Evaluating Diabetes Mellitus as a Risk Factor for Community-Acquired Infections

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(See the article by Muller et al. on pages 281–8)

Diabetes mellitus (DM) has long been suspected as a risk factor for community-acquired infections, but until recently, there was relatively little evidence to support this hypothesis. Laboratory studies have documented variations in immune function that could lead to a higher risk of infection in persons with DM. However, there are also other differences between persons with DM and those without DM that are important to consider when evaluating the association between DM and risk of infection. Persons with DM interact with the health care system more frequently and more intensively than the general population. They may therefore be more likely to seek medical attention for signs or symptoms of infection. Because the consequences of infection may be more significant in a person with DM, they may also be more likely, after seeking medical attention, to be assigned a diagnosis of infection or to receive a higher level of care for an infectious illness, compared with a person without DM. Lastly, persons with DM may have other comorbid factors, such as renal failure or functional disability, that are associated with an increased risk of infection; therefore, an elevated risk of infection in persons with DM could be a reflection of the higher prevalence of comorbid factors in that population.

The primary challenges in assessing whether DM is a risk factor for infection have, therefore, been to distinguish a true increase in risk from surveillance artifacts, such as those due to variation in medical care-seeking behavior, and from a confounding effect of other comorbidities. The ability of a study to distinguish among these possibilities is related to the study design, the study population, the outcomes evaluated, and the methods of identification of and adjustment for comorbid factors.

One approach to minimize the possible influence of variation in medical care-seeking behavior on the association of DM and risk of infection is to evaluate the risk associated with relatively severe infections. Several case-control studies have evaluated the association of DM with the risk of severe infections, adjusting for comorbid factors identified by medical record review or patient interview. These studies have identified DM as an independent risk factor for invasive group A [1] and group B [2] streptococcal infections in adults and for pyelonephritis in nonpregnant women <50 years of age [3] but not for invasive pneumococcal disease in adults <65 years of age [4] or for Escherichia coli bacteremia in seniors [5].

For less-severe infections, detection of which could be influenced by health care-seeking behavior or provider diagnosis patterns, prospective evaluations are the gold standard approach. Prospective studies are more costly and time consuming than are retrospective studies; therefore, there are few prospective evaluations of DM and infectious outcomes. However, the results of one prospective assessment that involved 1017 generally healthy postmenopausal women have recently been reported [6]. That study found that women with insulin-treated DM and those with DM of >10-years’ duration were at higher risk for symptomatic urinary tract infection than were women without DM in analyses adjusting for other prospectively identified factors, such as frequency of sexual intercourse and postvoid residual bladder volume. These results suggest that the severity of DM may be related to the risk of urinary tract infection in postmenopausal women.

In this issue of Clinical Infectious Diseases, Muller et al. [7] report the results of an analysis of data from the Second Dutch National Survey of General Practice, in which general practitioners recorded diagnosis codes associated with patient contacts over a 12-month period. The investigators compared adults who had received a diagnosis code of DM with...
an age-matched group of adults who had received a diagnosis code of hypertension. The risk of a medical encounter assigned a diagnosis code meeting the study definition of an upper or lower respiratory tract infection, urinary tract infection, or skin and mucous membrane infection during the 12-month period was compared between the DM and hypertension groups. The analyses adjusted for chronic disease covariates, defined by groupings of diagnosis codes assigned to medical encounters during the same 12-month period.

The authors found that the risk of a medical encounter assigned a diagnosis code meeting the definition of urinary tract infection was significantly higher among women defined as having either type 1 or type 2 DM than it was among women in the hypertension group, and was higher among men defined as having type 2 DM than it was among men defined as having hypertension. The risk of skin infection was also higher in the DM groups than it was in the hypertension group. Although patients in the DM groups were no more likely to have a medical encounter associated with a diagnosis code meeting the definition of upper respiratory tract infection than were patients in the hypertension group, the risk of a medical encounter associated with a diagnosis code meeting the definition of lower respiratory tract infection was significantly higher in the type 2 DM group than it was in the hypertension group.

The main question regarding the interpretation of these findings is whether the differences in risk of the outcome events between the DM and hypertension groups observed in this study are reflective of true differences in the risk of infections. The investigators selected persons with a diagnosis code of hypertension as the comparison group to minimize differences in health-care-seeking behavior between the DM groups and the comparison group. This approach is preferable to random selection of a comparison group, but it is still possible that persons in the DM groups may have been more likely either to seek care for signs or symptoms of infection or to receive a diagnosis code for an infectious outcome, compared with persons in the hypertension group, because the consequences of infection are potentially more severe in persons with DM than in persons with hypertension. The unvalidated outcomes evaluated in this study were, in general, defined by diagnosis codes indicative of relatively mild illnesses, and therefore, those associations may be particularly susceptible to surveillance artifact.

Another limitation of this study is the possibility that the association of DM with an increased risk of infectious outcome is due to a higher prevalence of comorbid factors in the DM groups than in the hypertension group. Muller et al. [7] included covariates defined by diagnosis codes in the analytic models, but this method may not have properly adjusted for important differences between the groups. The definitions of heart or lung disease, for example, included relatively broad groupings of diagnosis codes. The presence or absence of a diagnosis code assigned during a 12-month period also may not be a sensitive indicator of the presence or absence of disease. In addition, the severity of comorbid conditions is likely to be an important factor, and diagnosis codes are not sensitive discriminators of disease severity. Perhaps most importantly, potentially important factors, such as urinary catheterization and functional status limitations, cannot be defined on the basis of diagnosis codes, and so differences in risk that are related to those factors cannot be distinguished in studies relying on diagnosis codes.

Despite these limitations, the finding of an increased risk of urinary tract infection in women with DM in the study by Muller et al. [7] is consistent with the results of other retrospective studies that included a more-detailed assessment of comorbid factors [8, 9] and with the recent prospective study of risk of urinary tract infection in postmenopausal women [6]. Those findings—and the results suggesting an increased risk of respiratory and skin infections in persons with DM reported by this study—are biologically plausible, contribute to the evidence for an association of DM with an increased risk of certain community-acquired infections, and suggest hypotheses to be pursued in further studies.

Acknowledgments


References