Diabetes mellitus and infective endocarditis: the insulin factor in patient morbidity and mortality

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Introduction

Despite recent advances in the diagnosis and the treatment of infective endocarditis (IE), it remains a disease with a high mortality rate, with an overall in-hospital mortality rate of 20% in recent large studies.1-3 Identification of patients at highest risk of death could offer the opportunity to adapt IE management to their specific characteristics with the aim of improving their prognosis.

Previous studies have attempted to identify determinants of mortality of IE but have led to conflicting results.2-6 This is partly due to the polymorphism of the disease, of its management, and of the populations affected, but also to heterogeneity in variables included in the statistical analyses. Surprisingly, diabetes mellitus (DM), which is increasing in industrialized countries7 and a factor of poor prognosis in various bacterial infections,8 is generally not analysed on its own as participating in the prognosis of IE.9-12

Sometimes the role of DM is indirectly assessed through the analysis of co-morbidity index, which includes DM as one of the several variables.3,6,13,14

In the rare studies analysing DM specifically, results are conflicting2,4,15-17 and the impact of insulin use has not been analysed. However, the dependent or non-insulin-dependent state of DM patients could be of importance. First, as reported through in vitro and in vivo data, the adverse effects of hyperglycaemia on immune function (polymorphonuclear leukocyte function, leukocyte adherence, chemotaxis, or phagocytosis) are the most marked in highly hyperglycaemic and/or insulin-dependent patients.8,18 Second, micro and macrovascular complications of hyperglycaemia are more frequent in insulin-using patients. Third, differences in the characteristics of IE (type of microorganisms, valvular impair, treatment tolerance, and outcome) may also exist.

Therefore, the objectives of the present study were to determine the characteristics of IE in DM patients in a large cohort of definite IE and to assess the impact of insulin use on characteristics of IE and in-hospital death.

KEYWORDS
Infective endocarditis; Diabetes mellitus; Insulin; Staphylococcus aureus; Prognostic factors; Death

Aims To analyse the characteristics of infective endocarditis (IE) in patients with diabetes mellitus (DM), and to evaluate the prognostic significance of DM according to insulin use.

Methods and results A total of 559 patients with definite IE including 75 patients (13%) with DM (insulin use n = 22; oral antidiabetic n = 53) were evaluated. Comparison of insulin-DM, oral-DM, and non-DM patients showed an older age (66 ± 13, 66 ± 10, 58 ± 17, respectively; P = 0.004) in DM patients, and more frequent IE on prosthetic valves (32, 11, and 15%, respectively; P = 0.068) in insulin-DM patients. Oral streptococci (0, 8, and 18%, respectively; P = 0.016) were less frequently the causative organism than staphylococci (64, 26, and 29%, respectively; P = 0.002) in insulin-DM patients. Vegetations, dehiscence, abscess, and regurgitation rates did not differ among the three groups, nor did cardiac surgery rates (32, 47, and 48%, respectively; P = 0.334), but in-hospital mortality was higher in insulin-DM patients (50, 19, and 15%; < 0.001). In multivariable analysis, independently of other determinants of death (age, IE location, Staphylococcus aureus, history of heart failure, immunosuppression, creatinine serum), insulin-DM was a predictor of death (OR, 4.69; 95% CI, 1.77-12.44), whereas oral-DM was not.

Conclusion IE prognosis in insulin-DM patients is poor due to the coexistence of host and pathogen factors. Insulin-DM patients with IE may require specific management.

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Methods

Population of patients

We analysed all the cases of definite IE according to Duke criteria in patients older than 15 years, which occurred during the prospective population-based survey on IE that was conducted during a 16-month-period (December 1998–March 2000) in six French regions (a population of 16 million inhabitants). During this survey, 819 patients with a suspected diagnosis of IE were included, regardless of the type of medical centre. After review of each case by two expert investigators, who had not been involved in the care of the corresponding case, 260 patients were subsequently excluded for the following reasons: possible or rejected IE (n = 195), incomplete case report form (n = 11), patient's age below 15 years (n = 3), and non-resident of study area (n = 51). The final sample was composed of 559 patients with definite IE.

Clinical data

The following parameters were collected at diagnosis of IE and during hospitalization: age, sex, fever (temperature ≥ 38°C), previous heart disease (native valve diseases, prosthetic valve, pacemaker, IE), intravenous drug abuse, HIV infection, history of cancer, co-morbidity [including DM, hypertension, dyslipidemia, coronary artery disease (CAD)], New York Heart Association (NYHA) heart failure classification, serum creatinine, transthoracic and/or transesophageal echocardiographic findings (based on a standardized questionnaire), microbiological data, medical and surgical treatment, and outcome. Location of IE was determined according to echocardiographic and/or surgical findings.

