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Risk and impact of herpes zoster on patients with diabetes: A population-based study, 2009–2014

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ABSTRACT

Aims: This study was designed to assess the impact of diabetes on the risk and severity of herpes zoster (HZ), and the impact of HZ on diabetes. It focused primarily on immunocompetent patients aged ≥ 50 years who would be eligible for preventive vaccination.

Methods: Using population and healthcare databases of Valencia Region (Spain), a retrospective cohort of all subjects ≥ 50 years was followed up between 2009 and 2014. HZ and diabetes were defined using ICD-9 codes. We compared the incidence of HZ between non-diabetes and diabetes groups and healthcare resource consumption due to HZ in the 6 months following HZ diagnosis using different statistical generalized linear models (GLM). We also compared resources consumption due to diabetes treatment and haemoglobinA1c(HbA1c) levels before and after HZ.

Results: The cohort consisted of 2,289,485 individuals ≥ 50 years old, 397,940 of whom had diabetes. HZ incidence rate was 9.3 cases/1000 persons with diabetes-year (95% CI: 9.1–9.4). Incidence increased with age in all groups. The risk of HZ increased in the diabetes group compared to the non-diabetes group (RR 1.2, 95% credibility interval [CrI] 1.17–1.22). Patients with diabetes utilized more health care resources due to their HZ episodes than patients without diabetes. In 24% of well controlled patients with diabetes (HbA1C levels ≤ 6.5%), HbA1C increased after HZ.

Conclusions: Diabetes increased by 20% the risk of HZ. HZ contributed to the deterioration of glycaemic control and higher healthcare resource consumption in people with diabetes, becoming a priority population for HZ immunization.

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Introduction

Herpes Zoster (HZ) is a viral disease characterized by a painful rash. It is due to the reactivation of Varicella Zoster Virus (VZV), which remains latent in the sensory nerve ganglia following the primary infection (Varicella).[1] The reactivation is the result of a decreasing VZV- specific cell-mediated immunity (VZV-CMI), which might occur with ageing or in individuals with immunosuppressive disorders.[2] In spite of treatment,[3] the commonest complication of HZ is chronic pain in the affected area (post-herpetic neuralgia, PHN).[4] Both, HZ and PHN are responsible for a reduced quality of life as well as an increase in individual and social health care costs.[5]

HZ incidence increases sharply with age, being higher after the age of 50 years and may affect up to 50% of people who reach the age of 85 years.[6,7] Apart from age, underlying diseases such as diabetes, congestive heart failure or chronic obstructive pulmonary disease (COPD) seem to increase the risk, severity and impact of zoster episodes on senior population. A live-attenuated vaccine for the prevention of herpes zoster (Zostavax, Merk) has been licensed in many countries for the use in immunocompetent adults older than 50 years of age.[8,9] The Shingles Prevention Study (SPS) demonstrated that the use of the zoster vaccine reduced the burden of HZ by 61.1%, and the incidence of PHN by 66.5%.[8,10] Large and adequately powered studies are needed to evaluate the higher risk of HZ in individuals with underlying diseases and how the HZ may modify the evolution of the chronic condition. That would allow health authorities to identify the main risk groups for HZ immunization.

Diabetes Mellitus (DM) incidence is increasing in occidental countries.[11] Infections are frequent in patients with DM and are usually more severe than in individuals without diabetes.[12,13] It has been suggested that DM can be a risk factor for HZ,[14-18] however, the results from some older papers are contradictory.[19-22]

In DM it is well established that the cells which take part in the innate and adaptiveimmuneresponses havetheir function compromised.[13] Levels of VZV-CMI are lower in patients with diabetes than in healthy individuals.[23] This reduction in specific immunity might be responsible for the VZV reactivation and HZ development, making thus diabetes a risk factor for HZ. Moreover, HZ

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could induce glycaemic deterioration in patients with diabetes, which has never been studied previously to our knowledge.

