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Original research article for Diabetes Research and Clinical Practice

High rate of hypoglycemia in 6,770 type 2 diabetes patients with comorbid dementia: a multicenter cohort study on 215,932 patients from the German/Austrian diabetes registry

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Structured abstract

Aims: Dementia and type 2 diabetes (T2D) are two major phenomena in older people. To compare anti-hyperglycemic therapy and diabetes-related comorbidities between elderly T2D patients with or without comorbid dementia.

Methods: 215,932 type 2 diabetes patients aged ≥ 40 years (median[Q₁;Q₃]: 70.4[61.2;77.7] years) from the standardized, multicenter German/Austrian diabetes patient registry, DPV, were studied. To identify patients with comorbid dementia, the registry was searched by ICD-10 codes, DSM-IV/-5 codes, respective search terms and/or disease-specific medication. For group comparisons, multiple hierarchic regression modeling with adjustments for age, sex and duration of diabetes was applied.

Results: 3.1% (n=6,770; 57% females) of the eligible T2D patients had clinically recognized comorbid dementia. After adjustment for demographics, severe hypoglycemia (insulin group: 14.8 \pm 0.6 vs. 10.4 \pm 0.2 events per 100 patient-years, p<0.001), hypoglycemia with coma (insulin group: 7.6 \pm 0.4 vs. 3.9 \pm 0.1 events per 100 patient-years, p<0.001), depression (9.9 vs. 4.7%, p<0.001), hypertension (74.7 vs. 72.2%, p<0.001), stroke (25.3 vs. 6.5%, p<0.001), diabetic foot syndrome (6.0 vs. 5.2%, p=0.004) and microalbuminuria (34.7 vs. 32.2%, p<0.001) were more common in dementia patients compared to T2D without dementia. Moreover, patients with dementia received insulin therapy more frequently (59.3 vs. 54.7%, p<0.001), but metabolic control (7.7 \pm 0.1 vs. 7.7 \pm 0.1%) was comparable to T2D without dementia.

Conclusions: In T2D with dementia, higher rates of hypoglycemia and other diabetes-related comorbidities were observed. Hence, the risks of a glucocentric and intense diabetes management with insulin and a focus on tight glycaemic control without considering other factors may outweigh the benefits in elderly T2D patients with comorbid dementia.

Keywords: dementia, type 2 diabetes mellitus, hypoglycemia, diabetes-related complications, diabetes therapy, metabolic control

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1. Introduction

One major public health problem in older people is the occurrence of neurocognitive disorders such as dementia. The prevalence of dementia has increased over the last years, especially in people 85 years and older [1]. It is estimated that globally 35.6 million people live with dementia [2]. The most common type of dementia is Alzheimer's disease [3]. It accounts for 60% to 80% of cases [3]. Other forms of dementia are: i) vascular dementia, ii) mixed forms of dementia, iii) Lewy body dementia, iv) frontotemporal dementia, and v) dementia caused by other degenerative conditions (e.g. Creutzfeldt-Jakob disease, Parkinson's disease, normal pressure hydrocephalus) [3]. A review concluded that type 2 diabetes (T2D) is related to a 1.5 to 2.5-fold higher risk of dementia [4]. The etiology of dementia in T2D is suspected to be multifactorial [4]. Mechanisms linking T2D with dementia might be: acute hyperglycemia, recurrent hypoglycemia, hyperinsulinemia, insulin resistance, functional brain insulin deficiency and hypothalamic-pituitary-adrenal axis dysregulation [5,6]. Moreover, genetic predisposition, cerebral microvascular diseases, hypertension, dyslipidemia, macrovascular diseases, amyloid- β deposition, oxidative stress and inflammatory mediators are discussed [5,6]. Physical inactivity and obesity contribute to hypertension, insulin resistance and low-level inflammation, and thereby may also increase dementia risk [6]. Mayeda and colleagues reported that in the US the risk of dementia in T2D varies between ethnicities even after adjustment for sociodemographic and diabetes-related characteristics [7]. It is lowest in Asians and increased by 40-60% in Native or African Americans, and 19-30% in Latinos or non-Hispanic whites [7]. Besides genetic factors, behavioral or environmental factors are discussed, although more research is needed [7].

Dementia and its symptoms can influence the course of diabetes, namely diabetes therapy and diabetes-related complications [8-10]. The main objective of this research was to compare a large number of German/Austrian T2D patients with or without clinically recognized comorbid dementia with regard to diabetes therapy and outcome. Questions to be answered:

1. Do sex distribution and BMI differ between T2D with or without dementia?
2. Is insulin treatment more frequent in T2D with dementia?
3. Is metabolic control worse in T2D with dementia?
4. Are acute diabetes-related complications (e.g. hypoglycemia) or chronic comorbidities (e.g. hypertension, stroke, depression, microalbuminuria) more common in T2D with dementia?
5. Is hospital admission more frequent and duration of hospital stay longer in T2D with dementia?

