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Inverse relationship between ambient temperature and admissions for diabetic ketoacidosis and hyperglycemic hyperosmolar state: A 14-year time-series analysis

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ABSTRACT

This study aimed to investigate the association of admissions for diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) with ambient temperature and season, respectively in patients with diabetes mellitus (DM), after excluding known co-morbidities that predispose onset of acute hyperglycemia events. This was a time series correlation analysis based on medical claims of 40,084 and 33,947 episodes of admission for DKA and HHS, respectively over a 14-year period in Taiwan. These episodes were not accompanied by co-morbidities known to trigger incidence of DKA and HHS. Monthly temperature averaged from 19 meteorological stations across Taiwan was correlated with monthly rate of admission for DKA or HHS, respectively, using the 'seasonal Autoregressive Integrated Moving Average' (seasonal ARIMA) regression method. There was an inverse relationship between ambient temperature and rates of admission for DKA ($\beta = -0.035$, $p < 0.001$) and HHS ($\beta = -0.016$, $p < 0.001$), despite a clear decline in rates of DKA/HHS admission in the second half of the study period. We also noted that winter was significantly associated with increased rates of both DKA ($\beta = 0.364$, $p < 0.001$) and HHS ($\beta = 0.129$, $p < 0.05$) admissions, as compared with summer. On the other hand, fall was associated with a significantly lower rate of HHS admission ($\beta = -0.016$, $p < 0.05$). Further stratified analyses according to sex and age yield essentially similar results. It is suggested that meteorological data can be used to raise the awareness of acute hyperglycemic complication risk for both patients with diabetes and clinicians to further avoid the occurrence of DKA and HHS.

1. Introduction

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute metabolic complications of diabetes mellitus associated with a high case-fatality, and can occur in patients with both type 1 and 2 diabetes. Although a drastic improvement in survival of patients with DKA and HHS has been reported in developed nations in recent years, the potential threat to lives in patients developing DKA and HHS are still noticeable. For example, the overall DKA mortality recorded in the USA is <1%, but a higher rate is reported among patients aged >60 years and individuals with concomitant life-threatening illnesses (Centers for Disease Control and Prevention, 2015; Kitabchi et al., 2009) On the other hand, despite the incidence of HHS is estimated to be <1% of hospital admissions of patients with diabetes, death occurs in 5–16% of patients with HHS, a rate that is some 10-fold higher than that reported for DKA (Pasquel and Umpierrez, 2014). In Asia, Ko et al. from South Korea reported that the case-fatality rate for DKA in four university-affiliated urban hospitals was approximately 11.8% during 1985–2005, and this figure did not change largely over time (17.2, 11.5, and 12.2% in three consecutive 7-year periods) (Ko et al., 2005). Chen et al. reported a 28-day case-fatality rate of 6.10% and 18.83% for DKA and HHS, respectively in patients treated in a tertiary hospital over 1995 and 2005 in northern Taiwan (Chen et al., 2010a, 2010b).

Factors precipitating to DKA and HHS incidence and prevailing in specific seasons include socioeconomic status, certain co-morbidities such as cardiovascular disease, injury or infection, medications, and poor compliance or errors in compliance with treatment (Umpierrez and Korytkowski, 2016). Additionally, among the developed countries, the frequency of DKA is lower in countries where the background incidence of type 1 diabetes (T1DM) is higher (Lin et al., 2004), which highlighted the importance of overall diabetes awareness and health

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literacy of patients and their caregivers (Ritz, 2001). Other than the above mentioned factors, certain environmental factors have been found to associate with the incidence of DKA and HHS. Among them, geographical factors may influence the numbers of people affected. It may be that the high number of cases of DKA in countries nearer the equator is due to hot climates, which lead to more rapid dehydration and onset of hyperglycaemia, particularly in young children (Boyle et al., 2010). Despite that, a recent Canadian study by Butalia et al. explored the temporal variation in the hospitalization for DKA. Their data showed that December had higher than expected hospitalizations for DKA (Butalia et al., 2015). Because the study by Butalia et al. failed to take into account the season-specific clinical risk factors (e.g., infection and cardiovascular disease) in their analysis, it is hard to assess whether the observed seasonal variation in DKA/HHS incidence was due to ambient temperature or prevalence of clinical risk factors. In this study, we aim to further explore whether there is a seasonal clustering of DKA/HHS incidence by limiting our observation to the DKA/HHS hospitalizations not triggered by known season-related co-morbidities associated with diabetes.

2. Materials and methods

2.1. Research data

This time series correlation study was performed using Taiwan's National Health Insurance Research Data (NHIRD) and data of daily ambient temperature obtained from the Central Weather Bureau (CWB) of Taiwan. Our access to the NHIRD was approved by the Review Committee of the National Health Research Institutes. The study was also approved by the Research Ethics Committee of the National Cheng Kung University (approval number 103-010). The NHIRD were retrieved from Taiwan's National Health Insurance (NHI) program, which enrolls >99% of all Taiwanese residents (Shen et al., 2012). The NHIRD covered all medical claims from hospitals and clinics in Taiwan. Each claim data are involved with patients' demographic characteristics, disease diagnostic codes, prescription records, and medical expenditures.

