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ORIGINAL ARTICLE

Is the association between hip fractures and seasonality modified by influenza vaccination? An ecological study

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Abstract
Summary Osteoporotic hip fractures in 4344 patients were more common during winter. Lower temperatures were associated with higher rates of fracture only in those not vaccinated for influenza. Influenza outbreaks increased the risk of hip fractures. Further studies are needed to assess whether influenza vaccination can prevent hip fractures.
Introduction Winter seasonality of osteoporotic hip fracture incidence has been demonstrated, yet the explanation for the association is lacking. We hypothesize that the seasonality of osteoporotic hip fracture can be explained by an association between hip fractures and seasonal influenza outbreaks.
Methods This retrospective cohort study included all patients admitted to Soroka University Medical Center with a diagnosis of osteoporotic hip fracture (ICD-9 code 820) between the years 2001 and 2013. Patients with malignancies, trauma, and age under 50 were excluded. In a time series analysis, we examined the association between hip fracture incidence and seasonality adjusted for meteorological factors, and population rates of influenza infection and vaccination using Poisson models.
Results Four thousand three hundred forty-four patients with a hip fracture were included (69% females, mean age 78). Daily fracture rates were significantly higher in winter (1.1 fractures/day) compared to summer, fall, and spring (0.79, 0.90, and 0.91; $p < 0.001$). In analysis adjusted for seasons and spline function of time, temperatures were associated with hip fractures risk only in those not vaccinated for influenza ($n = 2939$, for every decrease of 5 °C, RR 1.08, CI 1.02–1.16; $p < 0.05$). In subgroup analysis during the years with weekly data on national influenza rates (2010–2013), the risk for hip fracture, adjusted for seasons and temperature, was 1.26 2 weeks following a week with high infection burden (CI 1.05;1.51 $p = 0.01$), while the temperature was not significantly associated with the fracture risk.
Conclusions Under dry and warm desert climate, winter hip fracture incidence increase might be associated with influenza infection, and this effect can be negated by influenza vaccination.

Keywords Hip fracture · Metrological parameters · Osteoporosis · Seasonality · Vitamin D

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Introduction

Osteoporotic hip fractures have become a major health-care issue due to the increasing size of the elderly population and the ongoing need for health-care resources to treat the disease

[1].The association between seasonality and hip fractures has been reported in several studies from different geographical areas around the world [2–17], most showing seasonal changes in hip fracture rates, while few showed no effect of seasonality [8, 10, 12, 14]. In almost all studies showing seasonality in hip fracture rates, rates where highest in the winter, including in countries like Hong Kong which has no snow or ice in winter. Interestingly, according to several studies, about half or more of hip fractures occur indoors [5, 15, 18]. Together, these data suggest that outdoor conditions are not the only contributor to the increased fracture rate in winter and raise questions as to the cause of increased hip fracture rates in this season [6]. Among the possible mediators for the effect of seasonality on hip fracture rates, some found temperature [2, 4, 5], wind speed [5, 8], and amount and type of precipitation [2, 3, 9, 10] to be contributors. Another explanation can be related to the seasonal fluctuations of vitamin D which is produced in the skin upon exposure to the sun [19]. Men and women over age 65 years with vitamin D deficiency are at greater risk for loss of muscle mass and strength and for hip fractures [20]. Yet, evidence as to the role of vitamin D deficiency as the cause of increased hip fracture rates in the winter is inconclusive.

Seasonal influenza infection has been implicated as an important contributor to many diseases affecting the elderly population, including cardiovascular morbidity such as acute myocardial infarction and ischemic stroke. Furthermore, it has been suggested that influenza vaccination may prevent some cases of cardiovascular morbidity and mortality [21–23]. Similar associations may apply to hip fractures in the elderly.

Understanding the influence of environmental factors on the incidence of hip fractures may contribute in formulating preventative measures. The data available in the literature are not consistent as to the causes of higher hip fracture rates in winter, and some of the studies showing conflicting results [2, 3, 7]. The associations found in several of these studies were obtained from univariate analyses and are therefore prone to confounding [2, 5]. It was therefore the objective of this study to examine the association between hip fracture incidence and seasonality, meteorological parameters (temperature, amount of rainfall, relative humidity, and hours of sunlight), weekly rates of influenza infection, and rates of influenza vaccination.

