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Identification of Risk Markers for Poorly Controlled Type 2 Diabetes Mellitus: A Retrospective Cross-Sectional Study with Focus on Quality Assurance Based on Real World Data

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Abstract

Introduction: Poor glycemic regulation in type 2 diabetes mellitus (T2DM) significantly increases the risk of complications. Therefore, we determined the prevalence of poorly controlled T2DM at a large inner-city out-patient clinic in Denmark and identified risk markers for poorly controlled T2DM.

Methods: Data were collected retrospectively on all diabetes patients attending at the out-patient clinic in 2016. Patients attending at the clinic > 2 yrs were categorized by HbA1c as tightly controlled (≤ 50 mmol/mol/ 6.7 %; n=46) or poorly controlled (≥ 75 mmol/mol/ 9.0 %; n=108) and compared across 55 variables.

Results: 313 out of 1202 (26 %) were poorly controlled T2DM patients. Poorly controlled patients had longer duration of diabetes (10.0 vs. 8.5 yrs), higher LDL values (2.34 vs. 1.86 mmol/L), higher triglyceride levels (2.15 vs. 1.63 mmol/L), received more diabetes drugs (3 vs. 2), had more insulin prescribed (85% vs. 52 %), more retinopathy (51% vs. 20%), more comorbidities (2 vs. 1), higher Charlson comorbidity index (4 vs. 3), more yearly consultations (4 vs. 3), and more often another anticipated place of origin than Denmark (57 % vs. 24 %) compared to tightly controlled patients.

Conclusion: Risk markers for poorly controlled T2DM were a more pronounced metabolic syndrome and anticipated place of origin, and not clinical inertia, patient attendance at the outpatient clinic nor compliance to medication.

Keywords: Type 2 diabetes, Glycemic control, Uncontrolled, Diabetes mellitus, HbA1c, Risk factor, Prevalence

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease defined by hyperglycemia. If not treated, chronic and even short periods (i.e. weeks) of undesirable hyperglycemia increases the risk for developing diabetic microvascular complications such as retinopathy, neuropathy, nephropathy, foot ulcers and amputations, and macrovascular complications such as cardiovascular disease including stroke [1,2]. Achieving a near-normal glycemic level reduces the risk of microvascular complications [3].

Current guidelines recommend individualized targets of hemoglobin A1c (HbA1c): <48 mmol/mol (6.5%) for younger patients with an early un-complicated T2DM, <53 mmol/mol (7.0%) when the tight control is difficult to achieve, <58 mmol/mol (7.5%) for patients with longer diabetes duration and established complications or a higher risk of hypoglycemia. Lastly, between 58 and 75 mmol/mol (7.5 – 9.0%) for patients who aim to be symptom-free only [4].

In Denmark, T2DM patients are treated at their general practitioner but are referred to specialized out-patient

clinics if HbA1c targets cannot be achieved or if the patient has severe complications [4]. Even though patients are attending a clinic consulting highly educated personnel and experts in T2DM, some patients still do not reach their recommended HbA1c target.

Identification of predictors for not achieving the glycemic targets is essential to effectively target clinical efforts to improve glycemic control. Therefore, the aim of the study was to determine the prevalence of poorly controlled T2DM patients and to identify risk markers for poorly controlled T2DM at a University Hospital out-patient clinic.

Materials and Methods

Participants

Patients were included from the diabetic outpatient-clinic of Bispebjerg University Hospital in Denmark in 2016. Prevalence of poorly controlled T2DM was determined by the latest HbA1c level in 2016 being ≥ 75 mmol/mol (9.0%).

