International Journal of Cardiology 278 (2019) 280–284

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Duration and complications of diabetes mellitus and the associated risk of infective endocarditis

Lauge Østergaard [a,*], Ulrik M. Mogensen [i], Johan S. Bundgaard [a], Anders Dahl [f], Andrew Wang [b], Christian Torp-Pedersen [c,d], Gunnar Gislason [e], Lars Køber [a], Nana Køber [f], Thomas Fremming Dejgaard [g], Christian Seerup Frandsen [h], Emil Loldrup Fosbøl [a]

[a] Heart Centre, Rigshospitalet, Copenhagen, Denmark
[b] Department of Medicine, Duke University Medical Center, Durham, NC, United States of America
[c] Department of Health Science and Technology, Aalborg University, Denmark
[d] Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Denmark
[e] Department of Cardiovascular Epidemiology and Research, The Danish Heart Foundation, Copenhagen, Denmark
[f] Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark
[g] Steno Diabetes Center Copenhagen, Copenhagen, Denmark
[h] The Juliane Marie Center, Rigshospitalet, Copenhagen, Denmark
[i] Zealand University Hospital, Roskilde, Department of Cardiology, Denmark

ARTICLE INFO

Article history:
Received 26 May 2018
Received in revised form 14 September 2018
Accepted 25 September 2018
Available online 1 October 2018

Keywords:
Diabetes mellitus
Diabetes late-stage complications
Infective endocarditis

ABSTRACT

Background: Long duration of diabetes mellitus (DM) is associated with an increased risk of infection, however no studies have yet focused on the duration of DM and the associated risk of infective endocarditis (IE).
Methods: Patients with DM were identified through the Danish Prescription Registry, 1996–2015. Duration of DM was split in follow-up periods of: 0–5 years, 5–10 years, 10–15 years, and >15 years. Multivariable adjusted Poisson regression was used to calculate incidence rate ratios (IRR) according to study groups. DM late-stage complications and the associated risk of IE were investigated as time-varying covariates using the validated Diabetes Complications Severity Index (DCSI).
Results: We included 299,551 patients with DM. In patients with DM duration of 0–5 years, 5–10 years, 10–15 years, and >15 years, the incidence rates of IE were 0.24, 0.33, 0.58, and 0.96 cases of IE/1000 person years, respectively. Patients with DM duration 5–10 years, 10–15 years, and >15 years were associated with a higher risk of IE with an IRR of 1.24 (95% CI: 1.02–1.51), 1.92 (95% CI: 1.52–2.43) and 3.05 (95% CI: 2.11–4.40), respectively, compared with DM duration 0–5 years. Patients with a DCSI score of 2, 3 and >3 were associated with a higher risk of IE compared with patients with a DCSI score of 0, IRR = 1.78 (95% CI: 1.34–2.36), IRR = 2.34 (95% CI: 1.73–3.16), and IRR = 2.59 (95% CI: 1.92–3.48), respectively.
Conclusion: This study shows a stepwise increase in the risk of IE with DM duration and severity independent of age and known comorbidity.

1. Introduction

Infective endocarditis (IE) remains a disease with a high morbidity and mortality and the presence of diabetes mellitus (DM) has been associated with even worse outcomes in patients with IE [1–4]. The prevalence of DM among IE-patients is around 17% [5]. However, no study has yet investigated the duration of DM and the associated risk of IE [6–11]. This is of considerable interest because the incidence of IE and DM is increasing and especially with the parallel increase in expected lifetime [12,13]. Long duration of DM has been linked to an impaired immune response, late-stage complications, high risk of wounds with delayed healing process, arteriosclerotic disease with impaired tissue vascularization and endothelial dysfunction, that all can contribute to increased risk of infections.

Several studies have shown that patients with DM have an impaired immune response to infections [6,7]. These studies in basic research are backed up by population-based studies showing an increased risk of hospitalization due to infection in patients with DM compared with a background population [14,15]. However, none of these studies have focused on IE. Further, patients with DM are prone to severe endothelial dysfunction, which is one of the central pathophysiologic steps in the development of IE [10,16,17].

* Corresponding author at: Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail address: laugeoestergaard@gmail.com (L. Østergaard).

https://doi.org/10.1016/j.ijcard.2018.09.106
0167-5273/

However, data are sparse on the incidence of IE in patients with DM. Therefore, we investigated the associated risk of IE in patients with DM stratified by DM-duration and diabetic late stage complications in a nationwide cohort.