2.2. Patients with diabetes

Data of annual number of patients with diabetes between 1998 and 2011 were retrieved from the medical claims of NHIRD. We first identified from diabetic ambulatory care claim records those patients coded with diabetes diagnoses by an code of 250 in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). An individual was classified as a patient with diabetes if he or she had an initial diabetes diagnosis in each year (1998–2011) and then experienced another one or more diagnoses within the subsequent 12 months. Moreover, the first and last outpatient visits during the 12 month period had to be separated by at least 30 days to avoid accidental inclusion of miscoded patients (Chen et al., 2006). The final annual population with diabetes therefore was 830,667, 859,995, 862,122, 915,305, 961,842, 986,325, 1,069,269, 1,116,120, 1,162,663, 1,230,738, 1,306,032, 1,389,605, 1,467,213, and 1,540,332, respectively from 1998 to 2011.

2.3. Episodes of DKA and HHS

The procedures identifying cases of DKA and HHS are summarized in Fig. 1. We selected all hospitalizations with ICD-9-CM diagnostic codes for DKA (ICD-9-CM: 250.1, $n = 66{,}736$) or HHS (ICD-9-CM: 250.2, $n = 74{,}237$) from January 1, 1998, to December 31, 2011. Each claim of hospitalization in NHIRD can have up to 5 discharge diagnostic codes. We excluded those admissions accompanied by the diseases that are known to trigger the occurrence of DKA and HHS, including acute myocardial infarction (ICD-9-CM: 410), ischemic heart disease (ICD-9-CM: 410–414), coronary revascularization procedures (ICD-9-CM procedure code: 36.0, 36.01, 36.02, 36.05, 36.06, 36.1, 36.10–36.19), non-traumatic hemorrhagic stroke (ICD-9-CM: 430–432), ischemic stroke (ICD-9-CM: 433–438), acute pancreatitis (ICD-9-CM: 577.0), urinary tract infection (ICD-9-CM: 590.1, 595.0, 595.9, 599.0), acute respiratory infections (ICD-9-CM: 460–466), pneumonia and influenza (ICD-9-CM: 480–488), tuberculosis (ICD-9-CM: 010–018), sepsis (ICD-9-CM: 995.92), acute renal failure (ICD-9-CM: 584.5–584.9), acute respiratory failure (ICD-9-CM: 518.81), hepatic failure (ICD-9-CM: 570), and disseminated intravascular coagulopathy syndrome (ICD-9-CM: 286.6) (Kitabchi et al., 2001; Stoner, 2005; Umpierrez and Kitabchi, 2003; Wachtel et al., 1991).

After the above exclusion, we finally identified 40,084 admission for DKA and 33,947 for HHS admission as our study sample, and summed the monthly number of admissions over the study period (i.e., 1998–2011). A total of 168 monthly number of DKA (or HHS) episodes were counted. Previous studies have demonstrated that age and sex are associated with the risk of DKA and HHS in patients with diabetes (Chen et al., 2010a, 2010b; MacIsaac et al., 2002).We therefore classified DKA/HHS episodes into 2 sex and 3 age groups of <15 years (children), 15–64 years (adolescents and adults), and >64 years (elderly) in the analysis.

2.4. Ambient temperature

Among the total number of 26 meteorological stations around Taiwan, 7 of them were excluded from the analysis, mainly because that these stations are located in mountainous or remote areas where very few people live. We first averaged daily temperature in each month to come up with monthly temperature for each of the 19 stations, and the monthly mean temperature was then calculated by averaging the monthly data from the selected 19 stations. We did not consider area-specific temperature in our analysis mainly because Taiwan is a small island, with a very high population density (23-million people on a land of 36,188 km^2. (Lee et al., 2006; Wang et al., 2012a, 2012b).

2.5. Statistical analysis

Monthly admission rates of DKA and HHS per 10,000 of the patients with diabetes calculated across 14 years was regressed against monthly mean temperature or season (i.e., spring [Mar. to May], summer [Jun. to Aug.], fall [Sep. to Nov.], and winter [Dec. to Feb.]) and a quadratic function of time, the errors term was further predicted by the 'seasonal Autoregressive Integrated Moving Average' (seasonal ARIMA) model. This method, which describes a univariate time series as a function of its past values and the independent variables of interest, has been used in many analogous studies as a means of testing for the effects of environmental exposure. The ARIMA model uses autoregressive parameters, moving average parameters, and the number of differencing passes to describe the series where a pattern is repeated over time (Lee et al., 2006), and the seasonal ARIMA model additionally includes seasonal effect which was constructed by seasonal autoregressive terms, seasonal differences, and seasonal moving average terms.

Because the autocorrelation function plot of admission rates of DKA/HHS showed a cyclic pattern and a trend of gradual decline, we employed a quadratic function of time in our model instead of performing differencing on the data; and used seasonal ARIMA to regress on the admission rates of DKA/HHS. As we removed quadratic trend of time, Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test for stationary on the series of admission rates of DKA/HHS was not rejected anymore. We checked the orders of ARMA by using extended autocorrelation function (EACF) (Tsay and Tiao, 1984). The order of ARMA(p, q) was determined by the upper left-hand vertex of the theoretical triangle of circles shown in EACF plot. The residuals were plotted against time in each model in order for examining if there was any pattern unexplained and a need for further improvement of model fitness. The model with a minimal AIC was determined as the final model. After