In this population-based study we have focused on the impact of diabetes on the risk and severity of HZ, estimating the incidence of HZ and also the health care resources consumption by these patients due to the episode of HZ. We have also assessed the impact of HZ on the underlying diabetes and its possible decompensation by comparing levels of haemoglobinA1c(HbA1c) and the number of outpatient visits, hospitalizations, and medication before and after the HZ episode.

Results

The final cohort included 2,289,485 subjects older than 50 years of age, residents in the Valencia Region between the 1st of January 2009 and the 31st of December 2014. This cohort included 397,940 (17%) patients with diabetes (52% male). 12% of the subjects with diabetes had also COPD and 11% had HF. Their demographic characteristics are shown in Table 1.

Impact of diabetes on HZ

Of the total cohort, there were 69,438 incident cases of HZ, corresponding to an incidence rate of 7.2 cases/1000 persons-year (95% CI: 7.2–7.3). There were 14,104 cases of herpes zoster (20% of the total cases of HZ) in the population with diabetes (IR 9.3 cases/1000 persons-year; 95% CI: 9.1–9.4). As in the population without diabetes, the HZ incidence rates increased with age and were higher in women (Table 2). The HZ recurrence rates were 4.2 and 4.5 per 100 persons-year for individuals without (95% CI: 4.1–4.4) and with (95% CI: 4.2–4.7) diabetes respectively.

Supplementary material 3 illustrates the incidence rate of HZ/1000 persons-year for populations with diabetes and other co-morbidities compared with "healthy" subjects (who had neither diabetes nor co-morbidities) by age. Individuals with multiple co-morbidities (COPD or HZ in addition to diabetes) had higher HZ incidence rates than those individuals with a single condition.

The adjusted risk of HZ increased by 20% among people with diabetes with respect to people without diabetes (relative risk [RR] 1.20, 95% CrI: 1.17–1.22) (Table 3). The HZ risk was 36% higher in women; it increased with age and in patients with other co-morbidities such as COPD (48%) and HF (25%).

People with diabetes consumed more health care resources in relation to their HZ episodes than those without diabetes (Table 4): they had 3% more outpatient visits, were prescribed 21% more antivirals and had 63% higher risk for hospitalization with a HZ code at any diagnostic position and 37% longer periods of sick leave.

HZ impact on underlying diabetes

Outpatient visits (RR 1.02; 95% CI: 1–1.05), medications (OR 1.03; 95% CI: 1.01–1.06) and hospitalizations (OR 1.27; 95% CI: 1.15–1.41) related to diabetes management were significantly higher after an HZ episode (Table 5). In relation to glycaemic control, 24% of patients with HbA1c $\leq$ 6.5% before the HZ diagnosis had increased their HbA1c levels after the HZ diagnosis (HbA1c > 6.5%). These results reflect that HZ may have an impact on the underlying diabetes.

Discussion

In general, patients with diabetes are at higher risk of infections.[12] This population-based study demonstrated that diabetes also increases the risk and severity of HZ episodes and indicated that HZ may contribute to a glycaemic deterioration of diabetes resulting in an increase of health care resources consumption.

Some studies have previously described the risk of HZ in subjects with diabetes using different analysis.[14,16,17,27,28] The increment of HZ risk in populations with diabetes varied among studies depending on methodological aspects such as age

Table 1. Demographic characteristics for population $\geq$ 50 years old in the Valencia Region from 2009 to 2014 (n = 2,289,485).