2. Methods

2.1. Data sources

Every Danish citizen is provided with a unique identifier. This makes it possible to cross-link different national administrative registries. We used the Danish Prescription Registry, the Danish National Patient Registry, the Danish Cause of Death Registry, and the Danish Population Registry. The Danish Prescription Registry holds information on every filled prescription from a Danish pharmacy since 1994. Drugs are classified according to the Anatomic Therapeutical Chemical Classification System (ATC code). Further, package size, dose of the drug, and date of prescription are registered. The Danish National Patient Registry was initiated in 1977, registering every patient admitted to a Danish hospital. In- and out-patient clinics are registered as well as the primary and secondary diagnoses of each patient. The discharge summary filled in by the physician is used for this registry. The International Classification of Diseases version 10 (ICD-10) has been used since 1994 and before that the ICD-8 was used. Since 1996, surgical procedure codes have been added to the Danish National Patient Registry, which is classified according to the Nordic Medico-Statistical Committee (NOMESCO) classification system and since 2000 data on medical examinations and treatments were added. The Danish Cause of Death Registry was used to identify date of death. The Danish Population Registry holds information on emigration date, birth date, and sex for every Danish citizen. The Danish registries are complete with high quality and have been described in further details in previously published papers [18–20].

2.2. Study population

The study population was defined from the Danish Prescription Registry as a patient who redeemed at least five prescriptions for a glucose lowering drug (see Supplementary Table 1 for drugs and corresponding ATC codes) in the period from January 1996 – December 2015. The index date was calculated from the fifth prescription of a glucose lowering drug. First line therapy of type 2 DM is life style interventions and change of diet [21,22]. We were able to follow patients from the initiation of antihyperglycemic treatment with drugs and not necessarily from the date of diagnosis. However, in this paper duration of DM will refer to the duration of DM treated with antihyperglycemic drugs. To investigate the incidence of IE according to duration of DM we split the follow-up time in periods of four: 0–5 years, 5–10 years, 10–15 years, and >15 years. A patient was thereby able to add risk-time to all four periods if the patient had DM for 20 years. Patient characteristics were examined at the initiating time point of every study period. Hence, for those included in the group of DM duration of 5–10 years, patient characteristics were identified at 5 years post index. Women under the age of 30 with a first prescription of metformin were defined as patients with poly cystic ovary syndrome and excluded from the study. Patients with IE prior to the index date was also excluded, see the Supplemental Figure for the patient selection process.

2.3. Follow-up and covariates

The study population was followed from index until: IE, emigration, end of study period, or death, whichever came first. Diabetic late-stage complications were defined as previously validated on ICD-10 codes [23,24]. Overall, diabetic late-stage complications were defined as retinopathy, nephropathy, neuropathy, cerebrovascular disease, cardiovascular disease, and peripheral vascular disease, as previously described and validated by Glasheen et al. [24] The validation study also included metabolic complications, however the registry used coded these complications differently compared with the validation study. Metabolic complications were included using specific codes for diabetes mellitus with coma and diabetes mellitus with ketoacidosis, see Supplemental Table 1. A late-stage complication was scored on the Diabetic Complications Severity Index (DCSI) where each complication could be scored as 1 or 2 depending on the severity of the diagnosis [24]. Diabetic late-stage complications were examined as time-varying covariates. Follow-up time was split at the diagnosis-date of a diabetic late-stage complication. The DCSI score was summed up at every date of diagnosis of a diabetic late-stage complication. Thereby, a patient could add risk-time to several DCSI scores.

2.4. Outcome

The primary outcome was hospitalization due to IE, which was defined as the ICD-10 codes: DI33, DI38, and DI39.8. These codes have been validated in the Danish National Patient Registry with positive predictive value of 90% for patients with a length of hospital stay ≥14 days [25,26], which we included as a criterion for having IE. In Denmark IE is treated in-hospital only.