Concerning DM status, patients were separated into three categories: patients with no DM, DM patients receiving only oral anti-diabetic medication (hereafter referred to as 'oral-DM patients'), and DM patients receiving insulin (hereafter referred to as 'insulin-DM patients'). Oral-DM patients and insulin-DM patients are hereafter referred to as 'DM patients'. The diagnosis of DM was established by the clinician, based on the patients' previously known medical history at admission.

Statistical analysis

For descriptive analysis, quantitative variables were expressed as their mean ± standard deviation (95% CI), and qualitative variables were expressed as percentages. Prognostic influence of variables on in-hospital mortality was tested first in a bivariable analysis (Pearson χ² test or ANOVA). The variables analysed were as follows: age; gender; insulin-DM; oral-DM; chronic renal failure; immunodepression, history of heart failure; other co-morbidities; cardiac history (history of native valve disease, prosthetic valve, previous episode of IE); at-risk procedures (dental extraction, history of intravenous drug use); types of microorganisms; location of IE (aortic, mitral, tricuspid, pulmonic, prosthetic valve, pacemaker); echocardiography (vegetation, cardiac abscess, dehiscence, regurgitation). Next, a multivariable stepwise logistic regression was performed. OR and their 95% CI were calculated.

Results

Patient clinical history on admission

Among the 559 patients with definite IE, there were 75 (13%) DM patients (51 males, 24 females) including 22 insulin-DM patients (14 males, 8 females), and 53 oral-DM patients (37 males, 16 females) (Tables 1 and 2). DM patients were significantly older than non-DM patients (66 ± 13, 66 ± 10, and 58 ± 17, respectively; P = 0.004). Comparison of insulin-DM, oral-DM, and non-DM patients showed more frequent cardiovascular risk factors in DM patients: hypertension and dyslipidaemia. History of CAD was more frequent in DM patients, and oral-DM patients more frequently had an intracardiac pacemaker (Table 1).

Clinical and echocardiographic findings

Clinical presentation was not different between non-DM patients and DM patients, except for Osler nodes, which tended to be more frequent in non-DM patients (4 vs. 0%; P = 0.066). IE location on cardiac valves was not different between these populations, whereas pacemaker IE was more frequent in insulin-DM and oral-DM patients (P = 0.002) (Table 1). Insulin-DM patients more frequently tended to have a prosthetic valve IE (32, 11, and 15%, respectively; P = 0.068), but frequency of cardiac abscess, valve dehiscence, or regurgitation was not different between the three categories of patients. The frequency of moderate and severe congestive heart failure was not significantly different within the three categories of patients, nor were the numbers of patients with septic shock or with serum creatinine above 180 μmol/L (Table 1). The same was true for the frequency of peripheral embolisms and stroke.

Causative microorganisms

When comparing microorganism distribution between non-DM patients and DM patients all together, the single significant difference was the lower rate of oral streptococci in DM patients (5% in DM patients vs. 18% in non-DM patients; P = 0.006). However, differences in the distribution of microorganisms were more apparent when insulin-DM and oral-DM patients were analysed separately (Table 1). Group D streptococci were the microorganisms most frequently isolated in oral-DM patients (30%), whereas staphylococci were more frequently reported in insulin-DM patients (64, 26, and 29% in insulin-DM, oral-DM, and non-DM patients, respectively, P = 0.002). Considering each category of microorganism, oral streptococci were significantly less frequent in DM patients (0, 8, and 18%, in insulin-DM, oral-DM, and non-DM patients, respectively; P = 0.016). S. aureus tended to be more frequent in insulin-DM patients (41, 19, and 21% respectively; P = 0.072). Coagulase negative staphylococci were significantly more frequent in insulin-DM patients (Table 1).

Cardiac surgery and mortality

The proportion of patients who underwent cardiac surgery (valve replacement or repair) during the acute phase of IE was not statistically different among the three categories of patients (32, 47, and 48%, in insulin-DM, oral-DM, and non-DM patients, respectively; P = 0.334). In-hospital death was significantly more frequent in DM patients (28% in DM
patients vs. 15% in non-DM patients; \( P = 0.006 \)). However, this largely reflected the extremely high mortality rate in insulin-DM patients (50, 19, and 15% insulin-DM, oral-DM, and non-DM patients, respectively; \( P < 0.001 \)) (Table 1).

