Characteristics of influenza in elderly patients with and without diabetes, hospitalized for severe acute respiratory infection in a tertiary care hospital from Bucharest Romania – a three-year prospective epidemiological surveillance study

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Abstract

Introduction Patients with diabetes may be at a higher risk of developing complicated influenza. We report the characteristics of influenza in hospitalized elderly patients with and without diabetes, in three consecutive influenza seasons.

Methods The study included patients admitted for severe acute respiratory infection (SARI) in the National Institute for Infectious Diseases “Prof. Dr. Matei Balș”, Bucharest, during a three-year active epidemiological surveillance study (2015/16, 2016/17, 2017/18), in the I-MOVE+ hospital network.

Results A total of 349 patients were tested by PCR over the duration of the study. The percentage of patients with diabetes was comparable throughout the seasons: 34.7%, 28.3% and 30.4% ($p=0.587$). Influenza A was the main viral type circulating in 2015/16 and 2016/17 (100% and 97.6%) in our study population, while in 2017/18, B viruses predominated (90.0%). Diabetics presented a higher median number of comorbidities (3 vs. 2) $p<0.001$, and two-fold higher odds of also associating obesity ($OR=2.1$, 95%CI:1.3-3.4, $p=0.003$), compared to those without diabetes. Diabetics also tested positive for influenza more often ($p=0.296$). Only 6 patients with diabetes (5.4%) from our study had been vaccinated against influenza, and most ($n=4$) of those who had been vaccinated tested negative for influenza.

Conclusions Our study is the first to describe the circulation of influenza viral types in elderly diabetic patients hospitalized for SARI. The results reinforce the national and international recommendation to vaccinate against influenza all patients with diabetes.

Keywords Influenza, elderly patients, viral types, diabetes, comorbidities.

Introduction

Patients with diabetes may be at a higher risk of developing complicated influenza, and at least three mechanisms have been clearly described,

specifically: 1) glycemic fluctuations, either inherent to diabetes or induced by influenza, may lead to pulmonary endothelial dysfunction which in turn may be responsible for a severe form of

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disease through impaired respiratory function;¹ 2) elevated glucose levels in pulmonary fluids may favor *in situ* viral and/or bacterial multiplication;¹ and 3) impaired neutrophil activation occurring during prolonged periods of uncontrolled hyperglycemic status may increase the risk of bacterial superinfection following influenza, particularly with *Streptococcus pneumoniae*, but also with *Staphylococcus aureus* or *Haemophilus influenzae*.^{1,3}

Diabetes is one of the main chronic conditions that warrant yearly vaccination against influenza. However, vaccine coverage rates are still not as high as needed in order to prevent influenza-related significant morbidity in this patient category.⁴

Our current study's aim was to assess the characteristics of influenza in hospitalized elderly patients with and without diabetes, in order to identify clinical or epidemiological particularities specific to this patient population.

Methods

The National Institute for Infectious Diseases “Prof. Dr. Matei Balș”, Bucharest, Romania is a tertiary care hospital specialized in infectious

diseases, with wide addressability for patients from the Bucharest-Ilfov county, and from a regional and national level in Romania.

We present the results of a three-year prospective epidemiological surveillance study of the characteristics of influenza in elderly patients with and without diabetes hospitalized for severe acute respiratory infection (SARI) in the institute during three consecutive influenza seasons (2015/16, 2016/17, and 2017/18), as part of the I-MOVE+ hospital network.^{5,6}

The study consisted of systematic screening of all patients aged 65 and older admitted to our hospital and meeting the following SARI case definition:⁷

- at least one of the following general signs or symptoms: fever or feverishness, malaise, headache, myalgia, altered clinical state (asthenia, anorexia, confusion, weight loss) PLUS
- at least one of the following respiratory signs or symptoms: cough, odynophagia, dyspnea.⁷

A medical questionnaire was filled out by the medical team for each patient, collecting information on the presence of any of the following comorbid conditions: diabetes (confirmed based on medical documents), cardiovascular disease, obesity (defined as body mass index ≥ 30 kg/m²), chronic pulmonary disease, chronic liver disease, chronic kidney disease, hematologic cancer, non-hematologic cancer, rheumatologic disease, immune suppression. Information was collected from interviews with patients (or their relatives) and hospital or general practitioner documents. Respiratory specimens were collected from each patient and submitted for real time reverse transcription polymerase chain reaction (RT-PCR) at the Cantacuzino Military-Medical Research-Development National Institute, Bucharest, Romania to test for the presence of influenza viruses A or B in all cases, and to perform virus typing and lineage determination, in a subset of cases. The kits used for the PCR were SuperScript® One-Step qRT-PCR System (Invitrogen, Carlsbad, CA, USA).