Methods

Study population

This is a retrospective cohort study that included all patients admitted to Soroka University Medical Center (SUMC) with a primary diagnosis of hip fracture (ICD-9 code 820) between the years 2001 and 2013. SUMC is the only medical center in southern Israel (the Negev), serving a population of approximately one million residents, and all patients with hip fracture are admitted to this hospital. Patients with malignancies, age less than 50 years, and those with fractures resulting from trauma were excluded from the analysis.

For each subject, we obtained the following data: age, gender, ICD-9 coded comorbidities (including osteoporosis, chronic heart disease, diabetes, hyperthyroidism, and hyperparathyroidism), and the status of seasonal influenza vaccination in the last winter preceding the hip fracture.

The study was approved by the Institutional Review Board.

Meteorological data

Daily data on average air temperature, relative humidity, and rainfall for the study period were obtained from a monitoring site of the Israel Meteorological Service located in Beersheba, the largest city in southern Israel. Daylight hours during study years were obtained from the website Time and Date (http://www.timeanddate.com).

The climate in the Negev area is relatively hot and dry with a negligible amount of rainfall through the entire year. Seasons were defined according to Alpert et al. [24], who developed an approach specifically for the Negev region; winter: December 7th–March 30th; spring: March 31st–May 30th; summer: May 31st–September 22nd; and autumn: September 23rd–December 6th.

Statistical analysis

Results are presented as mean ± SD, interquartile range (IQR), and range for continuous variables and as percentages for categorical data. We used the Student's *t* test or analysis of variance for the comparison of normally distributed continuous exposures, and Mann-Whitney or Kruskal-Wallis in cases where normality assumption was not met. Categorical exposures were compared using chi-square test.

In a time series analysis, we assessed the association between the rate of hip fractures, measured as the daily count of fractures, and the seasonal parameters, among subjects admitted to SUMC with hip fractures, using Poisson models [25]. Models were adjusted for a penalized spline function of time. We stratified the analysis by gender, age, and status of influenza vaccination.

Sensitivity analysis

As an additional sensitivity analysis, weekly influenza rates were obtained from the central national viral laboratory, analyzing all influenza samples in Israel, for the years 2010 to 2013. Every winter season, the National Influenza Center and the Israeli Center of Disease Control (ICDC) perform national monitoring in 20 different clinics located at different geographic parts in Israel. The viral genome was extracted from nasopharyngeal specimens obtained from sentinel patients with influenza-like illness (ILI) using NucliSENS® easyMAG® (BioMerieux, France). Influenza viruses were detected by real-time reverse transcription-PCR (rRT-PCR) assays as previously described: influenza A and B, influenza A(H1N1)pdm09 [26–28].

For additional examination of the link between hip fractures and influenza, we repeated our model in a subsample of weekly rates of hip fractures between the years 2010 and 2013 and assessed the association with weekly rates of influenza obtained from the national monitoring of positive nasopharyngeal specimens. Models were adjusted for a penalized spline function of time, temperature, and seasons.

Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NCM USA) and R3.1.0 software.

Results

We identified 4344 patients admitted to SUMC with osteoporotic hip fractures between the years 2001 and 2013.

Baseline characteristics of the study population according to the season at which hip fracture occurred are presented in Table 1, showing similar characteristics with significant but small age differences. The majority of the patients (35.8%) were admitted to the hospital in the winter season. Sixty-nine percent were female with a mean age of 78 years. Rates of comorbidities including osteoporosis, chronic heart disease, diabetes, hyperthyroidism, and hyperparathyroidism did not differ according to the seasons in which hip fracture occurred.

The mean daily fracture rates were significantly higher in winter (mean fractures/day ± SD):(1.1 ± 1), compared to the summer (0.79 ± 0.89), and fall (0.9 ± 0.97) or spring (0.91 ± 0.94) ($p < 0.001$) (Table 1).

Meteorological parameters including mean daily temperature, relative humidity, rain, and daylight hours for each season are presented in Table 2. The average daily temperature during the study period was 13.4 °C (56 °F) in the winter and 25.5 °C (78 °F) in the summer. Daylight time is about 2 h shorter in the winter and fall seasons compared to summer and spring. Relative humidity is lowest at spring (mean value of 60.60% ± 5.69) compared to an average value of 69% in other seasons. The median value of rainfall throughout the study period was 0 mm (maximal value of 3.29 mm in the winter and 0.03 mm in the summer; Table 2).