2.5. Statistics

The follow-up time was split at 5, 10 and 15 years of follow-up. Further, patient observations were split at the date of a diagnosis of a diabetic late stage complication. In that way, the final date of one patient observation was the index date of the subsequent patient observation. Age, calendar year, and patient characteristics were updated at every split conducted. Patient characteristics for the four study groups (0–5 years DM, 5–10 years DM, 10–15 years DM, and >15 years DM) were presented by median, 25 percentile, and 75 percentile for continuous variables and frequency (percentages) for categorical variables. The incidence rate of IE was calculated for the four study groups and cumulative incidence curves of IE and Kaplan-Meier plots were included. Multivariable adjusted Poisson regression was used to compare the associated risk of IE for the four study groups. The following covariates were included in the model: sex, age, ischemic heart disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, renal disease, gastritis, dementia, cancer, pacemaker, prosthetic heart valve, beta blocker treatment, vitamin K antagonist treatment, renin-angiotensin system inhibitor treatment, corticosteroid treatment, and calendar year. Multivariable adjusted Poisson regression was also used to assess the associated risk of IE according to the DCSI score (number of diabetic late-stage complications). Further, specific late-stage complications (nephropathy, neuropathy, retinopathy, cerebrovascular disease, cardiovascular disease, peripheral vascular disease, metabolic complications) and the associated risk of IE were examined. In a separate model, diabetes treatment time and DCSI-score were both included. Results were presented with an incidence rate ratio (IRR) with a 95% confidence interval (CI). To ensure that age was adjusted most optimally, we conducted a sensitivity analysis where the follow-up time was further split at every calendar year. We examined if there was an interaction with age on the primary outcome, IE. Further, we tested if there was an interaction with sex on the primary outcome. A p-value < 0.05 was considered statistical significant. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

We included 299,951 patients who initiated glucose lowering treatment in the period from 1996 to 2015. Patient follow-up was split according to length of DM and categorized in the four study groups with corresponding patient observations: 0–5 years: 299,951 patient observations, 5–10 years: 160,424 patient observations, 10–15 years: 70,307 patient observations, and >15 years: 20,576 patient observations. Patient characteristics are presented in Table 1. Overall, patients with a long duration of DM were older and had more comorbidities.

3.1. Incidence of infective endocarditis

The crude incidence rate of IE was 0.24/1000 person years (95% CI: 0.22–0.28) in patients with 0–5 years of DM duration, 0.33/1000 person years (95% CI: 0.29–0.39) in patients with 5–10 years of DM duration, 0.58/1000 person years (95% CI: 0.49–0.69) in patients with 10–15 years of DM duration, and 0.96/1000 person years (95% CI: 0.70–1.32) in patients with >15 years of DM duration. Fig. 1 panel A shows the cumulative incidence of IE for the four study groups, while Fig. 1 panel B shows the mortality rate for the four study groups.

Compared with DM-duration 0–5 years, patients with 5–10 years, 10–15 years and >15 years were all associated with a stepwise increase in the associated risk of IE, which is shown in Fig. 2.

We found no interaction between age and the associated risk of IE for the four study groups. Further, no interaction was found between sex and the associated risk of IE for the four study groups.

3.2. Late-stage DM-complications and infective endocarditis

A stepwise increase in the incidence rate was seen across the DCSI scores from 0.10 IE cases/1000 person years for a DCSI of score 0 to 0.74 IE cases/1000 person years for DCSI score > 3 as shown in the Supplemental Table 2. Fig. 3 shows the adjusted associated risk of IE by DCSI scores. From Fig. 3, an exposure-response relationship is seen between increasing DCSI score and an increased associated risk of IE. Adjusting for DM treatment time did not change the association between DCSI score and the risk of IE. Further, DM treatment time of 10–15 years and >15 years remained significantly associated with IE when including the DCSI score in the multivariable adjusted model. When examining specific DM-complications, we identified that neuropathy, nephropathy, cardiac arrhythmias, and heart failure were complications associated with an increased risk of IE, IRR = 1.36 (95% CI: 1.07–1.73), IRR = 1.54 (95% CI: 1.11–2.14), IRR = 1.38 (95% CI: 1.12–1.70), and IRR = 1.54 (95% CI: 1.14–2.08) compared with patients without the corresponding specific DM-complication.

Table 1
Patient characteristics for patients by diabetes mellitus duration.