The study protocol was approved by the Ethics Committee of the Cantacuzino Military-Medical

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Statistical analysis was performed with IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY, USA), and included the Chi-squared test along with risk calculation for categorical variables and Mann-Whitney's U test for continuous non-parametric variables. Logistic regression was also performed and its results are presented, together with the adjusted odds ratios (aOR). All tests were two-tailed and p values <0.05 were considered statistically significant.

Results

The study included 349 patients in the three influenza seasons (191 in 2015/16, 53 in 2016/17, and 105 in 2017/18). Four of these patients were excluded from the current analysis due to missing data regarding diabetes, leaving a total number of 345 analyzed for the purpose of the current study.

We identified the following circulation of influenza viral types in the study timespan: in the first two seasons (2015/16 and 2016/17) influenza A predominated (100% and 97.6%), while in the third season (2017/18) B viruses predominated (90.0%).

The percentage of patients with diabetes was comparable throughout the seasons: 66 patients (34.7%) in 2015/16, 15 patients (28.3%) in 2016/17 and 31 patients (30.4%) in 2017/18 ($p=0.587$). The two groups of patients (with and without diabetes) did not differ significantly in terms of baseline characteristics such as gender (45.5% vs. 43.3%, $p=0.729$) or age (median age of 73 vs. 74 years, $p=0.083$).

However, the median number of chronic diseases was significantly higher (3 vs. 2) in diabetics ($r=-0.5$, $U=4822$, $p<0.001$), and we found that particular types of comorbidities were significantly more frequent among patients who also had diabetes. Specifically, diabetics admitted to the hospital with SARI had almost two-fold higher unadjusted odds to also have cardiovascular disease (84.8% vs. 74.9%, $p=0.038$), chronic kidney disease (19.8% vs. 10.8%, $p=0.029$), and to present obesity (38.7% vs. 23.2%, $p=0.003$). Obesity was the only

variable that retained significance in multivariate regression analysis adjusting for the presence of other comorbidities in patients with diabetes ($\chi^2(9)=18.193$, $p=0.033$) – Table 1.

The impact of influenza appeared to be higher in patients with diabetes, compared to those without diabetes. Specifically, patients with diabetes tested positive for influenza more often 47.3% vs. 40.8% ($p=0.296$), and had slightly higher case fatality (3.6% vs. 1.7%, $p=0.281$) compared to patients without diabetes, but these results did not meet the criteria for statistical significance.

Only 6 patients with diabetes (5.4%) had been vaccinated against influenza, and most of those vaccinated ($n=4$) also tested negative for influenza.

A logistic regression was performed to ascertain the effect of each ILI criterion on the likelihood that patients with diabetes have laboratory-confirmed influenza. The logistic regression model was statistically significant, $\chi^2(7)=17.673$, $p=0.014$. It explained 19.5% (Nagelkerke R^2) of the variance in influenza and correctly classified 65.2% of cases. Patients with diabetes displaying fever were 7.5 times (95%CI: 1.2-48.7) more likely to have laboratory-confirmed influenza than afebrile patients. The same was true for diabetic patients displaying dyspnea (aOR=2.6, 95%CI: 1.1-6.4) and an inverse relation was found with malaise (aOR=0.07, 95%CI: 0.007-0.729).

Discussion

Our study has illustrated the frequency and clinical impact of influenza in elderly patients with diabetes, who cumulated a large number of risk factors putting them at risk for severe disease. In our study, this patient category also associated a higher number of chronic diseases that can be easily decompensated during influenza, and presented an overall higher case fatality during their hospitalization for SARI. Higher influenza-related mortality in patients with diabetes has also been reported in other studies,⁸ with a population-attributable risk percentage of 22.09% for mortality related to influenza and pneumonia in

Table 1. Characteristics of patients with and without diabetes included in the study