The association between rates of hip fracture, season, meteorological parameters, and influenza infection

The association between daily rates of hip fractures, season of admission, and meteorological parameters are presented in Table 3. In single exposure models, we found a significantly higher relative risk (RR) for hip fractures in the winter season compared to the summer (RR 1.32, 95% CI 1.22;1.42; $p < 0.01$). In addition, we found a significant increase in the RR for hip fractures with 5° decrease in mean daily temperatures (RR 1.11, 95% CI 1.08;1.114; $p < 0.01$), and with 1 h decreases in daylight hours (RR 1.07, 95% CI 1.05;1.09; $p < 0.01$). Meteorological parameters such as amount of rain and relative humidity were not associated with daily fracture rates. In a multivariate analysis with adjustment for season, temperature, and daylight hours, only the negative effect of each 5° decrease in mean daily temperatures remained statistically significant (RR 1.03, 95% CI 1.08;1.14; $p = 0.003$) (Table 3).

In a stratified analysis by age (above and below 65 years) and gender (supplemental Table 1), we observed a protective effect of lower temperature only in women and in those over age 65 (RR 1.12, 95% CI 1.06;1.19; $p < 0.05$ and RR 1.09, 95% CI 1.08;1.11; $p < 0.05$) (supplemental Table 1).

Table 1 Population characteristics of patients admitted to Soroka University Medical Center with hip fracture, by season of admission

Variable	Summer cases May 31–Sept. 22 $n = 1186$ (27.3%)	Fall cases Sept. 23–Dec. 6 $n = 881$ (20.3%)	Winter cases Dec. 7–Mar. 30 $n = 1559$ (35.8%)	Spring cases Mar. 31–May 30 $n = 718$ (16.5%)	p value
Age					
(Mean ± SD)	78.0 ± 10.0	78.7 ± 10.0	78.8 ± 9.7	77.7 ± 10.1	0.019
Male gender, n (%)	357 (30.1)	286 (32.4)	456 (29.2)	219 (30.5)	0.424
Marital status: married, n (%)	380 (32.0)	277 (31.4)	541 (34.7)	245 (34.1)	0.282
Osteoporosis, n (%)	282 (23.7)	204 (23.2)	354 (22.7)	164 (22.8)	0.925
Chronic heart disease, n (%)	435 (36.8)	318 (36.1)	540 (34.6)	249 (34.6)	0.617
Diabetes, n (%)	408 (34.4)	275 (31.2)	514 (32.9)	227 (31.6)	0.413
Hyperthyroidism, n (%)	12 (1.0)	10 (1.1)	25 (1.6)	7 (0.9)	0.445
Hyperparathyroidism, n (%)	7 (0.5)	6 (0.6)	5 (0.3)	5 (0.7)	0.544
Rate of fractures per day (mean ± SD)	0.79 (0.89)	0.90 (0.97)	1.1 (1.0)	0.91 (0.94)	<0.0001

Table 2 Summary statistics of meteorological parameters by season, between the years 2001 and 2013

Parameters	Winter Dec. 7–Mar. 30	Spring Mar. 31–May 30	Summer May 31–Sept. 22	Fall Sept. 23–Dec. 6
Temperature, °C (°F)	13.40 (56.12)	20.49 (68.88)	25.53 (77.95)	20.12 (68.23)
Mean ± SD	±1.75 (3.15)	±1.90 (3.42)	±1.01 (1.82)	±2.53 (4.55)
Maximal value	18.24	24.74	27.54	24.05
Relative humidity, %				
Mean ± SD	68.93 ± 8.68	60.60 ± 5.69	69.87 ± 5.54	67.58 ± 7.85
Maximal value	81.5	71.35	80.00	82.3
Rain, mm				
Median (IQR)	0.69 (0.35;1.46)	0.03 (0.00;0.10)	0.00 (0.00;0.00)	0.10 (0.00;0.41)
Maximal value	3.29	2.13	0.03	2.91
Daylight hours				
Mean ± SD	10.76 ± 0.71	13.09 ± 0.46	13.37 ± 0.68	10.85 ± 0.57
Maximal value	12.27	14.01	14.11	12.08

We performed a sensitivity analysis to examine the apparent associations between influenza and temperature and rates of hip fracture. First, we assessed the association between temperature and daily hip fracture rates among subjects who were and were not vaccinated against influenza prior to their fall (Table 4). Low temperature was associated with a higher risk of hip fractures only in those not vaccinated for influenza (n = 2923, for every decrease of 5 °C, RR 1.08, 95% CI 1.02–1.16; $p < 0.05$) while in patients who were vaccinated (n = 1405), season and temperature were not associated with daily rates of hip fracture.