	Total Cohort N (%)	Diabetes N (%)
Age (years)		
50–59	1,027,417	99,179
60–69	881,947	157,129
70–79	699,885	169,694
≥80	414,036	106,777
Gender		
Male	1,061,732 (46%)	206,227 (52%)
Female	1,227,753 (54%)	191,713 (48%)
Nationality	[a]N = 1,774,750	[a]N = 323959
Spanish	1,586,043 (89%)	304,923 (94%)
Other	188,707 (11%)	19,036 (6%)
Urban status	[a]N = 2,261,243	[a]N = 396963
Urban	2,191,837 (97%)	385,222 (97%)
Rural	69,406 (3%)	11,741 (3%)
Social Exclusion	[a]N = 1,739,725	[a]N = 321912
Risk	202,365 (12%)	29,457 (9%)
No risk	1,537,360 (88%)	292,455 (91%)
Comorbidities		
COPD	161,317 (7%)[b]	49,370 (12%)[b]
Heart Failure	103,240 (5%)[b]	44,260 (11%)[b]
Total (%)	2,289,485	397,940 (17%)[c]

[a]Number of subjects with available information for each category.
[b]Percentages calculated considering total of each column as 100%.
[c]Percentages calculated considering total cohort (2289485) as 100%.

Table 2. Incidence rates of HZ (per 1000 persons – per year) by age groups and sex in the Valencia region in 2009–2014.

	Non-Diabetes			Diabetes		
	Cases	IR	95% CI	Cases	IR	95% CI
Age (years)						
50 – 59	16557	5.3	(5.2–5.3)	1908	6.7	(6.4–7)
60 – 69	16910	7.2	(7.1–7.3)	4140	9.1	(8.8–9.3)
70 – 79	13356	8.2	(8–8.3)	4891	10.1	(9.8–10.4)
≥ 80	8511	8.6	(8.5–8.8)	3165	10.6	(10.2–10.9)
≥ 50	55334	6.8	(6.8–6.9)	14104	9.3	(9.1–9.4)
Gender						
Male	20227	5.5	(5.4–5.6)	6343	8.1	(7.9–8.3)
Female	35107	7.9	(7.8–8)	7761	10.4	(10.2–10.7)
	Cases	ReR	95% CI	Cases	ReR	95% CI
≥ 50	5541	4.2	(4.1–4.4)	1638	4.5	(4.2–4.7)

*IR % / Year: Incidence Rate per 1000 persons per year; CI: Confidence Interval. ReR: Recurrence rate per 100 persons (with a previous incident HZ) – per year.

Table 3. Relative risk estimates and 95% credible intervals (95% CrI) for the association between HZ incidence and diabetes, controlling for sex, age, comorbidities (COPD and HF), health department (as a random effect) and calendar year, using Bayesian Poisson regression.

		Relative Risk (95% CrI)
Diabetes	No Diabetes	1
	Diabetes	1.20 (1.17 – 1.22)
Sex	Man	1
	Woman	1.36 (1.33 – 1.38)
Age	50–59	1
(Years)	60–69	1.38 (1.35 – 1.41)
	70–79	1.53 (1.49 – 1.57)
	80_+	1.50 (1.46 – 1.54)
Comorbidity		
COPD	No COPD	1
	COPD	1.48 (1.44 – 1.52)
HF	No HF	1
	HF	1.25 (1.20 – 1.30)

Table 5. Diabetes-health care resources consumption during 6 months pre and 6 months post-HZ for diabetes cohort.

	PRE-HZ	POST-HZ
Outpatient visits for diabetes		RR (95% CI)
	1	1.02 (1–1.05)
Hospitalizations*		OR (95% CI)
	1	1.27 (1.15–1.41)
Length of hospital stay		Mean ratio (95% CI)
	1	1.11 (0.98–1.25)
Medication (Insulines + OA)		RR (95% CI)
	1	1.03 (1.01–1.06)
Medication (Insulin)		RR (95% CI)
	1	1.07 (0.99–1.17)
		RR (95% CI)
Medication (OA)	1	1.02 (1–1.05)

*Hospitalizations with a diabetes CIE-9 code in any diagnostic position; OA: Oral anti-diabetics.

