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Full Length Research Paper

Factors associated with infections in diabetic population

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Increase in the prevalence of diabetes worldwide and it becoming an epidemic has resulted in a clinical research shift to the management of diabetes mellitus globally. The study aimed to investigate the socio-demographic differences among diabetes patients with infection incidence. The study was conducted in an urban, governmental hospital in Penang Malaysia. The records of patients, more than and equal to age 18 years, who were admitted with diabetes mellitus between January 1, 2008 and December 31, 2010 were reviewed. Statistical analyses were performed using SPSS version 17®. This study was approved by the hospitals "Clinical Research Committee (CRC)" as well as "Ministry of Health Malaysia (MOH)". During the time period of January 2008 through December 2010, there were total 2174 diabetes patients admitted; 2174 (100%) patients' charts were reviewed. Of the total, 1063 (48.9%) were males and the rest, 1111 (51.1%), females. Mean and standard distribution (SD) showed females have less mean age distribution (35.2 ±4.187 years) as compared to males (37.9±5.724 years). A total of 798 (36.7%) had infection exposure before and/or during hospital admission; statistical significance (p<0.001) was found in association of diabetes ketoacidosis (DKA) and infection exposure. Though the rate of hospitalization increased among females, OR showed that males were more likely to get the infection severely as compared to females (1.81 (95%CI 1.1-2.40) *p* <0.021). Profound ethnic difference is three times more prone to severity rate of infection among Malay diabetic patients as compared to other non-Malays (OR 3.44 (95%CI 1.60-5.68) *p*<0.001). Further analysis showed that with the age of ≥ 65 years and history of diabetes (mean ± SD: 27.13 ± 2.782) average patient utilizes 135.7 days (average) of antibiotic course. Increased and recurrent use of antibiotic was found among Malays; also Malays predominantly experience clinical manifestations (poor glycaemic control) as compared to other ethnics. Every third patient with diabetes mellitus had infectious exposure.

Key words: Diabetes mellitus, infections, factors association, clinical management, metabolic disorder, endocrinology.

INTRODUCTION

Increase trend in the prevalence of diabetes worldwide and it becoming an epidemic has caused a clinical research shift to the management of diabetes mellitus globally (King and Rewers, 1991; Bjork et al., 2003). Based on estimations made, about 285 million people are currently with diabetes worldwide, so increase in number is set to be about 438 million by the year 2030 (Sicree et al., 2009). This is more prevalent in developing countries of the world where the disorder predominantly affects

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younger adults in the economic productive age group (Mather et al., 1987). The exact reasons why Asians are more prone to type 2 diabetes at a younger age and premature cardiovascular diseases (CVD) remain speculative (Deepa et al., 2006).

Study investigators calculated the risk ratios of having an infectious disease and of death due to infectious disease. Nearly half (46%) of all people with diabetes had at least 1 hospitalization or outpatient visit for infections compared with 38% of controls without diabetes (Shah and Hux, 2003). The risk ratio for diabetic vs non-diabetic persons was 1.21. The risk ratio for infectious disease-related hospitalization was up to 2.17, and was 1.92 for death attributable to infection. Many individual infections are more common in people with diabetes, Deasy remarked, including pneumonia caused by certain organisms; pyelonephritis; soft tissue infections, including the "diabetic foot"; necrotizing fasciitis; and mucocutaneous *Candida* infections. Others occur almost exclusively in diabetics: invasive (malignant) otitis externa, rhinocerebral mucormycosis, and emphysematous infections (cholecystitis and pyelonephritis). Some infections result in increased severity when they occur in diabetic patients and are associated with increased complications.

Data from a study by Bertoni and colleagues (Bertoni et al., 2001) suggest that diabetic adults are at greater risk for infection-related mortality, and that excess risk may be mediated by cardiovascular disease (CVD). The study authors found that when diabetes was combined with CVD, the relative mortality risk was 3.0 (1.8-5.0), while diabetic patients without CVD had a risk of 1.0 (0.5-2.2).