2. Subjects, materials and methods

2.1 Subjects and diabetes patient registry

Subjects for the present study were retrieved from the multicenter, prospective diabetes patient registry, DPV (Diabetes-Patienten-Verlaufsdokumentation). The registry data is collected by a standardized electronic health record system. For nearly 20 years, more than 400 specialized German/Austrian diabetes care centers enter demographics and clinical data on a regular basis. Every half year, the locally documented data are anonymized and transmitted to the University of Ulm, Germany. Inconsistent data are reported back to the centers for correction. The establishment and analysis of the database have been approved by the ethics committee of the University of Ulm, Germany. The local review board of each participating center has approved the anonymized data collection.

By March 2014, the registry comprised data on 338,981 patients with any type of diabetes. For the present study, 215,932 T2D patients aged ≥ 40 years from 161 German and 7 Austrian centers were considered (Fig. 1). To identify patients with clinically recognized comorbid dementia in the database, ICD-10 codes, DSM-IV and DSM-5 codes, specific search terms for a diagnosis of dementia and/or drugs specific for dementia treatment were used. Data entries were made by physicians and health care professionals at each site based on clinically available data from routine care. Dementia was either already diagnosed in patients, or diabetologists made the diagnosis jointly with neurologists. If a positive result in a mental status test used to screen for dementia (e.g. mini mental state examination, clock-drawing test) was documented, patients were also assigned to the dementia group. A mental status test was defined positive by using generally accepted cut-offs. As an abnormal mental status test is solely an indicator for cognitive impairment, on the patient level free-text entries were studied additionally. All 16 patients with a pathologic mental status test could be clearly allocated to a specific type of dementia. For each patient included, the most recent year of care was studied. In case of multiple patient contacts per year, data were aggregated.

2.2 Metabolic control and diabetes therapy

Hemoglobin A1c (HbA1c) was used to assess metabolic control. To consider different laboratory methods, HbA1c values were mathematically standardized to the reference range of the Diabetes Control and Complications Trial (DCCT; 20.7-42.6 mmol/mol) by using the multiple of the mean method [11].

Diabetes therapy was specified as i) insulin therapy alone or in combination with other anti-diabetic medication, ii) oral anti-diabetic drugs (OAD)/glucagon-like peptide-1 agonists (GLP-1), iii) non-pharmacological therapy (dietary and physical advice only). Insulin dose per kilogram body weight was calculated and the frequency of patients using sulfonylureas or metformin was studied.

2.3 Diabetes-related complications

Hypertension was defined as an elevated median systolic and/or diastolic blood pressure above 140/90 mmHg [12] or the use of anti-hypertensive medication. The use of lipid-lowering agents and/or at least one lipid parameter on average in the abnormal range within the last year of care was classified as dyslipidemia. Thresholds for abnormal lipid values were defined according to the Adult Treatment Panel III (ATP III) criteria as: total cholesterol >5.2 mmol/l, LDL >3.4 mmol/l, triglycerides >1.7 mmol/l, HDL <1.0 mmol/l (men)/<1.3 mmol/l (women) [13]. Severe hypoglycemia was defined as a state in which patients require assistance by another person [14,15]. Among those events, the sub-group ‘hypoglycemia with coma’ was defined by loss of consciousness [14,15]. Depression was defined as either a clinical diagnosis and/or the use of antidepressive medication as described in ref. [16]. Definitions of diabetic foot syndrome, myocardial infarction, stroke, retinopathy, microalbuminuria and renal failure are given in detail elsewhere [14]. Repeated inpatient care was classified as having at least two inpatient stays within the most recent year of care.

2.4 Statistical methods

SAS (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA) version 9.4 was applied for statistical analysis. Descriptive statistics were performed and results are displayed as median with quartiles for continuous variables and as proportions for binary data. Continuous variables were compared by Kruskal-Wallis test and binary data by χ^2 -test. As multiple tests were performed, p-values were adjusted using Bonferroni step-down correction (Holm method).

For the comparison of metabolic control, diabetes therapy and the presence of diabetes-related complications between groups, multiple hierarchic regression modeling was implemented to account for potential confounders. Basically, models were adjusted for the following demographics: age, sex and known duration of diabetes. Each model included treatment center as a random factor (Cholesky covariance structure).