	DM duration 0–5 years	DM duration 5–10 years	DM duration 10–15 years	DM duration > 15 years
Demographics				
Number of patients contributing	299,951	160,424	70,307	20,576
Female, %	43.5	44.0	44.1	45.1
Age (years), median (IQR)	62.5 (52.1–72.0)	64.6 (54.6–73.4)	66.8 (57.2–75.1)	68.2 (57.5–76.2)
DCSI score, mean (SD)	1.26 (1.79)	1.47 (1.90)	1.73 (2.00)	1.83 (2.04)
Medical history				
IHD, %	14.6	17.7	20.7	22.8
Heart failure, %	6.9	7.4	8.6	9.8
Aortic valve disease, %	1.5	1.9	2.6	3.3
Mitral valve disease, %	0.7	0.8	0.8	0.9
Rheumatic heart disease, %	0.2	0.2	0.2	0.2
Peripheral artery disease, %	4.5	5.9	7.7	9.1
CVD, %	8.2	9.4	11.1	12.4
COLD, %	6.7	6.6	6.9	6.9
Renal disease, %	1.6	2.6	4.4	6.4
Dialysis treatment, %	0.1	0.1	0.3	0.5
Gastritis, %	6.7	7.7	8.9	9.4
Dementia, %	0.3	0.3	0.4	0.6
Cancer, %	10.1	9.7	11.1	11.9
Pacemaker, %	1.1	1.6	2.3	3.1
Prosthetic heart valve, %	0.4	0.6	0.9	1.1
Medication prior to index				
Insulin, %	6.7	11.0	27.1	62.5
Beta blocker, %	20.8	23.3	25.8	27.6
Aspirin, %	26.8	35.9	41.1	41.2
VKA, %	5.0	5.3	5.7	5.6
Lipid lowering medication, %	40.2	54.6	62.0	63.0
RAS inhibition, %	41.0	55.3	62.2	63.2
Corticosteroids, %	6.9	4.3	4.2	3.7

A patient was able to participate in several study groups dependent on the duration of DM. Patient characteristics were examined at the initiating time point of the study period. Abbreviations: DM: diabetes mellitus; DCSI: diabetes complications severity index; IHD: ischemic heart disease; IQR: interquartile range; CVD: cerebrovascular disease; COLD: chronic obstructive lung disease; VKA: vitamin K antagonist; RAS: renin angiotensin system.

3.3. Sensitivity analysis

Follow-up time was further split at every new calendar year as a sensitivity analysis to ensure improved adjustment of age. Patients with a DM duration of 5, 10, and 15 years were associated with an increased risk of IE, IRR = 1.10 (95% CI: 0.90–1.34), IRR = 1.69 (95% CI: 1.33–2.14), and IRR = 2.84 (95% CI: 1.93–4.19), respectively, compared with patients with a DM duration of 0 years.

4. Discussion

This study investigates the duration and late-stage complications of DM and the associated risk of IE and has two major findings. First, we identified a stepwise increase in the associated risk of IE with increasing duration of DM – an effect independent of age. Second, we found an increase in the associated risk of IE with an increased severity and number of diabetic late-stage complications.

Few population-based studies have investigated DM as a risk factor for IE [27,28]. In a population-based case-control setting, Strom et al. identified DM as a risk factor for IE [28]. The study by Strom et al. was not conducted with DM as the main focus and an analysis of the duration of DM and DM-late-stage complications were not assessed [28]. A study by Cooper et al. investigated the number of patients with diabetes in a cohort of *Staphylococcus aureus* bacteremia. The authors found that almost half of the patients had DM and that the DM-group had a statistically significant higher risk of IE [27]. Our study is able to extend the knowledge on this area and address the duration of DM and late-stage complications in a larger sample size.

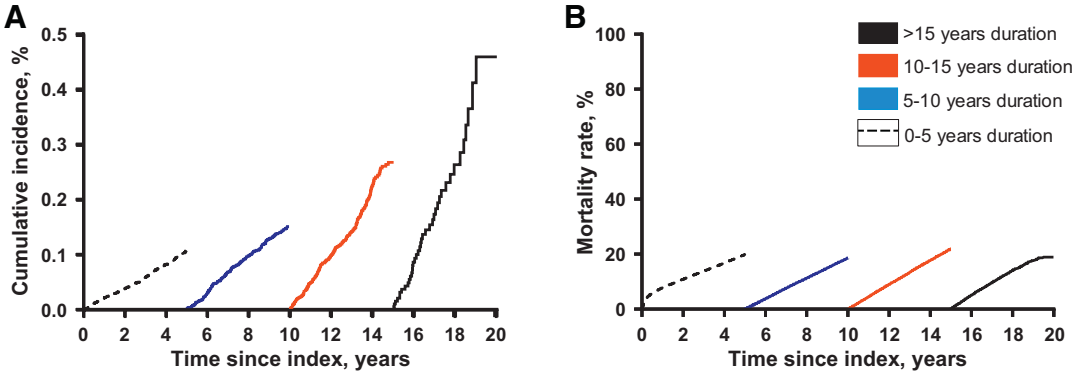

Fig. 1. Cumulative incidence of infective endocarditis and mortality rate by study groups. Panel A shows the cumulative incidence of IE and panel B shows the mortality rate in the four study groups. IE: infective endocarditis.