Infections also cause considerable morbidity and mortality in patients with diabetes. They may precipitate metabolic derangements and, conversely, the metabolic derangements of diabetes may facilitate infection (Votey and Peters, 2005). Several immune function factors are related to this increased risk, Deasy said. First, neutrophil function is depressed, affecting adherence to endothelium, chemotaxis, and phagocytosis. The antioxidant systems involved in bacteriocidal activity may be compromised, and cell-mediated immunity is probably depressed. These impairments are exacerbated by hyperglycemia and acidemia but are reversed substantially, if not entirely, by normalization of pH and blood glucose levels (Votey and Peters, 2005; Tan, 2000).

Although there is no proof that diabetics are more susceptible to infection, they seem to have more difficulty handling infection once it occurs (Hoffman et al., 2003; Charfen and Fernandez, 2005). Indeed, several aspects of immunity are altered in diabetic patients: polymerphonuclear leukocyte function is depressed, particularly when acidosis is present, and leukocyte adherence, chemotaxis, phagocytosis and bactericidal activity may also be impaired (Joshi et al., 1999; Delamaire et al., 1997; Gallacher et al., 1995; Muchova et al., 1999; Gomez et al., 1996). Joshi et al. (1999) reported the lack of clinical evidence that diabetic patients are more susceptible to infection than non-diabetic patients. Nevertheless, infection is a well-recognized trigger of DKA. But studies in non-diabetic patients have consistently shown a relationship between the presence of leukocytosis and the existence of bacterial infections (Zukin et al., 1998; Hamilton and Anemia, 1998).

World Health Organization (WHO) estimated 12% annual death with diabetes and chronic respiratory diseases, actively reporting that at least 80% of mortality can be prevented with the management of premature heart disease, stroke and type 2 diabetes mellitus (World Health Organization, 2011). Globally, the figure for unwarranted antibiotics prescriptions stands at roughly 50%. According to figures gathered by surveys presented to WHO in 2000, about 60% of antibiotics in Nigeria were prescribed unnecessarily. In Nepal, over 50% of antibiotics prescribed in 1996 were not needed and 40% of medicine expenditure in the same year was wasted due to inappropriate prescriptions. Retrospective analysis of case records in Nepal in 2003 showed that, in 26.2% cases, the use of the antimicrobials was irrational. The World Health Organization pointed out that nearly 2 out of every 3 anti-diarrhoeal preparations sold in 12 countries in Latin America in 1990 contained an antibiotic. Similarly, a survey carried out in 1989 showed that nearly one out of two antidiarrhoeal products in Third World countries contained an unnecessary antibiotic.

The conclusions drawn at the consultative group discussion (http://mednet3.who.int/icium/icium2004/resources/ppt/CH011.ppt) in Peru were that the results suggested ever increasing potential of irrational use of antibiotics for children, including short courses, over-prescribing, and self medication.

So far no study has been done to investigate the sociodemographic differences among diabetes patients with infection incidence and also to evaluate the factors associated with combined severity of disease in infection.

METHODOLOGY

The study was conducted in an urban, governmental hospital in Penang Malaysia. The records of patients, more than and equal to age 18 years, who were admitted with diabetes mellitus between Jan 1, 2008 and December 31, 2010 were reviewed. The charts were identified by the ICD-9 admission and/or discharge codes of 'diabetes mellitus'. In this review, DKA was defined by an elevated serum glucose ≥ 250mg/dL, a serum bicarbonate ≤ 15 meg/L and pH ≤ 7.35.

The entire medical record was reviewed for each hospital admission. Clinical evaluations, including a search for potential infections, as well as all treatment decision were conducted at the discretion of the admitting physicians. Demographic characteristics were recorded on each patient in addition to the initial serum glucose, Body Mass Index (BMI), compliance to medication (theoretically defined as patient with multiple admissions because of hyperglycemia recognized as non-compliant), history of diabetes mellitus and average antibiotic used since first admission after diagnosis of diabetes mellitus. All admissions were included in the analysis, including those with missing data.