When adjusting for other independent prognostic factors (i.e. old age, gender, IE location, \( S. aureus \), history of heart failure, immunodepression, embolic event, serum creatinine), insulin-DM remained a strong predictor of death (OR 4.69; 95% CI 1.77–12.44; \( P = 0.0004 \)), whereas oral-DM did not (OR 0.91; 95% CI 0.41–2.04; \( P = 0.82 \)) (Table 2). Figure 1 shows the in-hospital survival rates in the three groups of patients.

**Discussion**

The present study shows that insulin-DM, which has not been considered in previous analyses of IE prognosis factors, has a strong prognostic value in patients with IE. Furthermore, it clearly shows that IE has different characteristics in patients with insulin-treated DM than in oral-DM patients.

This study is unique in several ways. First, its population-based nature permitted the collection of representative data of IE in France, and eliminated referral bias which is present in nearly all existing studies on IE. Second, the prospective assessment of a large number of cases in a very limited period of time increased the homogeneity of both the diagnosis of IE and of its management and allowed us to analyse relatively infrequent conditions such as DM. Finally, this is the only cohort of patients to date that has provided information on IE characteristics according to whether patients were receiving insulin or oral antidiabetic agents.

The rate of DM among patients with IE seems to present geographic variations with the highest values in the USA.
higher rate of DM in the USA in 558 patients with definite (ICE)-prospective cohort study confirmed the significantly data from the International Collaboration on Endocarditis.15 38% in Fowler consistent with previous reports in DM patients (30% in Moreno responsible for IE of DM patients found in this study is con- plained, as prevalence of valvular regurgitation, which is a major cause of cardiac valve surgery, does not appear more frequent in individuals with DM.20 Another reason could be a higher incidence of IE in diabetic patients with prosthetic valve as compared with others; however, there are no published data to support this hypothesis. The 25% rate of S. aureus among the microorganisms responsible for IE of DM patients found in this study is consistent with previous reports in DM patients (30% in Moreno et al.,15 38% in Fowler et al.1). One of the major contributions of the separated analysis of oral-DM and insulin-DM patients is the identification of their specific microbiological profiles. In fact, although microbiological profile of DM and non-DM patients was quite similar except for the higher proportion of oral streptococci in the former, the major role of staphylococci (S. aureus and coagulase negative staph.) in insulin-DM patients with IE was revealed by this analysis. The high rate of S. aureus in IE could be explained in DM patients by (i) the higher rate of nasal carriage rate of S. aureus that has been proved to be a source of sub- sequently bacteraemia,21,22 (ii) an increased relative risk for bacterial skin and mucous membrane infection,23 (iii) a more frequent and more intensive interaction with the healthcare system, which could favour nosocomial or noso- husial infections, and (iv) a close association between S. aureus bacteraemia and IE in DM patients.24 However, there is to date no proof of a higher incidence of IE in DM patients. Of note is that S. aureus was still the most prevalent microorganism when the analysis was reduced to patients without prosthetic valves or pacemaker (data not shown). The identification of this high rate of S. aureus among insulin-treated DM patients is all the more important given that S. aureus has been identified by several authors as being associated with higher rates of both complications and mortality in IE.2,3,6,11,25 However, the higher mortality of insulin-DM patients in our study was not totally explained by the preponderance of S. aureus since the higher risk of in-hospital death in insulin-DM patients persisted after adjustment for infection with S. aureus.

In this study, IE did not appear to be more aggressive in DM patients, as cardiac anatomic complications, heart failure, or embolic events were not more frequent. These data are consistent with the non-statistically different rate of cardiac surgery in DM patients of the present study. Nevertheless, IE prognosis appeared poorer in DM patients. The 28% rate of death in the present study is quite similar to the 31–36% reported by others.2,4,15 However, this rate, obtained when considering DM patients all together regardless of insulin use, hides high variations according to the type of diabetes. Indeed, the rate fell to 19% when only oral-DM patients were considered and appeared to be closer to those of non-DM patients (15%), whereas IE prognosis was poor in insulin-DM patients, with a rate of death as high as 50%.

Higher in-hospital mortality rate was also reported in DM patients by Wallace et al.4 (36 vs. 16%) and by Moreno et al.15 (31 vs. 15%), however, it did not reach the statistically significant level. This could be due to the lack of statistical power of these two studies involving a low number of DM patients (14 and 13 patients, respectively). On the contrary, Chu et al. in their study, which included 88 DM patients, found DM as being associated with in-hospital mortality in multivariable analysis (OR 2.48; 95% CI 1.24–4.96). In this study, DM patients were analysed all together without differentiating oral-DM patients and insulin-DM patients. In our study, taking into account whether DM required insulin or not before the onset of IE revealed that the independent association between diabetes and mortality was attributable to insulin-DM patients but not to oral-DM patients. In prognos- stic studies of IE, it thus appears crucial to consider DM on its own and also to address whether DM requires insulin or not rather than including DM in a co-morbidity score.