adjustments or comorbidities among others, whereas other previous studies did not find any association between diabetes and HZ.[19-22] However, these last studies were not specifically designed to address this issue and some of the study populations suffered other comorbidities. Despite methodological differences (the age of the study population over 30 years, the study period of one year [2006], population of 26,793 subjects with diabetes in front of our 397,940 patients with diabetes and the use of aggregated data from primary care database), a previous Spanish study also concluded that diabetes increases the risk of HZ.[16]

Different immunological mechanisms seem to be involved in the predisposition of patients with diabetes to infections.[13] The innate immune responses by polymorphonuclear cells and monocytes/macrophages are lower in patients with DM.[13] Additionally, the insulin degrading enzyme, which may be associated with the pathogenesis of the predominant type 2 diabetes, is a cellular receptor mediating VZV infection and cell-to-cell spread.[29] These observations along with the demonstration of a decrease in VZV-CMI levels in patients with diabetes compared to healthy individuals,[23] could in part explain the association between diabetes and HZ. We also found higher HZ recurrence rate in individuals with diabetes than in the ones without diabetes, which seems to support this hypothesis.

The present study also demonstrates that healthcare resources consumption due to HZ is higher among patients with diabetes. They attended more frequently outpatient clinics due to HZ, were hospitalized more often and received more antiviral medications than patients without diabetes. These data indicate that HZ episodes were more severe in people with diabetes. HZ also resulted in longer periods off work for patients with diabetes adding indirect costs to the society.[30] Furthermore, the HZ contributed to a glycaemic deterioration of the underlying diabetes, reflected by an increase in the number of outpatient visits, hospitalizations, and medication for diabetes after the HZ episode in comparison with the six months previous to the HZ, as well as an increase in HbA1c levels. These results confirm the hypothesis that HZ could have a negative impact on the underlying diabetes contributing to a worsening of glycaemic control and a reduced quality of life of people with diabetes.

Table 4. HZ-health care resources consumption by people with diabetes in relation to non-diabetic ones.

	DIABETES
Outpatient visits for HZ	RR (95% CI) 1.03 (1.02–1.05)
Medication for HZ	RR (95% CI) 1.21 (1.17–1.25)
Hospitalizations*	OR (95% CI) 1.63 (1.38–1.91)
Length of hospital stay	Mean ratio (95% CI) 0.96 (0.85–1.08)
Sick leave	Mean ratio (95% CI) 1.37 (1.06–1.76)

*Hospitalizations with a HZ CIE-9 code in any diagnostic position; CI: Confidence interval; RR: Relative risk; OR: Odds ratio.

As it has been demonstrated before, HZ incidence increases significantly with age.[6,7] The incidence rate for HZ in patients with diabetes aged 60 years or more (9.1 cases/1000 persons-year; 95% CI: 8.8–9.4) was higher than the incidence rates in patients older than 80 years without diabetes (8.6 cases/1000 persons-year; 95% CI: 8.5–8.8), which indicates that patients with diabetes are prone to develop HZ at a younger age than patients without diabetes. Based on our results it is possible that the vaccine against HZ/PHN could be useful when managing patients with diabetes. It reinforces the cell-mediated immunity specifically against the latent VZV, impeding thus its reactivation and the associated complications. The vaccine prevents effectively against HZ and PHN and also reduces the severity of the HZ symptoms. Currently it is used in the prevention of HZ/PHN in various European countries and in USA in patients over 50 years of age and especially in those suffering from COPD, diabetes or cardiovascular disease. A recent study in Spain[31] showed that a vaccination program to include at least 30% of adults with an age over 50 years could be cost effective, increasing thus the benefits of the program for adults over 65 years old.

Our study has some limitations. Population-based studies using health databases reflect the actual care of the entire population. However, there may be some limitations like codification errors. Trained personnel codify CMBD with almost no errors. Previously evaluated positive predictive value of those databases' diagnostic codes was 92.7% (95% CI: 89.1–95.4) for HZ and 93% (95% CI: 87%-96%) for intussusception.[7,32] Case definition was based on physician consultation and hospital records, and thus data regarding undiagnosed or misdiagnosed cases of HZ or diabetes and complications were unavailable. To

avoid missing cases as much as possible, we used also data from the drug prescription and dispensation databases.