The followings are a priori classification regarding infection type:

Patients first incidence, relapse within 3 months (readmission with infection), relapse in between 3 to 6 months (readmission with infection) or super-infection with primary infection (during admission). Patients with the documentations of symptoms, signs and/or radiographs consistent with upper and/or lower respiratory tract infections, for which no antibiotics were given, were defined as having presumed viral infection. Patients treated with antibiotics, as deemed necessary by the treating physicians, were defined as having bacterial infection.

For primary purpose of descriptive analyses, the patients with bacterial infection were further divided into minor and major infection categories based on the likelihood of serious sequel as evidenced in the diabetes literature. Statistical analyses were performed using SPSS version 17®. Analyses included the use of student t-test and ANOVA for the normally distributed data, the Mann-Whitney U rank sum and Kruskall-Wallis tests for continuous, non-nominal data and chi-square for dichotomous variables. When comparisons were made between continuous predictive variables, including age, temperature, white blood cell count and cell differential and the dichotomous outcome variables of infection, diabetes ketoacidosis, and compliance to medication, and body mass index (BMI) stepwise logistic regression analysis for parametric data was performed.

All reported p-values are 2-tailed and significance was established at $p \leq .05$. Data are presented as mean ± standard deviation (SD) unless otherwise indicated. Odds ratios with 95% confidence intervals (95% CI) are presented when applicable. Power calculations using measured proportions were made using Sample Power Version 1.00 (SPSS, Chicago, IL). This study was approved by the hospitals "Clinical Research Committee (CRC)" as well as "Ministry of Health Malaysia (MOH)".

RESULTS

During the time period of January 2008 through December 2010, there were total 2174 diabetes patients admitted; 2174 (100%) patients' charts were reviewed. Of total 1063 (48.9%) males and the rest 1111 (51.1%) were females. Mean and Standard Distribution (SD) showed females have less mean age distribution (35.2 ±4.187 years) as compared to males (37.9±5.724 years). A total of 798 (36.7%) had infection exposure before and/or during hospital admission; statistical significance was ($p<0.001$) found in association of diabetes ketoacidosis (DKA) and infection exposure. Majority of 384 (48.1%) infection type was relapsed cases within 3 months; further analysis showed that infection presumed to be the same likely organism as with first exposure and multiple admission represents the inappropriate management of antibiotics. Treatment limitation with known allergy was only found among 352 (16.2%) patients. Noncompliance and tendency to get multiple hospital admission with indication of hyperglycemia was found among 67.8% (1474) patients. Surprisingly all diabetic patients in this study received 32.97 ± 9.325 days (mean ±SD) of antibiotic course till date (Table 1).

Significant outcome was revealed against the infections among diabetic population in this study. Current clinical outcomes of infection showed significant association with 'not recovered' ($p< 0.047$), 'recovered with complications' ($p<0.001$), 'progression of disease infection' ($p<0.001$) and 'death' ($p<0.012$). Findings showed that complete clinical recovery without complication is still not achievable in the practice except few exceptions (Table 2).

In second phase of analysis, identification of the factors associated with combined severity of disease or infection was performed. Significant relationships were identified with sociodemographic distribution with the respective outcome of infection. Although the rate of hospitalization increased among females but OR showed that males were more likely to get the infection severity compared to females (1.81 (95%CI 1.1-2.40) $p <0.021$). Age in years provided sufficient evidence to increase the severity rate of infection with the increase of age in years (35-44 years: OR 5.76 (95%CI 3.25-10.76) $p< 0.001$ and ≥ 45 years: OR 10.98 (95%CI 5.33-20.64) $p< 0.000$). Ethnic difference in Malay diabetic patients can make them three times more prone to severity rate of infection compared to other non-Malays (OR 3.44 (95%CI 1.60-5.68) $p<0.001$). Findings suggested that diabetes ketoacidosis episode produced ten times more likelihood to get infection as compared to non-diabetic ketoacidosis patients (OR 10.51 (95%CI 5.27-20.12) $p<0.001$). Other significant factors were also identified that had a direct impact on the infection and severity (Table 3).