Although including a representative sample of IE from a very large area, this study suffers from the probable hetero- geneity of the management of IE in the 125 different centres, which was probably greater than in referral centres. Although this was a prospective study, no

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**Table 2** Multivariable association between characteristics of the patients and in-hospital death

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (60–70 vs. &lt;60 years)</td>
<td>1.64</td>
<td>0.81–3.03</td>
</tr>
<tr>
<td>Age (&gt;80 vs. &lt;60 years)</td>
<td>1.66</td>
<td>0.62–4.35</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>1.44</td>
<td>0.85–2.42</td>
</tr>
<tr>
<td>Mitral location (yes vs. no)</td>
<td>2.37</td>
<td>1.39–4.06</td>
</tr>
<tr>
<td>Aortic location (yes vs. no)</td>
<td>2.23</td>
<td>1.26–3.95</td>
</tr>
<tr>
<td>S. aureus (yes vs. no)</td>
<td>0.59</td>
<td>1.41–2.74</td>
</tr>
<tr>
<td>Insulin-DM (yes vs. no)</td>
<td>4.69</td>
<td>1.77–12.44</td>
</tr>
<tr>
<td>History of heart failure (yes vs. no)</td>
<td>2.47</td>
<td>1.34–4.55</td>
</tr>
<tr>
<td>Embolic event (yes vs. no)</td>
<td>1.29</td>
<td>0.77–2.15</td>
</tr>
<tr>
<td>Serum creatinine &gt;180 μmol/L (yes vs. no)</td>
<td>1.76</td>
<td>1.02–3.03</td>
</tr>
<tr>
<td>History of immunodepression (yes vs. no)</td>
<td>3.08</td>
<td>1.44–6.60</td>
</tr>
</tbody>
</table>

Hosmer and Lemeshow goodness-of-fit test non significant, and accuracy of classification (c-index = 0.756).

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**Figure 1** In-hospital survival curves by DM status.
standardized examination timeline was imposed; and because of the dynamic nature of the active phase of IE, the variability of clinical, echocardiographic, and radiological findings throughout this period may have had an impact on the results of the analysis.

Although our study was one of the largest cohorts of IE, the relatively low number of insulin-DM patients may have limited the statistical power to detect differences in characteristics of IE; this may explain why we failed to elucidate the reasons why insulin-DM patients are at higher risk of mortality. The separation of the survival curves more than 20 days after the diagnosis of IE may suggest that their poor prognosis could be due to their poorer overall health status rather than directly to IE. Furthermore, data on the quality of the glycaemic monitoring before and during the IE episode was not collected; had it been, it might have helped in interpreting IE characteristics in those patients.

Insulin treated DM patients with IE are thus at high risk of in-hospital mortality independent of S. aureus infection and old age, which are identified prognostic factors and more frequent in DM patients. Because of the poor outcome of IE in this population, a practitioner whose DM patients present a fever of unknown origin, a S. aureus infection or other IE risk factors should consider the possibility of screening for IE. Early anti-IE intervention and specific management could prove beneficial, even vital, in these patients.

Based on the adverse effects of hyperglycaemia on immune functions, a randomized controlled trial showed that intensive control of hyperglycaemia with insulin therapy in critically ill patients reduced the mortality rate. It has been suggested that improved glycaemic control in DM patients with IE could have a beneficial effect on the outcome. In our study, the apparently slight difference in-hospital mortality rates in non-DM patients and in oral-DM patients does not seem to support the interest of introducing insulin in the treatment of oral-DM patients with IE in order to improve their prognosis. This being said, whether improved glycaemic control in insulin-DM patients with IE has a beneficial effect on outcome remains to be established.

Recent studies pointed out the increasing rate of IE due to S. aureus and the major role of medical progress in the development of those IE. As DM prevalence is expected to increase in the coming years, IE could be more frequently reported in DM patients. The interest of IE-preventive strategies such as limiting nasal carriage of S. aureus, vaccinating patients against S. aureus, and limiting invasive procedures, should be evaluated in this population.

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Conflict of interest: The authors have not commercial or other associations that might pose a conflict of interest.

Appendix


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