Sensitivity analyses were performed where appropriate. The confounder 'age' was categorized as 40-<50 y, 50-<70 y, 70-<90 y and ≥ 90 y. Duration of diabetes was divided into tertiles. For continuous target variables, linear regression was applied and for binary variables logistic regression. Poisson regression models were created to compare count data. As estimation technique residual maximum likelihood was used in linear regression and maximum likelihood in logistic or Poisson regression. To compute denominator degrees of freedom, between-within method was applied. Adjusted estimates (means \pm SE) were calculated based on observed marginal frequencies of each confounding variable. A two-sided $p < 0.01$ was considered significant.

3. Results

3.1 Description of study population

In 3.1% (n=6,770) of the eligible T2D patients an additional clinically recognized dementia was reported.

Further analysis on the specific type of dementia revealed:

- i) 5,560 (82.1%) cases with vascular dementia
- ii) 695 (10.3%) cases with Alzheimer's disease
- iii) 125 (1.8%) cases with other specific types of dementia (e.g. frontotemporal dementia, Parkinson's dementia, Lewy body dementia)
- iv) 390 (5.8%) cases with dementia not otherwise specified or mixed forms of Alzheimer's disease and vascular dementia

The overall frequency of dementia increased with age: in the youngest age group (40-<50 y), 0.3% of T2D patients had comorbid dementia. In the 50-<70 year olds and the 70-<90 year olds, clinically recognized dementia was present in 1.0% and 5.0% of cases. In the oldest age group (≥ 90 y), frequency of dementia amounted to 13.1%.

Fig. 2 depicts the sex ratio for T2D patients with or without comorbid dementia as well as for the general German population [17]. For the Austrian population, no relevant difference in sex ratio compared to the German population exists. Below 70 years of age, the percentage of males was higher in T2D patients with or without dementia compared to age-matched people of the general population (Fig. 2). Above 70 years, no clinically relevant difference in sex ratio was observed. However, a female preponderance was present in all three groups aged 90 years or older.

Table 1 displays further baseline characteristics of the study population. Adjustment for demographics did not alter the significance for the lower body weight and body mass index (BMI) in T2D with dementia (body weight: 82.8 ± 0.3 vs. 86.8 ± 0.2 kg, $p < 0.001$; BMI: 29.1 ± 0.1 vs. 30.5 ± 0.1 kg/m², $p < 0.001$), even after additional adjustments for therapeutic regimen, or insulin therapy and metformin use, or the interaction between age and sex.

3.2 Metabolic control and diabetes therapy

Table 2 summarizes the comparison of metabolic control and diabetes therapy between T2D with or without comorbid dementia after demographic adjustment. Additional adjustment for therapeutic regimen did not alter the finding on metabolic control. Moreover, demographically adjusted frequencies for insulin therapy and OAD/GLP-1 treatment (also: use of metformin or sulfonylureas separately) persisted after additional adjustment for BMI. By contrast, for non-pharmacological therapy, a slight but significant difference could be observed if additionally adjusted for BMI (dementia vs. no dementia: 15.0 vs. 16.7%, $p = 0.003$).

3.3 Diabetes-related comorbidities

Acute and chronic diabetes-related comorbidities with a significant difference between T2D with or without dementia after adjustment for demographics are given in Table 3. In people on anti-hyperglycemic medication typically conveying a risk for hypoglycemia i.e. insulin or sulfonylureas, the rate of severe hypoglycemia or hypoglycemia with coma was still higher in dementia patients if adjusted additionally for HbA1c or the interaction between age and sex (each $p < 0.001$). However, as hypoglycemia may also occur in patients with other anti-hyperglycemic medication (OAD/GLP-1) or even in patients with no pharmacological therapy, we additionally analyzed the rate of severe hypoglycemia and hypoglycemia with coma in all patients and again observed higher rates in dementia patients if adjusted for demographics plus insulin therapy and use of sulfonylureas (Table 3). Except for diabetic foot syndrome, the higher frequencies of hypertension, anti-hypertensive medication, stroke and microalbuminuria in dementia patients persisted after additional adjustment for therapeutic regimen and HbA1c. Moreover, the rate of depression in patients with comorbid dementia was still higher if adjusted additionally for BMI. Further adjustment for BMI or therapeutic regimen plus BMI did not alter the frequency or duration of hospital care.