DISCUSSION

Early detection of bacterial infection in patients with diabetes mellitus is a clinical priority. This need is based on the higher morbidity associated with infections in adults with diabetes. Impaired host responses may be responsible for this increased severity of infection. For example, it has been shown that polymorphonuclear leukocytes in diabetic patients, particularly when acidosis is present, may have defects in adherence, chemotaxis, phagocytosis and antioxidant activity involved in bactericidal function [Joshi et al., 1999]. Moreover, diabetic patients with ketoacidosis have alterations in monocyte receptor functions [Steward et al., 1991]. Finally, a decreased responsiveness of T-cell lymphocytes to mitogenic stimulation had been shown [Lebovitz, 1995].

Compliance

Previous studies done in Malaysia reported the majority of diabetes population had poor glycaemic control regardless of type of diabetes, age or treatment centres (Mafauzy, 2006, 2005; Ismail et al., 2001).

Multicenter studies have shown that depression is common among people with diabetes (Peyrot et al., 2005). Depressive symptoms had been shown to be associated with poor self-care practices and glycaemic control, functional impairment and higher health cost (Ciechanowski et al., 2000; Lin et al., 2004; Lustman et al., 2000). In the findings of our study, we find out the majority of patients about 67.8% have poor glycaemic

Table 1. Patients' characteristics in the study population.

Characteristic	Frequency (%)
Gender	
Male	1063 (48.9)
Female	1111 (51.1)
Age (Mean ± SD)	
Male	37.9±5.724 years
Female	35.2±4.187 years
Ethnic	
Malayu	915 (42.1)
Chinese	798 (36.7)
Indian	461 (21.2)
Infection complications	798 (36.7)
Sepsis grade 2 (DFU)	304 (14.0)
UTI	102 (4.7)
Pneumonia	26 (1.2)
Scalp hematoma	26 (1.2)
Gastritis, acute tonsilitis with URTI/UTI	48 (2.2)
Infected BKA stump with DFU	22 (1.0)
Systemic infection	22 (1.0)
Meningitits with septicemia	48 (2.2)
Infected left knee charcot's joint	54 (2.5)
Community acquired pneumonia followed by DFU	87 (4.0)
Nosocomial pneumonia	59 (2.7)
Infection type	
First infection	69 (8.7)
Relapse within 3 months	384 (48.1)
Relapse in between 3-6 months	261 (32.7)
Superinfection with primary infection	84 (10.5)
Diabetes ketoacidosis	
Yes	967 (44.5)
No	1207 (55.5)
Other complications	
Yes	563 (25.9)
No	1611 (74.1)
Known allergy	
Yes	352 (16.2)
No	1822 (83.8)
Compliance to diabetic drugs	
Yes	700 (32.2)
No multiple admission because of Diabetes	1474 (67.8)
History of diabetes mellitus (Mean±SD)	14.47 ± 8.099 years
Antibiotic use until date (Mean±SD)	32.97 ± 9.325 days

Table 2. Significance of outcomes against the infection among diabetic patients.

Characteristics	Frequency (%)	*p*-Value *
Recovered	126 (15.9)	0.861
Not recovered	148 (18.5)	0.047
Recovered with complications	194 (24.3)	0.001
Progression of disease infection	222 (27.8)	0.001
Death	108 (13.5)	0.012
Total infection cases	798 (36.7)	
Total study population	2174 (100)	

*Response to each domain is dichotomous, chi-square $p<0.05$ against infection (yes/no).

Table 3. Factors associated with combined severity of disease or infection.