Characteristics	Patients without diabetes (n=233)	Patients with diabetes (n=112)	Overall (n=345)	Unadjusted statistical analysis	Logistic regression adjusting for presence of comorbidities
Male gender, n (%)	101 (43.3%)	51 (45.5%)	152 (44.1%)	p=0.729	N/A
Age, median (IQR)	74 (68, 82)	73 (67, 79)	74 (68, 80)	p=0.083	N/A
Cardiovascular disease, n (%)*	173 (74.9%)	95 (84.8%)	268 (78.1%)	OR=1.9, 95%CI: 1.03-3.4, p=0.038	p=0.066
Obesity, n (%)**	54 (23.2%)	43 (38.7%)	97 (28.2%)	OR=2.1, 95%CI: 1.3-3.4, p=0.003	aOR=2.2, 95%CI: 1.3-3.6, p=0.003
Chronic pulmonary disease, n (%)	51 (21.9%)	27 (24.1%)	78 (22.6%)	p=0.681	p=0.939
Chronic liver disease, n (%)	14 (6.0%)	7 (6.2%)	21 (6.1%)	p=1.000	p=0.528
Chronic kidney disease, n (%)*	25 (10.8%)	22 (19.8%)	47 (13.7%)	OR=2.1, 95%CI: 1.1-3.8, p=0.029	p=0.063
Hematologic cancer, n (%)	7 (3.0%)	2 (1.8%)	9 (2.6%)	p=0.724	p=0.847
Non-hematologic cancer, n (%)	21 (9.0%)	9 (8.0%)	30 (8.7%)	p=0.841	p=0.781
Rheumatologic disease, n (%)***	33 (14.3%)	15 (13.5%)	48 (14.0%)	p=1.000	p=0.823
Immune suppression, n (%)	6 (2.6%)	3 (2.7%)	9 (2.6%)	p=1.000	p=0.914
Testing positive for influenza, n (%)	95 (40.8%)	53 (47.3%)	148 (42.9%)	p=0.296	N/A
Influenza A, n (%)	59 (62.1%)	33 (62.3%)	92 (62.2%)	p=1.000	N/A
Influenza B, n (%)	36 (37.9%)	20 (37.7%)	56 (37.8%)		
Death during hospitalization, n (%)	4 (1.7%)	4 (3.6%)	8 (2.3%)	p=0.281	N/A

The table presents the results of the Chi square test for categorical variables, with unadjusted odds ratios, and the results of the Mann-Whitney U test for non-parametric continuous variables, as well as the results of logistic regression after adjusting for the presence of comorbidities.

*Missing data for 2 patients. **Missing data for 1 patient. ***Missing data for 3 patients.

aOR – adjusted odds ratio; IQR – interquartile range; OR – unadjusted odds ratio; 95%CI – 95% confidence interval.

patients with diabetes, compared to those without diabetes.⁹ Vaccination is the only effective means to prevent hospital admission for influenza or influenza-associated decompensation of underlying conditions, and to decrease all-cause mortality in patients with type 2 diabetes mellitus.¹⁰

The percentage of patients with diabetes in our study (32.5%) was almost three-fold-higher compared to that reported for the general Romanian population (11.6%) in the PREDATORR study.¹¹ This may be in part be

associated with the fact that our study has specifically looked at elderly patients, and the prevalence of diabetes increases significantly with age. However, the prevalence of diabetes in the age group 60-79 years old in the PREDATORR study was reported at 22%,¹¹ suggesting that there is a true predisposition for patients with diabetes to require hospitalization for SARI at a higher rate compared to the general population.

International recommendations state that all patients with diabetes should be vaccinated against influenza on a yearly basis, and national

vaccination policies are in place in Romania ensuring the availability of inactivated influenza vaccines distributed by the Ministry of Health, through general practitioners, to patients with comorbidities, diabetes included. However, in our study only 6 patients among those with diabetes had been vaccinated against influenza, amounting to a vaccine coverage rate of 5.4%. While this rate might be somewhat higher in the general population of patients with diabetes, since those vaccinated will have a lower risk of being admitted to an infectious diseases hospital for influenza-related SARI,¹⁰ it is still worrisomely low. Our study's results strongly reinforce the recommendation to vaccinate against influenza all patients with diabetes, and specific interventions can be developed to increase their access to vaccination. For example, a recent study by Shin et al. has looked at factors influencing influenza vaccine uptake in diabetic patients, and has found a positive association between recent health check-ups and vaccination,¹² which suggests that any type of engagement with the healthcare system, including regular diabetologist consults, should be used as an opportunity to inform about influenza vaccination and to ideally implement on site vaccination, where feasible.

Our study is the first to present data on influenza in patients with diabetes in Romania. However, the present study also has some limitations, specifically the fact that there was a very high prevalence of other comorbidities in patients with and without diabetes included in the study. Therefore, the underlying diseases could also have acted as potential confounding factors, not allowing an exact quantification of the specific effect of diabetes on the presentation, course and outcome of influenza in this patient population.

Conclusions

Elderly patients with diabetes admitted to the hospital with SARI had two-fold higher odds of associating cardiovascular disease, chronic kidney disease and obesity, compared to patients without diabetes, leading to a cumulus of risk factors for severe influenza. Diabetics also tested positive for influenza more often, and had a slightly higher case fatality, while the vaccine coverage was extremely low, at 5.4%, warranting local and

national initiatives to increase vaccine uptake in this particular patient population.