A cross-sectional comparison between tightly and poorly controlled T2DM was performed to identify risk markers. Definitions were based on current guidelines for being poorly controlled: HbA1c levels ≥ 75 mmol/mol (9.0%) since no target was considered healthy above 75 mmol/mol, and tightly controlled: HbA1c levels ≤ 50 mmol/mol (6.7 %) chosen as the middle value of 48 mmol/mol and 53 mmol/mol. Criteria were that more than one HbA1c measurement in a 12-month period including the last measurement should be within the tightly or poorly controlled cut-off definition. The patients should have a diabetes duration of more than two years and should have attended the endocrinology outpatient-clinic of Bispebjerg University Hospital for more than 2 years. These criteria ensured that the study was based on the treatment given at the clinic. The study was approved by the Danish Data Protection Agency (2018-41-5329).

Data collection

55 variables expected to play a role in controlling diabetes regarding glycemic control were investigated. Variables such as age, sex, disease duration, body mass index (BMI), blood pressure, lipids (low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides), eye status, amputation status, biothesiometry, estimated glomerular filtration rate (eGFR), exercise, alcohol consumption, smoking habits and anticipated place of origin were extracted from the Diabetes Rask, a local patient registry. Alanine-aminotransferase (ALAT) and the albumin/creatinine ratio were extracted from a laboratory database. Dietician appointments and marital status was obtained from the former patient record database. For information on drug prescriptions and the redemption of the prescriptions a public database was used. Data on the number of consultations in the clinic, the patient's stability in showing up for these consultations and diagnoses related to the Charlson Comorbidity Index [5], mental illness and diabetes complications were collected from a patient administrative system.

Data analysis

Descriptive statistics were performed for all 55 variables. To estimate the actual differences between the two groups, Fisher's test was performed for categorical data and either a t-test or a Mann Whitney U test for numerical data depending on normality distribution. Statistical analyses were conducted in Excel 2016 and R studio 3.4.3.

Results

During the study period (Jan - Dec 2016), 1883 patients with diabetes attended the outpatient clinic at Bispebjerg University Hospital. Out of these, 1278 patients were diagnosed with T2DM, 76 of these patients had no record of HbA1c levels in 2016, which resulted in a study population of 1202 patients. 313 of the 1202 T2DM patients were poorly controlled resulting in a prevalence of 26 %. According to inclusion and exclusion criteria, the population of 1202 T2DM patients was separated into tightly controlled (n=46) and poorly controlled (n=108) (Figure 1).

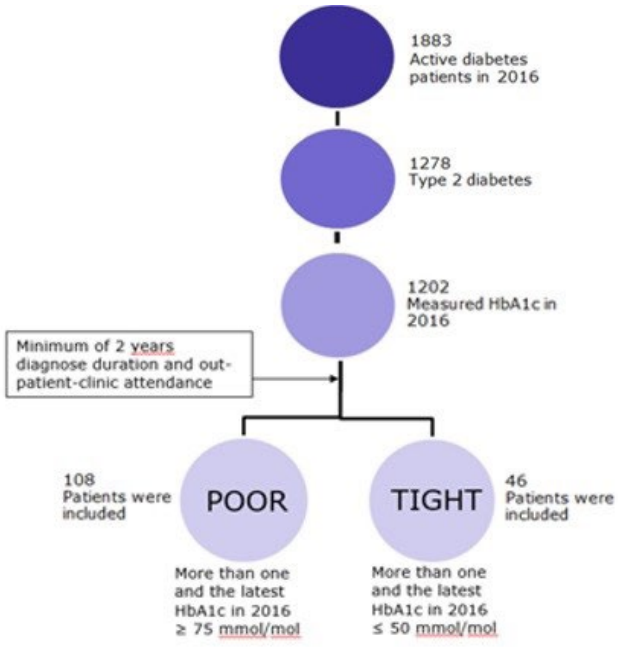

Figure 1: Patient flow. Inclusion and exclusion of patients for characterization of poorly and tightly controlled type 2 diabetes.