Conclusion

Our results indicate that individuals with diabetes have an increased risk of developing HZ and use more healthcare resources compared to people without diabetes, which might be the consequence of a more severe HZ. Moreover, HZ seems to be responsible for the higher health-related resources consumption by patients with diabetes after a HZ episode. People with diabetes ought to be considered as an important risk group for HZ. Our study could be one step to evaluate the impact of a future implementation of the HZ vaccine to this population.

Methods

This is a retrospective population-based study using health databases of the Valencia Region (Spain) to evaluate the impact of underlying diabetes on the risk of developing HZ, its associated resource consumption, and the impact of HZ on patients with diabetes.

Setting and study population

The Valencia Region of Spain has a population of approximately 5,000,000 inhabitants.[24] Over 98% of them are insured by the Regional Health System (RHS),[25] which consists of 24 Health Departments. Each one of them includes at least one hospital, one centre with specialists, and a variable number of primary care centres. All primary care visits and hospitalizations are recorded in clinical databases.

About 37% of the Valencian population is 50 years age or older. The study cohort included all individual aged 50 years or older, living in the Valencia Region and insured by the RHS between the 1st of January 2009 and the 31st of December 2014. Subjects were included in the cohort if they were aged 50 years or older on 1st January 2009, or on the day of entry into RHS, or on their fiftieth birthday, whichever occurred latest. Follow-up ended when they left Valencia (data of deletion from RHS), on their death or at the end of the study (31 December 2014), whichever occurred first. Patients with immunosuppressive conditions diagnosed before the beginning of the follow up period were excluded (determined by the presence of a diagnostic International Classification of Diseases 9th Clinical Modification [ICD-9-CM] code for Human immunodeficiency virus [HIV], organ transplantation, cancers, immunodeficiency disorders and autoimmune diseases).[14] If a subject developed one of the aforementioned immunosuppressive conditions during the follow up period, they were excluded from the study at this point.

Data source: Electronic databases

Primary care electronic medical notes were implemented in 2006 (SIA) and all medical contacts (visits) are registered and ICD coded.[26] For hospitalization we used the Hospitalization Minimum Data Set (CMBD in Spanish), where discharge diagnoses are also ICD-9-CM coded. Care Provision Management (GAIA) is the medication information system available to all those professionals involved in prescription and dispensation, created by the Department of Health. Data from these databases can be linked through a unique personal identification number (SIP).[7]

Case definitions

An incident case of HZ is the first appearance of a HZ-related ICD-9-CM code (053.*), in either SIA or CMBD (in any position). Any outpatient medical contact or visit, or hospital admission related to HZ was considered as a medical encounter. A recurrent HZ case was considered when an ICD-9 code for HZ appeared 6 months after a previous HZ encounter. The positive predictive value (PPV) of the HZ diagnostic code in these databases is 92.7%; 95% CI 89.1–95.4.[7]

Patients with diabetes were identified when a diagnostic ICD-9-CM code for diabetes (all ICD-9-CM 250 codes) was entered in SIA or in any diagnostic position in CMBD and when a prescription or dispensation for specific medication for diabetes was detected in GAIA (insulin and/or oral anti-diabetic drugs).

Variables

Age, gender, nationality, urban/rural residence, social exclusion risk and health department were recorded for each person. Rural residence was classified based on the law for sustainable development of the rural environment by the Regional Government. Rural areas were classified according to: population density (less than 100 inhabitants per Km^2), urban nucleus proximity, population trend, percentage of employment in primary, secondary and tertiary sectors and territorial structure. Social exclusion risk was obtained from electronic database (SIP), where its classification is based on aspects such as unemployment, non-citizen in irregular situation or without resources.[26] COPD and heart failure (HF) were included also as co-variables. Their status was identified when a diagnostic ICD-9 code for COPD (491, 492 or 496) or for HF (428 – 428.9) was detected in SIA or in any position in CMBD and when a prescription or dispensation for inhaled corticosteroids for COPD was detected in GAIA.