Variable	Unadjusted OR (95% CI)	Adjusted AOR (95% CI)
Gender		
Female	1	-
Male	1.81 (1.1-2.40)	-
Age		
18-34	1	1
35-44	5.76 (3.25-10.76)	4.96 (2.26-8.92)
≥ 45	10.98 (5.33-20.64)	8.80 (2.00-13.23)
Ethnic		
Indian	1	-
Malay	3.44 (1.60-5.68)	-
Chinese	1.87 (0.71- 9.88)	-
Infection type		
First infection	1	1
Relapse within 3 months	0.49 (0.18-1.35)	0.51 (0.20-1.35)
Relapse in between 3 and 6 months	1.21 (.045-3.29)	0.82 (0.30-2.2.5)
Super infection with primary infection	3.13 (1.18-8.31)	2.76 (1.24-5.87)
Diabetes ketoacidosis		
No	1	1
Yes	10.51 (5.27-20.12)	7.54 (4.21-11.65)
Body mass index (kg/m^2)*		
≤ 23.0	1	*
≥ 23.1	6.13 (2.98-11.46)	
Other complications		
Yes	1	-
No	0.98 (0.54-1.81)	-
Known allergy		
Yes	1	-
No	0.64 (0.33-1.25)	-
Compliance to diabetic drugs		
Yes	1	1

Table 3. Contd.

No multiple admission because of diabetes	8.45 (3.61-15.98)	4.21 (1.82-8.75)
History of diabetes mellitus		
Newly diagnosed	1	-
> 5 years	9.57 (3.18-26.83)	
Average antibiotic use until date		
≤ 15 days	1	1
16-25 days	2.60 (0.96-7.54)	1.98 (0.34-2.83)
≥ 25 days	6.77 (3.26-14.02)	3.84 (1.74-5.69)

*For Asians, obese considered at 23.4, for the others, obese consider if above 24.5; no enough data to calculate AOR.

control and cause multi-hospitalizations. Also due to poor glycaemic control patients are eight times more likely to get co-morbidity infections as compared to patients with good compliance (OR 8.45 (95%CI 3.61-15.98) $p<$ 0.000).

When assessing the incidence of diabetes ketoacidosis, an acute complication, Malaysia tops the list with 26.3 events per 100 patient-years. Hence it was not surprising that only 36.6 events per 100 patient-years for hypoglycaemia event were reported by Malaysian subjects (Craig et al., 2007). Despite these concerns, studies have failed to identify reliability predictors of infection in the most severe diabetics, namely those with ketoacidosis. Campbell et al (2007) evaluated 140 adults with DKA and concluded that total WBC, blood glucose and bicarbonate had little or no value for predicting infection. Slovis et al. (1987) attempted to identify adults with occult bacterial infections by examining the records of 169 patients with DKA. He found that 30 (21%) of the patients admitted had occult infections (11 minor infections and 19 major infections) that were not diagnosed initially but within the first 48 h of administration. He concluded that, of all the variables examined, only a band neutrophil counter greater than 10% could reliably predict major occult bacterial infections in adult patients with DKA.

Until now it is unknown what is the impact of diabetes ketoacidosis on the co- morbidity infection rate and also DKA incidence rate among diabetic population. This study answers this question in this way: every 2nd patient with diabetes mellitus has had at least one exposure of DKA during treatment. Secondly with every single episode of DKA diabetic patient is ten times more likely to get infection as compared to non-diabetic ketoacidosis patients (OR 10.51 (95%CI 5.27-20.12) $p<0.001$).