For the presence of myocardial infarction or retinopathy no significant difference was observed between groups, neither after adjustment for demographics (dementia vs. no dementia: myocardial infarction 8.9 vs. 8.3%, $p=0.07$; retinopathy 23.4 vs. 21.4%, $p=0.04$) nor after additional adjustment for therapeutic regimen and HbA1c (myocardial infarction: 8.5 vs. 8.2%, $p=0.43$; retinopathy: 21.5 vs. 20.2%, $p=0.16$). Moreover, the frequency of dyslipidemia (dementia vs. no dementia: 82.8 vs. 82.9%, $p=0.78$) or renal failure (3.0 vs. 3.1%, $p=0.53$) and the use of lipid-lowering medication (33.8 vs. 33.4%, $p=0.60$) were comparable between T2D with or without dementia if adjusted for demographics.

4. Discussion

The present multicenter study among a large T2D cohort ($n=215,932$) from Germany and Austria aimed to compare diabetes therapy and diabetes-related outcome between patients with or without an additional clinically recognized dementia. Our main findings were that T2D patients with comorbid dementia had more diabetes-related complications, primarily hypoglycemia, besides a more intense diabetes management with insulin and a comparable metabolic control.

The higher presence of diabetes-related comorbidities in dementia patients can be partially attributed to the relationship between diabetes-related factors and subsequent dementia risk. Whithmer and colleagues reported in T2D an elevation of dementia risk depending on the number of hypoglycemic episodes [18]. On the other hand, a recently published US study found that older T2D patients with dementia are at high risk for hypoglycemia and that this risk is associated with intense diabetes treatment (i.e. tight glycaemic control and use of insulin/sulfonylureas) [19]. A possible explanation might be that patients with dementia are less able to recognize hypoglycemia, to treat it adequately, and to prevent it by modifying diabetes therapy. Moreover, a reduced ability to communicate complications when they arise may play a role. Hence, a bidirectional relationship may explain the higher rate of hypoglycemia observed in our dementia patients, especially in those treated with insulin or sulfonylureas which typically convey a high risk for hypoglycemia. As depression is a known risk factor for dementia [20], a higher rate in our dementia patients was suspected. A recent narrative review concluded that depression in later life is also a prodrome to dementia [20]. Even though latest research pointed out that late onset hypertension might be no risk factor for dementia in very old people (>90 y) [21], several studies revealed an increased risk for dementia and cognitive decline in

diabetes patients with hypertension [22,23]. As stroke could be a cause for vascular dementia [24], the higher presence of stroke in T2D with dementia is not surprising. Less ability to recognize foot injury and to perform adequate foot care might be one reason for the higher frequency of diabetic foot syndrome in T2D with dementia. Moreover, the first risk score for the prediction of dementia in T2D elucidated diabetic foot syndrome as predictive [25]. Independent of metabolic control, an association between microvascular damage and dementia or cognitive decline in T2D was reported [26,27] and underlines the higher presence of microalbuminuria observed in dementia patients. Overall, dementia itself and the higher frequency of diabetes-related comorbidities may contribute to the more frequent inpatient care and the longer duration of hospital stays.

An easier application and a better compatibility with social structures (e.g. residential homes, welfare centers, family members) as well as reimbursement might be possible reasons for the higher insulin use in T2D with dementia observed in this study as well as in previous investigations [10,28]. Moreover, as indicated by our data, hospitalization is more likely in dementia patients and many patients with dementia may live in residential and nursing homes or are cared for at home by nursing services. For these institutions, injection of insulin might be the preferred type of anti-diabetic treatment due to time constraint, practicability and cost-efficiency. Another aspect is that insulin therapy in combination with OAD has been shown to be effective in slowing cognitive decline compared to OAD treatment alone [29]. Moreover, the anabolic potential of insulin is favorable in patients with age-related or diabetes-associated sarcopenia.

Mann et al. mentioned previously growing concerns about a glucocentric approach of diabetes management (i.e. focus on the achievement of tight blood glucose control at the expense of controlling other parameters such as hypertension or dyslipidemia) [30]. Mainly in frail older patients, the dangers of a glucocentric and intense diabetes management with insulin and focus on tight glycemic control without considering patient preferences or other factors may outweigh the benefits. For example, the risk of hypoglycemia [19] and of treatment burden should be kept in mind in older patients with limited life expectancy who may not profit from tight glycemic control. Most modern guidelines suggest individualization of HbA1c targets in older people [31,32]. For demented patients, a higher target up to 8.5% (70 mmol/mol) is appropriate [32].