Statistical analysis

HZ incidence rates and 95% CI were calculated by age, sex and year using the Poisson exact method. We estimated and compared the incidence of HZ between both populations (with and without diabetes) and the health care resource consumption due to HZ during 6 months after the HZ diagnosis. HZ recurrence rates were calculated as number of HZ cases per 100 persons (with a previous incident HZ) per year.

The risk of developing HZ in subjects with diabetes was estimated by Bayesian mixed Poisson regression, adjusted by gender, age, health department (as a random effect), calendar year, other comorbidity (COPD and HF) and the group variable (corresponding with records from the database) as a random effect to avoid the over-dispersion problem. Results are presented with 95% Credible Intervals (CrI) that correspond to 95% CI in frequentist statistics.

To compare the health care resources consumption among the groups we used the number of outpatient visits, number and length of hospitalizations with a HZ code, number and duration of sick leave due to HZ and prescriptions for HZ during the six months following the HZ diagnosis (for medication see supplemental digital content 1). We performed different statistical General Linear Models (GLM) to compare the populations with and without diabetes (see supplementary material 2).

The HZ impact on the underlying diabetes was assessed in patients with diabetes during a six months follow up pre- and post-HZ. Health care resources consumption was compared between both periods (number of outpatient visits, number and length of hospitalizations and medication measured in terms of number of insulin and oral antidiabetics [OA] prescriptions). We also compared levels of HbA1c during the pre and post-HZ periods and considered as being well controlled those patients with HbA1c levels $\leq$ 6.5. Recurrent HZ episodes were included in the analysis only when periods did not overlap. Different statistical GLM were developed to compare the pre and post-HZ periods (see supplementary material 2).

Ethical considerations

The study protocol was approved by the Ethics Committee of Dirección General de Salud Pública / Centro Superior de Investigación en Salud Pública, which allowed for the linkage of the different databases by the administrators database using a codified SIP number.

Disclosure of potential conflicts of interest

JDD and his institution received research grants from SPMSD related to HZ vaccine. He also acted as advisor for these vaccines to GSK and SPMSD. CMQ has attended several congresses and her registration, travel and accommodation costs have been covered by SPMSD. MLL has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. FJAB has participated as a national advisor and as a speaker for Sanofi-Pasteur- MSD (SPMSD).

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First World Association for Infectious Diseases and Immunological disorders (WAidid) Congress, 18–20 February, Milan, Italy.

European Union Geriatric Medicine Society (EUGMS), 5-8 October, Lisbon, Portugal.

Author contributions

JDD is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

CMQ contributed to study conception and design; data acquisition, analysis, and interpretation; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. CMQ takes responsibility for the integrity of the data and the accuracy of the data analysis and serves as principal author.

MLL contributed to data acquisition, data cleaning, analysis and interpretation; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

JDD and FJAB contributed to study design; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Dr. Cintia Muñoz-Quiles confirms that the study objectives and procedures have been honestly disclosed. Moreover, she has reviewed study execution data and confirms that procedures were followed to an extent that convinces all authors that the results are valid and generalizable to a population similar to that enrolled in this study.

Financial/nonfinancial disclosures

This study was funded by Sanofi Pasteur MSD (SPMSD). JDD and his institution received research grants from SPMSD related to HZ vaccine. He also acted as advisor for these vaccines to GSK and SPMSD. CMQ has attended several congresses and her registration, travel and accommodation costs have been covered by SPMSD. MLL has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. FJAB has participated as a national advisor and as a speaker for SPMSD.

Role of the sponsors

The company (SPMSD) had no role in the analysis or discussion of the results.

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