Mortality

The World Health Organization (WHO) has announced that the average life expectancy of individuals with diabetes is shortened by 10-15 years (World Health Organization, 1999). Diabetes is one of the top ten leading causes of death in many countries around the world. Roglic (2000) reported that the burden of mortality attributed to diabetes in the year 2000 was 2.9 billion deaths, equivalent to 5.2% of all deaths globally. The excess mortality attributed to diabetes accounted for 2%-3% of deaths in poorest countries and over 8% in the United States, Cannada and Middle East (Roglic et al., 2005). In individuals younger than 35 years of age and with diabetes, 75% of all deaths were attributed to this disease. In individuals with diabetes aged 35-64 years, 59% of deaths were attributed to diabetes while in individuals with diabetes and older than 64 years, diabetics accounted for 29% of all deaths (Boutayeb, 2006). In Malaysia about 27 million population is experiencing a diabetic epidemic (http://www.statistics.gov.my/images/graf/pop2007.jpg;). In 2006, the second national mortality and morbidity survey reported the prevalence of diabetes have reached 11% of the adult population as compared to rate of 0.6% in the 1960 (Ministry of Health Malaysia, 2006). Many factors influence this massive increase, one of them is the path of urbanization, industrialization and motorization. This has resulted in the population becoming more overweight/obese and sedentary (Ministry of Health Malaysia, 2006). This is especially common in the young and well as the Malay and Indian females population (Ministry of Health Malaysia, 2006; Ismail et al., 2002; Mohamad et al., 1996). This study also finds that the mean year age to get hospitalization with diabetes is significantly lower as compared to males and Malays are more profound to get diabetic co morbidity as compared to other ethnic in Malaysia.

Unfortunately till date no clinical research has been able to provide sufficient information on the biomarkers, to ensure the complete recovery status of diabetic patients with infection. Furthermore identification of infections in early stage among diabetes population is an important issue to be re-looked. Irrational prescribing of antibiotics has been widely reported both from the developed

as well as the developing countries (Roglic et al., 2005). The cost of irrational use of drugs consequent to irrational prescribing is enormous in terms of both scarce resources and adverse clinical consequences such as ineffective or unsafe treatment, exacerbation or prolongation of existing illness, iatrogenic illness and emergence of resistance to antimicrobials (International Diabetes Federation, 2008; Wild et al., 2004; Yoon et al., 2006). The emergence of antibiotic resistant bacterial pathogens on a large scale over last two decades is taken as an inevitable consequence of this overuse of antibiotic worldwide (Cockram, 2000; Funnell et al., 1998). The incidence of infections is increased in patients with diabetes mellitus (DM). Some of these infections are also more likely to have a complicated course in diabetic than in nondiabetic patients (Deresinski, 1995). Irrational use of antibiotics is one of the extensive polypharmacy among diabetic patients; somehow immunity dysfunction is concordant among diabetes mellitus patients.

This study aimed to provide the minimum baseline information regarding the use of antibiotic in treatment line of hospitalization. Findings showed that a diabetic patient takes antibiotic mean of about 32.97 days. Further analysis showed that with the age of ≥ 65 years and history of diabetes (mean ± SD: 27.13 ± 2.782) average patient utilizes 135.7 days (average) of antibiotic course. However our finding also revealed 80.8% relapse cases from first exposure to within 6 month. Inappropriate drug selection or inappropriate dosing is associated in this concern. Malaysian current policies or control measures are ineffective against the antibiotic treatment compliance and addition to certain community practices cause an irrational antibiotic use leading to non compliance with antibiotics (Syed et al., 2010).

Conclusion

Increased and recurrent use of antibiotic was found among Malays; also Malays predominantly experience clinical manifestations (poor glycaemic control) as compared to other ethnics. Every third patient with diabetes mellitus had infectious exposure. Increased use of antibiotics is considered to influence progression of infection and leads to high incidence of superinfections. Furthermore, diabetic patient at the age of ≥ 65 years and with history of diabetes (mean ± SD: 27.13 ± 2.782) utilizes 135.7 days (average) of antibiotic course.

Limitations of the study

Our study is limited to certain important factors, which had important influence on our findings but due to limited resources and missing data in patients' profiles, the following parameters are not included in the part of this study:

1. HbA1c values
2. Antibiograms of Blood/Urine sample
3. Severity of infection categorization
3. No follow up after discharge

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