Sociodemographic data and comorbidities

The poorly controlled patients were characterized by longer diabetes duration (8.5 vs. 10.0 years), a higher number of comorbidities (1 vs. 2) and Charlson Comorbidity Index (3 vs. 4) compared to the tightly controlled patients. In addition, a higher percentage of poorly controlled patients were diagnosed with a cardiovascular (24 vs. 41 %), pulmonary (7 vs. 19 %) and/or psychiatric disease (2 vs. 12 %). A higher number of yearly consultations were booked for the poorly controlled patients (3 vs. 4), yet both poorly and tightly controlled patients had an equally high meeting stability (98 % vs. 96 %) at the clinic and redeemed most of their prescriptions (87 vs. 87%). The weekly consumption of alcohol was significantly lower in the poorly controlled patients (3.0 vs. 0.9 units/week) but within the recommendations for both groups. No large differences were found within other selfcare parameters such as smoking, exercise, and dietitian appointments. Poorly controlled patients were more frequently anticipated to have a different place of origin than Denmark (24% vs. 57%) (Table 1).

Table 1: Sociodemographic data and comorbidities.

Variable	Tight n=46	Poor n=108
Age (years)	60.6 (± 12.2)	62.7 (± 12.1)
Duration of diabetes (years)	8.5 (3.0 - 11.0)	10.0 (7.0 - 15.3)*
Sex		
Male	65%	57%
Female	35%	43%
Marital status		
Married	35%	45%
Not married	65%	55%
Never smoked (Yes)	48%	48%
Alcohol consumption (units/week)	3.0 (± 6.21)	0.9 (± 3.36)**
Dietitian appointment (Yes)	65%	59%
Exercise (Yes)	65%	50%
Redemption of prescriptions[1]	87%	87%
Consultation frequency in 2016	3 (2.0- 4.0)	4 (3.0- 6.0)***
Meeting stability[2]	98%	96%
Anticipated place of origin[3]		
Denmark	70%	38%***
Other	24%	57%
Unsure	6%	5%
Number of comorbidities[4]	1 (0.0- 2.0)	2 (0.0- 4.0)**
Charlson Comorbidity Index [5]	3 (2.0- 4.8)	4 (3.0- 7.0)*
Psychiatric diagnosis (Yes)	2%	12%
Cardiovascular diagnosis (Yes)	24%	41%
Hypertension and/or Hyperlipidemia (Yes)	41%	57%
Chronic pulmonary diagnosis (Yes)	7%	19%

The data are presented as mean (± standard deviation) or median (inter-quartile range) or for categorical data in percent.

[1]Calculated by dividing collected prescriptions by all medicine prescribed
[2]Calculated by dividing attended consultations by all consultations requested
[3]A qualitative prediction based on etymology of Danish first names and surnames
[4]Comorbidities related to the Charlson Comorbidity Index [5], mental illness and diabetes complications
* $0.01 < P < 0.05$; ** $0.001 < P < 0.01$; *** $P \leq 0.001$

Biomedical variables and diabetes complications

Both tightly and poorly controlled patients were overweight with a BMI of 31.7 ± 5.9 and 30.7 ± 5.5, respectively. The poorly controlled patients had a worse lipid profile than the tightly controlled patients (triglycerides (1.63 vs. 2.15 mmol/L); LDL (2.01 vs. 4.34 mmol/L)), though on average the lipid profile and blood pressure levels of both groups were close to target references. Albumin/creatinine levels in spot urine were tending to be higher in poorly controlled patients (19 vs. 42 mg/g) and eGFR values were below reference values for both groups (73.5 vs. 81.5 ml/min per 1.73 m^2). In the poorly controlled patients, the prevalence of retinopathy was significantly higher (20% vs. 51%) and almost 2% had amputations (Table 2).

Drugs for diabetes and other conditions

Both poorly and tightly controlled patients had a high total number of drugs prescribed. On average, poorly controlled patients were prescribed 1 extra diabetes drug and a higher percentage received insulin treatment (52% vs. 85%). No large differences were found between the other drugs prescribed (Table 3).

Table 2: Biomedical variables and diabetes complications.

