic diseases. The gender distribution was equal, and 76 for both men and women. The average age was 56.11 (SD:18.78, between 18-96). The numbers of patients with chronic diseases including DM, hypertension (HT), chronic hearth diseases (CHF), chronic obstructive pulmonary diseases (COPD), cerebrovascular diseases (CVD), dementia, chronic renal failure (CKF), cancer and asthma were 49 (32.2%), 45 (29.6%), 23 (23%), 9 (5.9%), 5 (3.3%), 12 (7.9%), 2 (1.3%), 4 (2.6%) and 4 (2.6%), respectively (Table 1).

The mortality rates and COVID-19. The mortality rate for all patients was 14.5% (n=22) and for chronic diseases its rates among all patients were as follows: 8.6% (n=13, DM), 8.6% (n=13, HT), 1.3% (n=2, COPD), 3.9% (n=6, CHF), 1.3% (n=2, CVD), 4.6% (n=7, Dementia), 0.7% (n=1, CKF), 1.3% (n=2, Cancer) and 0.7% (n=1, Asthma) (Table 1). The chi-square test was used to compare the diseases versus the fatal cases, and the comparisons indicated that the rates of mortality were significantly higher in patients with DM, HT, and dementia than the rest of diseases for both gender. Just in patients with DM, the rate of mortality was significantly different in gender, and the diabetic men (n=9, 40.9%) were found to have higher rates of mortality than women (n=4, 18.2%) (Pearson Chi-square: 7.246, p:0.001). The numbers of diabetic women and men were 13 (17.1%) and 36 (47.4%), respectively, in this study ($p<0.05$). In the mortality group (n=22), the numbers of diabetic men and women were 9 (40.9%) and 4 (18.2%), respectively ($p<0.05$, Pearson Chi-square value:7.246). But the number of non-diabetic men and women were 5 (22.7%) and 4 (18.1%), respectively ($p>0.05$).

The length of stay and COVID-19. While the mean of length of the stay for all subjects was 8.39 (SD:18.78), the means for HT, DM, COPD, asthma, CKF, cancer, CHF, CVD and dementia in days were 8.27 (SD:11.41), 8.43 (SD:11.71), 9.22 (SD:7.3), 8.33 (SD:5.85), 38 (SD:48.08), 4.5 (SD:5.74), 7.3 (SD:5.89), 23.6 (SD:28.11) and 9.58 (SD:9.28), respectively (Table 1). The length of stay at hospital for fatal cases and survivors was 10.55 (SD:15.81) and 8.02 (SD:8.02), respectively. For men and women, the length of stay was 8.53 (SD:10.21) and 8.25 (SD:8.29). We compared the chronic diseases with the length of stay in one-way ANOVA and found that it was significantly higher in patients with CVD, Dementia and CKD ($p<0.05$).

Table 1. The mortality rates and the length of stay in chronic diseases of the patients diagnosed with COVID-19.

Diseases	The numbers of patients (%)	Length of stay (mean,days ± SD)	The number of fatal cases (%)
Diabetes Mellitus	49 (32.2%)	8.43 ± 11.71	13 (8.6%)
Hypertension	45 (29.6%)	8.27 ± 11.41	13 (8.6%)
COPD*	9 (5.9%)	9.22 ± 7.3	2 (1.3%)
Chronic hearth diseases	23 (23%)	7.3 ± 5.89	6 (3.9%)
Chronic renal failure	2 (1.3%)	38 ± 48.08	1 (0.7%)
Cancer	4 (2.6%)	4.5 ± 5.74	2 (1.3%)
Cerebrovascular diseases	5 (3.3%)	23.6 ± 28.11	2 (1.3%)
Dementia	12 (7.9%)	9.58 ± 9.28	7 (4.6%)
Asthma	4 (2.6%)	8.33 ± 5.85	1 (0.7%)
All	152	8.39 ± 18.78	22

*COPD: Chronic obstructive pulmonary diseases.

DISCUSSION

The glucose regulation in diabetics is important for patients with COVID-19 as well as for those without the disease. As a result of suppressed innate and humoral immune functions in DM, the risk of morbidity and mortality during acute infections increases. Diabetes was recorded as an independent risk factor for morbidity and mortality during the 2002-2003 outbreak of SARS-CoV-1 (12). During the 2012 outbreak, the mortality rate in patients with MERS who had diabetes was 35% (13). As shown in other studies that COVID-19 is common in patients with DM, HT, and CVD, from the ten studies with 2209 subjects, and also the prevalence of HT, DM and CVD was as follows: 21%, 11% and 7%, respectively (14). Similarly, in a meta-analysis with a total of 46,248 patients, the same diseases were reported as 17%, 8% and 5%, respectively (15).