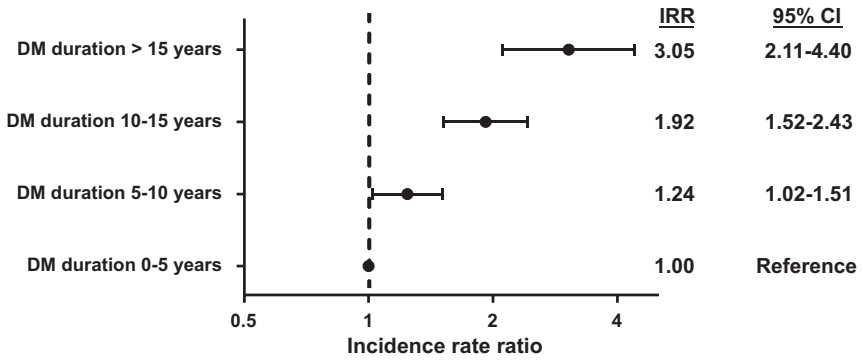

Fig. 2. DM duration and the associated risk of IE. The figure shows the associated risk of infective endocarditis by duration of diabetes mellitus. Adjusted for: sex, age, ischemic heart disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, renal disease, gastritis, dementia, cancer, pacemaker, prosthetic heart valve, beta blocker treatment, vitamin K antagonist treatment, renin-angiotensin system inhibitor treatment, corticosteroid treatment, and calendar year. IRR: incidence rate ratio, CI: confidence interval, DM: diabetes mellitus.

Several studies have shown that DM leads to endothelial dysfunction [10,29,30]. This can lead to the adhesion of bacteria and has been suggested to play a vital part in the development of IE [31]. Our study takes the in-vitro findings to a broader population-based scale where we identified that increasing duration and late-stage complications of DM increase the associated risk of IE. Further, in-vitro studies have shown that patients with DM are associated with an impaired immune response [32,33]. These studies are backed up by data from a large population based study from the US, which identified that DM was associated with a higher risk of soft and skin tissue infections compared with a matched background population [34]. Further, the authors observed that patients with DM had a higher rate of complications to skin and soft tissue infections (e.g. bacteremia, osteomyelitis, and IE) [34]. These data are supported by a population-based study from Canada, which identified a higher associated risk of infections among patients with DM compared with a matched background population [15]. Another population-based study investigated the risk of IE in patients with DM compared with patients with hypertension. The authors identified a higher associated risk of DM compared with the population with hypertension (OR = 1.9, 95% CI: 1.8–2.1) [11]. These well-conducted studies had a large sample size, however our study supplement the current knowledge in a unique way: 1) we included patients above 65 years of age, 2) Patients with DM were compared by duration of DM and the number of late-stage complications and 3) the main focus of the analysis was IE and not infections in general.

Patients with DM are closely followed in out-patient clinics and the potential risk of health-care interventions must be acknowledged due to the fact that there has been reported an increased number of health-care associated endocarditis in the past decades [35]. Further, a study by Larsson et al. has suggested an increased risk of aortic stenosis among patients with diabetes and patients with aortic stenosis has been suggested to be at moderate risk of IE [36,37].

Our study is a piece in the puzzle in understanding cross-links within the pathophysiological mechanisms of DM and IE. A review by Richard et al. suggested that the pathophysiological cascade leading to foot infections in patients with DM are found in the diabetology (immunopathy, neuropathy, angiopathy), the anatomy of the foot, and the pathogen-related factors (virulence, biofilm, density) [38]. Several of the factors suggested by Richard et al. are much likely applicable to the risk of IE in patients with DM as well.

4.1. Strengths and limitations

The study population investigated was derived from the Danish National Prescription Registry. We believe that this is a more solid approach than using ICD-10 codes derived from the Danish National Patient Registry as patients treated by the general physician are not included in this registry.