Second, we performed a sensitivity analysis in which we included the weekly rates of hip fracture between the years 2010 and 2013 and assessed the association with weekly mean temperature and weekly rates of influenza as reported by the Israel Center of Disease Control (Table 5). During the years 2010–2013, the majority of influenza cases were observed between December and February, where the weekly number of cases was 1.5 to 25 times higher than the background. When adjusted for seasons and temperature, the risk for hip fracture (weekly rates) was 1.26 higher 2 weeks following a week in which the weekly rate of influenza was higher than the 95th percentile (i.e., more than two confirmed cases) (CI 1.05;1.51, p = 0.01). In this model, temperature ceased to be significantly associated with the fracture risk.

Discussion

In our study, we examined the associations between seasonality, meteorological parameters, influenza infection rates, vaccination for influenza, and the incidence of hip fractures. The study was conducted in patients over age 50 living in the southern part of Israel. We found daily rates of hip fracture

Table 3 The association between daily rates of hip fractures, season, and metrological parameters, results of a Poisson regression (n = 4344)

Parameter	Unadjusted RR[a] (95% CI)	p value	Adjusted RR[a,b] (95% CI)	p value
Season				
Summer	Reference		Reference	
Fall	1.13 (1.04;1.23)	0.004	0.98 (0.84;1.15)	0.839
Winter	1.32 (1.22;1.42)	<0.01	1.02 (0.85;1.21)	0.806
Spring	1.14 (1.04;1.25)	0.004	1.06 (0.94;1.18)	0.348
Temperature[c], °C	1.11 (1.08;1.14)	<0.01	1.03 (1.08;1.14)	0.003
Daylight[d], hours	1.07 (1.05;1.09)	<0.01	1.03 (0.98;1.08)	0.300
Rain, mm	1.01 (0.99;1.01)	0.192		
Relative humidity, %	1.00 (0.99;1.00)	0.903		

[a] Models were adjusted for a natural spline function of time

[b] All the factors are adjusted to others as listed in the table

[c] OR per decrease of 5 °C

[d] OR per decrease in 1 h

Table 4 The association between daily rates of hip fractures, season, and temperature, stratified by influenza vaccination status (Poisson regression; $n = 4344$)

Parameter	95% CI	
	Vaccinated $n = 1405$	Non-vaccinated $n = 2939$
Season		
Summer	Reference	Reference
Fall	0.95 (0.73;1.23)	0.98 (0.82;1.18)
Winter	1.16 (0.87;1.56)	0.95 (0.78;1.17)
Spring	1.07 (0.88;1.30)	1.03 (0.91;1.18)
Temperature[a], °C	1.06 (0.97;1.16)	1.08 (1.02;1.16)*

[a] OR per decrease of 5 °C

*$p < 0.05$

to be the highest in the winter; the unadjusted relative risk of hip fracture was 32% higher in the winter compared to summer. In multivariate analysis of several meteorological parameters tested including season, only mean daily temperature was found to have a significant effect on daily fracture rates. This effect of temperature on daily rates of hip fracture was lost among patients who received influenza vaccination prior to hip fracture, which suggests that influenza infection is a confounder for the association between seasonality, temperature, and hip fracture rates. In accordance with this, we found weekly hip fracture rates to be significantly higher 2 weeks following an influenza outbreak.

Our results are in agreement with several studies showing seasonality in hip fracture rates with the highest rates in the winter [2–6, 10, 11, 13], despite originating in different parts of the globe with different climates. Not all studies performed a multiple risk factor adjustment, and only one examined the association with vitamin D levels [2, 5, 10, 13, 14]. To our knowledge, we are the first to assess an association between influenza infections and rates of hip fracture.

In adjusted relative risk assessment, we found that season alone does not contribute to the increase in daily fracture rates, but that each 5° decrease in mean daily temperature increased the daily fracture rate by 3%. Several other studies have found changes in temperature to be the most important in predicting seasonal changes in rates of hip fractures [2, 4, 5, 9]. Similar to our findings, Lin et al. [4] found that the protective effect of higher temperature intensifies with increasing age. Several mechanisms have been suggested to mediate the effect of lower temperatures to increase fracture rates including the effect of low temperature on hemodynamic status and blood pressure, as well as compromised dexterity, reduced neuromuscular function, and reduced reaction times which increase the risk for falls [2, 4, 5, 29–31]. In addition, cold weather has been suggested as a cause for decreased physical activity, resulting in deconditioning, bone loss, and bone fragility [4].