Variable	Reference values	Tight n=46	Poor n=108
ALAT (U/L)	≤ 70 [19]	24.0 (18.0-33.0)	24.0 (19.0-34.5)
Systole (mmHg)	≤ 130 [4]	130.2 (± 17.9)	133.0 (±17.9)
Diastole (mmHg)	≤ 80 [4]	76.5 (± 9.9)	77.3 (± 10.8)
HDL (mmol/L)	≥ 1.0 [19]	1.09 (0.90-1.35)	1.05 (0.88-1.33)
LDL (mmol/L)	≤ 2.5 [4]	1.86 (± 0.66)	2.34 (± 1.00)**
Triglycerides (mmol/L)	≤ 2.0 [19]	1.63 (1.27-2.34)	2.15 (1.52-3.20)**
BMI	≤ 25 [19]	31.7 (± 5.9)	30.7 (± 5.5)
Biothesiometry (mV)	≤ 25 [20]	20.0 (12.0-29.5)	21.0 (15.8-33.0)
Albumin/creatinine in spot urine (mg/g)	≤ 30 [19]	19 (7.0-69.3)	42 (13.0-111.0)
Retinopathy (Yes)		20%	51%***
eGFR (ml/min per 1.73m^2)	≥ 90 [19]	73.5 (58.8- 86.1)	81.5 (54.4- 90.0)
Amputation (Yes)		0%	2%

The data are presented as mean (± standard deviation) or median (inter-quartile range) or for categorical data in percent. * 0.01<P<0.05; ** 0.001<P<0.01; *** P ≤ 0.001

Table 3: Drugs for diabetes and other conditions.

Variable	Tight n=46	Poor n=108
Number of drugs	7 (5.0-12.0)	10 (6.0-13.0)
Number of diabetes drugs	2 (1.0-3.0)	3 (2.0-4.0)**
Insulin	52%	85% ***
Insulin IE/day	44 (25.5-65.0)	55 (28.0-80.0)
Metformin	74%	64%
Sulfonylurea	7%	12%
Combination of blood glucose lowering drugs	2%	4%

DPP-4 antagonists	11%	18%
SLGT-2 inhibitors	26%	30%
GLP-1	24%	21%
Acetylsalicylic acid	30%	37%
Anticoagulants excl. ASA	22%	18%
Antihypertensives excl. diuretics	80%	78%
Diuretics	26%	36%
Heart therapy drugs	11%	19%
Lipid modifying drugs	70%	72%
Corticosteroids for systemic use	2%	3%
Antiepileptics	4%	10%
Antipsychotics	2%	7%
Anxiolytics	0%	3%
Hypnotics and sedatives	9%	14%
Antidepressants	20%	22%
Psychostimulants	0%	0%
Drugs for obstructive pulmonary diseases	7%	11%
The data are presented as mean (± standard deviation) or median (inter-quartile range) or for categorical data in percent of use of the drug. * 0.01<P<0.05; ** 0.001<P<0.01; *** P ≤ 0.001		

Discussion

In the present study, the prevalence of poorly controlled T2DM was 26%. Results from previous studies have shown the prevalence of poorly controlled T2DM to range between 12% to 74% with cut-offs ranging from 47.5 mmol/mol (6.5%) to 63.9 mmol/mol (8%) [6-10].

Patients with poorly and tightly controlled T2DM were compared across several variables to identify risk markers for poorly controlled T2DM. We found that poorly controlled T2DM was related to a longer diabetes duration, a worse lipid profile and an anticipated origin different from Denmark. Patients with poorly controlled T2DM had an average 1.5 years longer diagnose duration, which is in agreement with previous studies [8,9,11,12] and might be explained by the increased insulin resistance found with age and diagnose duration [11]. The poorly controlled diabetes patients had significantly higher LDL and triglyceride values, but the recommended values were almost achieved for both groups concerning both parameters. Higher levels of plasma lipids have been reported in other studies [6,8,13]. The slight elevation of lipids may also be part of the metabolic syndrome caused by insulin resistance which increases with age and duration of T2DM [11]. Thus, a more pronounced metabolic syndrome in the poorly controlled T2DM patients may explain the difficulties in achieving target values [14]. A tendency was detected between high LDL-levels and not taking lipid-controlling drugs (mostly statins) (p=0.054) suggesting clinical inertia for dyslipidemia. The poorly controlled T2DM patients' anticipated place of origin, were more likely to be other than Denmark than the tightly controlled group. This suggests that treatment regimens should be tailored to individual patients taking all variables into account since variations in basic disease mechanisms may vary with ethnicity [11,13,15].