ICD-10 codes were used to assess DM late-stage complications using the Diabetes Complications Severity Index (DCSI) as done previously by Glasheen et al. [24] However, to the knowledge of the authors, no validation studies of the diagnostic codes for retinopathy, neuropathy or nephropathy has been carried out in the Danish National Patient Registry. This study investigated DM duration and diabetic late stage complications as individual factors associated with IE. No differences in the estimates were seen when late stage complications were adjusted for DM treatment time. Although multivariable adjusted models were performed, the observational design of the study must be acknowledged, and unmeasured confounders may be present. This may explain why we identified a higher associated risk of IE by increasing DM

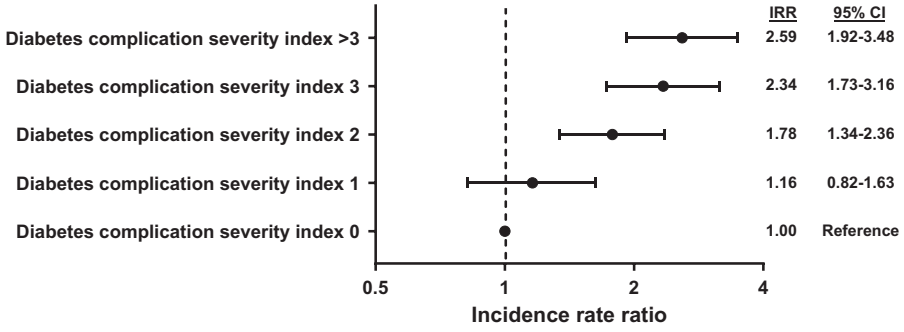

Fig. 3. Diabetes complication score index and the associated risk of infective endocarditis. The figure shows the associated risk of infective endocarditis by Diabetes Complications Severity Index. Adjusted for: sex, age, ischemic heart disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, renal disease, gastritis, dementia, cancer, pacemaker, prosthetic heart valve, beta blocker treatment, vitamin K antagonist treatment, renin-angiotensin system inhibitor treatment, corticosteroid treatment, and calendar year. Diabetes Complications Severity Index: Nephropathy = 1 or 2 dependent on severity Retinopathy = 1 or 2 dependent on severity Neuropathy = 1 Cerebrovascular disease = 1 or 2 dependent on severity Cardiovascular disease = 1 or 2 dependent on severity Peripheral vascular disease = 1 or 2 dependent on severity Metabolic complications = 2 Supplemental Table 1 shows specific ICD-10 codes. IRR: incidence rate ratio, CI: confidence interval, DCSI: diabetes complications severity index.

treatment time when adjusting for several DM late-stage complications. However, a diabetic late-stage complication may be seen as a mediator in the potential causal pathway of the development of IE and not a confounder.

Data on echocardiography, microbiological etiology and obesity status was not available from the registry. These data could have helped characterize the study population and patients with IE in more detail. Finally, we were not able to differentiate between patients with type 1 and type 2 DM.

This study identified a stepwise increase in the risk of IE with DM duration and severity independent of age and known comorbidity. Further, we observed an increased risk of IE with an increase in the Diabetes Complications Severity Index. These findings suggest an increased clinical awareness of IE in patients with long DM duration or DM late-stage complications.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.106.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgement

None.