Authors' contributions statement: All authors had equal contributions.

Conflicts of interest:

DP: Technical project manager for the GIHSN project funded by Sanofi Pasteur and Foundation for Influenza Epidemiology. Principal investigator of the I-MOVE+ study funded through the European Union's HORIZON 2020 research and innovation programme. Technical project manager for the DRIVE study, that has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking (DRIVE, grant n° 777363). No conflict of interest.

MN: Principal investigator of the I-MOVE+ study 2016/17 funded through the European Union's HORIZON 2020 research and innovation programme. No conflict of interest.

AnSC: Principal investigator of the I-MOVE+ study 2017/18 funded through the European Union's HORIZON 2020 research and innovation programme. Member of the research team of the DRIVE study, that has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking (DRIVE, grant n° 777363). Subinvestigator in influenza clinical trials by Shionogi and Roche; no conflict of interest.

RB: No conflict of interest.

AEI: Coordinator of the molecular detection of influenza type and subtype by Real-Time Reverse Transcription PCR through I-MOVE+ project. No conflict of interest

ML: Coordinator of the genetic characterization of influenza strains. No conflict of interest.

CMC: Coordinator of the isolation of influenza viruses in cell culture and antigenic characterization in I-MOVE+ study. No conflict of interest

MDC: No conflict of interest.

VA: Member of the research team of the GIHSN project funded by Sanofi Pasteur and Foundation for Influenza Epidemiology. Member of the research team of the I-MOVE+ study funded through the European Union's HORIZON 2020 research and innovation programme. No conflict of interest.

ASC: Member of the research team of the GIHSN project funded by Sanofi Pasteur and Foundation for Influenza Epidemiology. Member of the research team of the DRIVE study, that has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking (DRIVE, grant n° 777363). Principal investigator in influenza clinical trials by Shionogi and Roche. No conflict of interest.

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References

1. Hulme KD, Gallo LA, Short KR. Influenza virus and glycemic variability in diabetes: A killer combination? *Front Microbiol* 2017;8:861. [[Crossref](#)]
2. Miron V, Drăgănescu A, Vișan C, et al. Mechanisms of interaction between *S. pneumoniae* and influenza viruses - literature review. *J Contemp Clin Pract* 2017;3:8-13. [[Crossref](#)]
3. Miron V, Drăgănescu A, Săndulescu O, et al. Pneumococcal colonization and pneumococcal disease in children with influenza - clinical, laboratory and epidemiological features. *Revista de Chimie* 2018;69:2749-53.
4. Goeijenbier M, van Sloten TT, Slobbe L, et al. Benefits of flu vaccination for persons with diabetes mellitus: A review. *Vaccine* 2017;35:5095-101. [[Crossref](#)]
5. Săndulescu O, Drăgănescu A, Pițigoi D. Influenza redefined - clinical and epidemiological insight. *Germs* 2019;9:60. [[Crossref](#)]
6. Rondy M, Larrauri A, Casado I, et al. 2015/16 seasonal vaccine effectiveness against hospitalisation with influenza A(H1N1)pdm09 and B among elderly people in Europe: results from the I-MOVE+ project. *Euro Surveill* 2017;22. pii: 30580. [[Crossref](#)]
7. Drăgănescu A, Săndulescu O, Florea D, et al. The influenza season 2016/17 in Bucharest, Romania - surveillance data and clinical characteristics of patients with influenza-like illness admitted to a tertiary infectious diseases hospital. *Braz J Infect Dis* 2018;22:377-86. [[Crossref](#)]
8. Beumer MC, Koch RM, van Beuningen D, et al. Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality. *J Crit Care* 2018;50:59-65. [[Crossref](#)]
9. Li S, Wang J, Zhang B, Li X, Liu Y. Diabetes mellitus and cause-specific mortality: a population-based study. *Diabetes Metab J* 2019;43:319-41. [[Crossref](#)]
10. Vamos EP, Pape UJ, Curcin V, et al. Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes. *CMAJ* 2016;188:E342-51. [[Crossref](#)]
11. Mota M, Popa SG, Mota E, et al. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. *J Diabetes* 2016;8:336-44. [[Crossref](#)]
12. Shin HY, Chung JH, Hwang HJ, Kim TH. Factors influencing on influenza vaccination and its trends of coverage in patients with diabetes in Korea: A population-based cross-sectional study. *Vaccine* 2018;36:91-7. [[Crossref](#)]

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