In our cohort, as in some other studies, we did not find a statistically significant association between daily fracture rates and the amount of precipitation [4–6]. Mirchandani et al. [5] showed that the majority of hip fractures occur indoors, thus making precipitation less relevant as a risk for falls and hip fractures. In accordance with this, Levy et al. reported that the effects of inclement weather on hip fracture rates were highest in younger persons possibly reflecting more time spent outdoors [9]. Douglas et al. [6] compared hip fracture rates in three countries located at different latitudes and found seasonal variation three times higher in Hong Kong which has no ice and snow compared to Scotland, providing powerful evidence against conditions underfoot causing extra falls in winter. Our study, conducted in the southern part of Israel which is characterized by very dry weather, strengthens the observation that precipitation is less likely to be a key factor in the higher rate of hip fractures observed in the winter.

Interestingly, the association between temperature and daily hip fracture rates was lost among elderly who received an influenza vaccine prior to hip fracture. This suggests that the higher risk for hip fractures in winter and low temperature may be a complication or consequence of influenza

Table 5 Sensitivity analysis: the association between temperature, influenza, and weekly rates of hip fractures; results of a Poisson regression between the years 2010 and 2013 ($n = 1412$)

Parameter	RR[a] (95% CI)	p value	RR[a,b] (95% CI)	p value
Temperature, °C	1.12 (1.02; 1.23)	0.017	1.07 (0.97; 1.19)	0.151
Weekly number of influenza cases (lag2[d])	–	–		
0 case			Reference group	
1–2 cases			1.11 (0.90;1.37)	0.307
>2 cases			1.26 (1.05;1.51)	0.011

[a] Adjusted for a penalized spline function of time and seasons

[b] Adjusted for a penalized spline function of time, seasons, and influenza seasons

[c] OR per decrease of 5 °C

[d] Refers to the association between the weekly hip fracture rate and the total number of influenza cases 2 weeks before

infection. This was further supported by the positive association between weekly rates of influenza infection 2 weeks prior to hip fracture, and weekly rates of hip fracture, an association that is independent of temperature and season. Similar observations on influenza infection and benefit of vaccination have been shown for cardiovascular disease and stroke [21–23]. Influenza infection in the elderly population has several negative consequences on activities of daily life, muscle strength, and functional status. Taken together, these changes may increase the propensity to fall and thus increase the risk for hip fracture [32–34]. It is less likely that the association between hip fracture and influenza infection is explained by the effect of the inflammatory response on bone structure or strength, though this is an area where further investigation is needed.

A strength of this study is the large study population in one geographical region, making it a true population-based study. This was possible because SUMC is the single institution which treats patients with hip fractures in southern Israel. In addition, due to the structure of the "Clalit" health system, we had access to demographic and medical data of all patients both from the community and from hospitalizations. The fact that the weather conditions in our region are devoid of snow, ice, or extremely low temperatures allows us to observe the isolated effects of season and temperature on hip fracture rates. Finally, the association found between influenza infections and rates of hip fractures is novel and may have clinical implications on the prevention of hip fractures in the elderly through more vigorous influenza vaccination.

The limitations of our study are mainly its retrospective nature. For this reason, we were unable to obtain a vitamin D sample in proximity to the incidence of a hip fracture in most patients and also could not document whether the fracture occurred indoors or outdoors. In addition, fractures were not validated radiographically and we relied on ICD-9 codes. This method of identification of hip fracture events may have also caused some underestimation of actual fracture rates due to undercoding or miscoding. Influenza rates were not validated to our population but rather reported for the whole population of the State of Israel, and status of living (home vs. nursing homes) which may have affected vaccination rates was also not available. Our findings may not be generalizable worldwide; other geographic regions may wish to perform a similar analysis.

In conclusion, we found that under dry and warm desert climate, winter hip fracture incidence increase might be associated with influenza infection and this effect can be negated by influenza vaccination. Further research is needed in order to validate this association and to evaluate the efficacy of influenza vaccination on the prevention of hip fractures in the elderly.

Compliance with ethical standards The study was approved by the Institutional Review Board.

Conflicts of interest None.

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