Interestingly, we found that patients with poorly controlled T2DM had similar selfcare behavior (smoking and exercise habits and alcohol consumption) and compliance rate (meeting stability and prescription redemption) as tightly controlled patients. The patients with poorly controlled T2DM were attending more consultations at the clinic and were prescribed more drugs for their T2DM and a higher percentage received insulin treatment suggesting that, despite intensive care, some patients still do not meet their target glycemic level.

The poorly controlled patients were prescribed significantly more glucose lowering drugs (2 vs. 3), suggesting that the poor control is not caused by physicians' hesitation in pharmacological treatment. Both groups were given a dosage corresponding to 86% of the maximal dosage for all the glucose lowering drugs, when corrected for e-GFR. A significantly higher number of diabetes drugs prescribed combined with the fact that the poorly controlled diabetes patients received a significantly higher number of consultations than the tightly controlled group (3 vs. 4) indicates a group of treatment-resistant diabetics, meaning patients not responding to the recommended treatment, which is also seen in other studies [6].

Additionally, the poorly controlled patients were significantly more likely to receive insulin treatment (52% vs. 85%), and this is in line with findings in other studies [6,9,13,15-17]. Even in cases with steatosis or an extremely high insulin-resistance, insulin will act anti-hyperglycemic at high doses [18]. Hesitation to increase insulin doses may be due to a combination of increased risk for hypoglycemia, the cost, and the risk for weight gain.

The fact that patients in both groups redeemed 87% of all their prescriptions at the pharmacy suggest a drug-compliance, given that the patients take the medicine they collect at the pharmacy. The patients' exact compliance degree is difficult to determine. In some cases, the patients' anxiety for needles or hypoglycemia can play a role [6,15-17].

Additionally, poorly controlled patients had more comorbidities and a higher Charlson Comorbidity Index explained by a higher percentage being diagnosed with cardiovascular, pulmonary, and/or psychiatric disease, together with a more frequent diagnosis of retinopathy. These diagnoses might be a consequence of or a reason for a poorer glycemic control. No statistically significant difference between the groups concerning admissions to the hospital could be demonstrated, but patients with more comorbidities were followed in multiple clinics at the hospital. In support of previous studies and current guidelines on HbA1c targets, our data support that chronic glycemic levels above the recommended lead to a higher risk of microvascular complications [2,3], emphasizing the importance of glycemic control.

Other studies have shown differences in age, gender, marital status, BMI, blood pressure, smoking habits, diet, and exercise between tightly and poorly controlled patients [6-9,12,13,16]. This was not confirmed in the present study.

This study may serve as quality assurance at the out-patient clinic. However, the study holds some limitations. Many variables were self-reported by the patients, redemption of prescription was used to investigating drug compliance, and place of origin was estimated by surnames. Disparities may still be present for other characteristics not assessed in this study, including income, education, and other social and economic factors. Further cross-validation needs to take these precautions into account.

Conclusion

The prevalence of poorly controlled T2DM was 26% at this out-patient clinic in Denmark. Risk factors for poorly controlled T2DM were neither clinical inertia, patient attendance at the outpatient clinic nor the estimated compliance to medication. Eligible variables for poorly controlled T2DM were anticipated place of origin and a more pronounced metabolic syndrome caused by insulin resistance.

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