References

[1] Y.-A. Que, P. Moreillon, Infective endocarditis, Nat. Rev. Cardiol. 8 (2011) 322–336.
[2] W.M. Kourany, J.M. Miro, A. Moreno, G.R. Corey, P.A. Pappas, E. Abrutyn, B. Hoen, G. Habib, V.G. Fowler, D.J. Sexton, L. Olaison, C.H. Cabell, I.C.E.M.D. Investigators, Influence of diabetes mellitus on the clinical manifestations and prognosis of infective endocarditis: a report from the International Collaboration on Endocarditis-Merged Database, Scand. J. Infect. Dis. 38 (2006) 613–619.
[3] X. Duval, F. Alla, T. Doco-Lecompte, V. Le Moing, F. Delahaye, J.-L. Mainardi, P. Plesiat, M. Célard, B. Hoen, C. Leport, Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI), diabetes mellitus and infective endocarditis: the insulin factor in patient morbidity and mortality, Eur. Heart J. 28 (2007) 59–64.
[4] F. Chirillo, F. Bacchion, A. Pedrocco, P. Scotton, A. De Leo, F. Rocco, C. Valfrè, Z. Olivari, Infective endocarditis in patients with diabetes mellitus, J. Heart Valve Dis. 19 (2010) 312–320.
[5] E. Cecchi, F. Chirillo, A. Castiglione, P. Faggiano, M. Cecconi, A. Moreo, A. Cialfi, M. Rinaldi, S. Del Ponte, A. Squeri, S. Corcione, F. Canta, O. Gaddi, F. Enia, D. Forno, P. Costanzo, A. Zuppiroli, G. Ronzani, F. Bologna, A. Patrignani, R. Belli, G. Ciccone, F.G. De Rosa, Clinical epidemiology in Italian Registry of Infective Endocarditis (RIEI): focus on age, intravascular devices and enterococci, Int. J. Cardiol. 190 (2015) 151–156.
[6] C.W. Farnsworth, C.T. Shehatou, R. Maynard, K. Nishitani, S.L. Kates, M.J. Zuscik, E.M. Schwarz, J.L. Daiss, R.A. Mooney, A humoral immune defect distinguishes the response to *Staphylococcus aureus* infections in mice with obesity and type 2 diabetes from that in mice with type 1 diabetes, Infect. Immun. 83 (2015) 2264–2274.
[7] P.J. Martinez, C. Mathews, J.K. Actor, S.-A. Hwang, E.L. Brown, H.K. De Santiago, S.P. Fisher Hoch, J.B. McCormick, S. Mirza, Impaired CD4+ and T-helper 17 cell memory response to *Streptococcus pneumoniae* is associated with elevated glucose and percent glycated hemoglobin A1c in Mexican Americans with type 2 diabetes mellitus, Transl. Res. 163 (2014) 53–63.
[8] Diabetes Control and Complications Trial Research Group, D.M. Nathan, S. Genuth, J. Lachin, P. Cleary, O. Crofford, M. Davis, L. Rand, C. Siebert, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, N. Engl. J. Med. 329 (1993) 977–986.
[9] P. Reichard, B.Y. Nilsson, U. Rosenqvist, The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus, N. Engl. J. Med. 329 (1993) 304–309.
[10] E.C. Eringa, E.H. Serne, R.I. Meijer, C.G. Schalkwijk, A.J.H.M. Houben, C.D.A. Stehouwer, Y.M. Smulders, V.W.M. van Hinsbergh, Endothelial dysfunction in (pre)diabetes: characteristics, causative mechanisms and pathogenic role in type 2 diabetes, Rev. Endocr. Metab. Disord. 14 (2013) 39–48.
[11] M.R. Movahed, M. Hashemzadeh, M.M. Jamal, Increased prevalence of infectious endocarditis in patients with type II diabetes mellitus, J. Diabetes Complicat. 21 (2007) 403–406.
[12] P. Erichsen, G.H. Gislason, N.E. Bruun, The increasing incidence of infective endocarditis in Denmark, 1994–2011, Eur. J. Intern. Med. 35 (2016) 95–99.
[13] C.D. Mathers, D. Loncar, Projections of global mortality and burden of disease from 2002 to 2030, PLoS Med. 3 (2006), e442.
[14] M. Dryden, M. Baguneid, C. Eckmann, S. Corman, J. Stephens, C. Solem, J. Li, C. Charbonneau, N. Baillon-Plot, S. Haider, Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections, Clin. Microbiol. Infect. 21 (Suppl. 2) (2015) S27–S32.
[15] B.R. Shah, J.E. Hux, Quantifying the risk of infectious diseases for people with diabetes, Diabetes Care 26 (2003) 510–513.
[16] S.Y.C. Tong, J.S. Davis, E. Eichenberger, T.L. Holland, V.G. Fowler, *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management, Clin. Microbiol. Rev. 28 (2015) 603–661.