People are confined at home in many places due to lockdowns and they now lack in physical activities and social mobility. Moreover, a stressful life during pandemic leads to mental diseases, which result in alterations in the dietary intake to some extent. All in one cause, diabetic people to be predisposed to related problems, including infections, ketoacidosis, or coronary diseases. In the presented study among patients with COVID-19 that charged in hospital, the percentages of DM, HT and CVD were 32.2%, 29.6% and 23%, respectively. The percentages of diabetic patients died from infection were 8.6% (n=13) in all groups and 59.09% in the mortality group. Almost the same percentages (65%) were reported in a UK cohort with 95 cases, and diabetes was found to be significantly more common in those who died (16). But the gender differences in mortality rates of patients with DM is not well documented in the literature of COVID-19 studies. With this presented study, we revealed that diabetic men were at a higher risk of mortality (men 40.9% and women 18.2%; $p<0.05$, Pearson Chi-square value:7.246) and the rates of admission (women 17.1% versus men 47.4%) were higher for them from COVID-19 than women compared to other diseases. These findings could be valuable to shed on light for the further studies to understand why the COVID-19 is fatal for men rather than women. Several studies try to explain the gender differences among patients with COVID-19, but it is still unclear why the men are more at risk of infection and mortality (17, 18). Variabilities of innate immunity, steroid hormones and factors related to sex chromosomes make men to be more susceptible to viral infections (19, 20). The higher levels of antibodies were found in women's circulation, and these antibodies live longer in women than men (20). It is mostly accepted that little or no sex bias plays a role in either Type I or Type II diabetes mellitus (21).

One of the limitations of this study is that the results are not for the universe since it was studied with small samples and also the variations among populations such as races, occupations, nutrition could change the results. We did not ask patients the type of drugs and the duration of using them during the study, which also could change the results of, especially diabetic groups.

As the glucose regulation is essential for all diabet-

ic patients with COVID-19 infection, during the pandemic, the men should be aware of their higher risk level of mortality compared to women. Telemedicine could be a solution for diabetic patients in present times with limited access to healthcare facilities. We hope that the present study would be a reference for the next extensive and long-run studies on the gender differences of patients with COVID-19.

REFERENCES

1. Moutschen MP, Scheen AJ, Lefebvre PJ. 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 Metab* 1992;18:187-201.
2. Knapp S. Diabetes and infection: is there a link?--A mini-review. *Gerontology* 2013;59:99-104.
3. 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* 2010;216:126-131.
4. Li L, Liu Y, Wu P, Peng Z, Wang X, Chen T, et al. Influenza-associated excess respiratory mortality in China, 2010-15: a population-based study. *Lancet Public Health* 2019; 4(9):e473-e481.
5. Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. *Diabetes Res Clin Pract* 2020;162:108118.
6. Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. *Metab Clin Exp* 2020; 107:154216.
7. Iqbal A, Prince LR, Novodvorsky P, Bernjak A, Thomas MR, Birch L, et al. Effect of hypoglycemia on inflammatory responses and the response to low-dose endotoxemia in humans. *J Clin Endocrinol Metab* 2019;104:1187-1199.
8. Mozafari N, Azadi S, Mehdi-Alamdarlou S, Ashrafi H, Azadi A. Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. *Med Hypotheses* 2020;143:110111.
9. Kohio HP, Adamson AL. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. *Virology* 2013;444:301-309.
10. Dunn EJ, Grant PJ. Type 2 diabetes: an atherothrombotic syndrome. *Curr Mol Med* 2005;5:323-332.
11. Zhang W, Xu YZ, Liu B, Wu R, Yang YY, Xiao XQ, et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *ScientificWorldJournal* 2014;2014:603409.
12. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006;23:623-628.
13. Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, et al. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. *Clin Infect Dis* 2014;59:160-165.
14. Singh AK, Gupta R, Misra A. Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. *Diabetes Metab Syndr* 2020;14:283-287.
15. 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. *Int J Infect Dis* 2020;94:91-95.
16. Tomlins J, Hamilton F, Gunning S, Sheehy C, Moran E, MacGowan A. Clinical features of 95 sequential hospitalised patients with novel coronavirus 2019 disease (COVID-19), the first UK cohort. *J Infect* 2020;81: e59-e61.
17. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020;41:145-151.
18. The Lancet. The gendered dimensions of COVID-19. *Lancet* 2020;395: 1168.
19. Taneja V. Sex hormones determine immune response. *Front Immunol* 2018;9:1931.
20. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J Biol Regul Homeost Agents* 2020;34:339-343.
21. Gale EA, Gillespie KM. Diabetes and gender. *Diabetologia* 2001;44:3-15.