[17] D. Tousoulis, A.-M. Kampoli, C. Stefanadis, Diabetes mellitus and vascular endothelial dysfunction: current perspectives, Curr. Vasc. Pharmacol. 10 (2012) 19–32.
[18] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H.T. Sørensen, The Danish National Patient Registry: a review of content, data quality, and research potential, J. Clin. Epidemiol. (2015) 449, https://doi.org/10.2147/CLEP.S91125.
[19] M. Schmidt, L. Pedersen, H.T. Sørensen, The Danish Civil Registration System as a tool in epidemiology, Eur. J. Epidemiol. 29 (2014) 541–549.
[20] H.W. Kildemoes, H.T. Sørensen, J. Hallas, The Danish National Prescription Registry, Scand. J. Public Health 39 (2011) 38–41, https://doi.org/10.1177/1403494810394717.
[21] American Diabetes Association, 4. Lifestyle Management, Diabetes Care 40 (2017) S33–S43.
[22] American Diabetes Association, 8. Pharmacologic approaches to glycemic treatment, Diabetes Care 40 (2017) S64–S74.
[23] B.A. Young, E. Lin, M. Von Korff, G. Simon, P. Ciechanowski, E.J. Ludman, S. Everson-Stewart, L. Kinder, M. Oliver, E.J. Boyko, W.J. Katon, Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization, Am. J. Manag. Care 14 (2008) 15–23.
[24] W.P. Glasheen, A. Renda, Y. Dong, Diabetes Complications Severity Index (DCSI)-update and ICD-10 translation, J. Diabetes Complicat. 31 (2017) 1007–1013.
[25] J. Sundbøll, K. Adelborg, T. Munch, T. Frøslev, H.T. Sørensen, H.E. Bøtker, M. Schmidt, Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study, BMJ Open 6 (2016), e012832.
[26] L. Østergaard, K. Adelborg, J. Sundbøll, L. Pedersen, E. Loldrup Fosbøl, M. Schmidt, Positive predictive value of infective endocarditis in the Danish National Patient Registry: a validation study, Epidemiol. Infect. (2018) 1–3.
[27] G. Cooper, R. Platt, Staphylococcus aureus bacteremia in diabetic patients. Endocarditis and mortality, Am. J. Med. 73 (1982) 658–662.
[28] B.L. Strom, E. Abrutyn, J.A. Berlin, J.L. Kinman, R.S. Feldman, P.D. Stolley, M.E. Levison, O.M. Korzeniowski, D. Kaye, Risk factors for infective endocarditis: oral hygiene and nondental exposures, Circulation 102 (2000) 2842–2848.
[29] J. Pernow, A. Shemyakin, F. Böhm, New perspectives on endothelin-1 in atherosclerosis and diabetes mellitus, Life Sci. 91 (2012) 507–516.
[30] I.A.M. van den Oever, H.G. Raterman, M.T. Nurmohamed, S. Simsek, Endothelial dysfunction, inflammation, and apoptosis in diabetes mellitus, Mediat. Inflamm. 2010 (2010), 792393.
[31] C. Golias, A. Batistatou, G. Bablekos, A. Charalabopoulos, D. Peschos, P. Mitsopoulos, K. Charalabopoulos, Physiology and pathophysiology of selectins, integrins, and IgSf cell adhesion molecules focusing on inflammation. A paradigm model on infectious endocarditis, Cell Commun. Adhes. 18 (2011) 19–32.
[32] J.M. Alexiewicz, D. Kumar, M. Smogorzewski, M. Klin, S.G. Massry, Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function, Ann. Intern. Med. 123 (1995) 919–924.
[33] M. Delamaire, D. Maugendre, M. Moreno, M.C. Le Goff, H. Allannic, B. Genetet, Impaired leucocyte functions in diabetic patients, Diabet. Med. 14 (1997) 29–34.
[34] J.A. Suaya, D.F. Eisenberg, C. Fang, L.G. Miller, Skin and soft tissue infections and associated complications among commercially insured patients aged 0–64 years with and without diabetes in the U.S, PLoS One 8 (2013), e60057.
[35] N. Toyoda, J. Chikwe, S. Itagaki, A.C. Gelijns, D.H. Adams, N.N. Egorova, Trends in infective endocarditis in California and New York State, 1998–2013, JAMA 317 (2017) 1652–1660.
[36] A.S. Dajani, Prevention of bacterial endocarditis: recommendations by the American Heart Association, JAMA 277 (1997) 1794.
[37] S.C. Larsson, A. Wallin, N. Håkansson, O. Stackelberg, M. Bäck, A. Wolk, Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases, Int. J. Cardiol. 262 (2018) 66–70.
[38] J.-L. Richard, J.-P. Lavigne, A. Sotto, Diabetes and foot infection: more than double trouble: complexity of DFI, Diabetes Metab. Res. Rev. 28 (2012) 46–53.