Although metformin is the first-line treatment in T2D, it was used less frequently in patients with comorbid dementia. This can be either related to a difference in prescribing patterns in dementia versus non-dementia patients, or to differences in drug effects on cognitive decline. Metformin is prescribed especially in obese

patients due to its beneficial metabolic effects. As patients with dementia had lower body weight and BMI, this may contribute to the lower prescription of metformin. Moreover, impaired renal function is a contraindication for metformin. Thereby, the potential risk of acute reduction of renal function in older and multi-morbid patients (e.g. by medication with non-steroidal anti-inflammatory drugs, drug interactions or diarrhea) often deters physicians from prescribing metformin. Appropriate treatment of elderly patients with the risk of cognitive decline may involve choices that tailor diabetes treatment to individual patient characteristics. Few studies on anti-diabetic medication and dementia are available with conflicting results. In patients using metformin, an association with poor cognitive performance and a higher risk for dementia were suspected [33,34]. However, there are studies revealing positive effects of metformin in terms of protecting against cognitive decline [35,36]. Thereby, the latter findings may also contribute to the lower use of metformin in patients with already impaired cognitive function. For sulfonylureas, either no association with cognition or a decreased risk of dementia was reported [34-36].

To date, there is no consistency regarding an association between HbA1c and cognitive function. Some previous studies revealed no difference in HbA1c between dementia and non-dementia patients [10,28], whereas others indicate that uncontrolled diabetes or even higher average blood glucose values are associated with increased dementia risk [37,38]. One explanation for the comparable metabolic control in our study might be that patients had a lifetime diagnosis of dementia and as dementia patients are cared for more intensively, this may implicate also a more intensive diabetes care.

It is well known that dementia is associated with weight loss due to impaired taste and olfaction, inability to prepare and eat food, restlessness and wandering, increased energy expenditure, inflammatory processes and comorbid diseases. Therefore, it was no wonder that T2D patients with comorbid dementia had a lower BMI and body weight than non-dementia patients.

The proportion of clinically recognized dementia observed in T2D patients of this study is similar to the prevalence found in the respective age group of the German population [39]. However, as diabetes is a risk factor for dementia, the observed frequency in our study cohort is lower than expected. Due to differences in age range of patients included or different assessment methods for dementia (e.g. observational vs. screening), comparison to other research is not simple. There are reports indicating that dementia affects up to 17.1% of T2D patients aged ≥ 60 years and 24.2% aged ≥ 75 years [7,10], besides a UK cohort study

among hospitalized T2D patients aged ≥ 30 years that reported a similar frequency to our study (3.2% vs. 3.1%) [40]. Moreover, a declining prevalence of dementia over the past years has been reported for Germany [41] and other developed countries in Europe as well as for the US [42]. Our data are in good correlation with population based studies in diabetes patients that show a continuous increase of dementia with age [10,40]. A higher percentage of dementia in males of younger ages was also reported in the EURODEM study and in a UK nation-wide study among younger people [43,44]. One reason might be the occurrence of vascular dementia as a consequence of more pronounced exposition to vascular risk factors in males. A Swedish study among young men (mean age: 18 y) who were followed for an average of 37 years, identified alcohol intake, stroke, use of antipsychotics, depression, drug-intoxication other than alcohol, and high systolic blood pressure as independent risk factors for young-onset dementia, especially vascular dementia and dementia of unspecified types [45]. In the UK, Alzheimer's disease accounted for only 34% of dementia cases in people younger than 65 years, whereas in older people it amounted to 80% [43]. The female preponderance in older ages is related to the longer life expectancy and the lower risk for death due to e.g. stroke or myocardial infarction, and does not reflect a generally higher risk for dementia in females. As indicated by Fig. 2, above 90 years of age a female predominance was also present in the general population. Another aspect to be considered is the potential influence of estrogen on dementia risk. Whereas in younger females, higher levels of estrogen were shown to be protective against dementia, a recent study indicated a higher risk for dementia in older females (≥ 65 y) with high levels of endogenous estrogen [46].

Major strengths of this study are its large number of patients included from real-life care and the inclusion of younger T2D patients. Many previous studies investigated patients aged 60 years or older. One limitation of the study is that the definition of dementia was based on a diabetes registry and thereby the type of dementia could not be specified in some patients. Moreover, people allowing only the documentation of diabetes and not of dementia could not be considered as dementia patients. In clinical practice a diagnosis of dementia is not always simple and is often made with caution due to insurance reasons. Therefore, a limitation that should be acknowledged is the potential under-reporting of dementia in the database which may explain the low proportion of T2D patients with dementia compared to given literature reports.

In conclusion, there are clear differences between T2D patients with or without clinically recognized comorbid dementia. A major focus in clinical care should be on the avoidance of hypoglycemia in patients with dementia. Goals and therapeutic choice should be reconsidered in elderly T2D patients with comorbid dementia as the benefits of an intense diabetes management with insulin and focus on tight glycemic control without considering other factors appear to be outweighed by the risks.

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Contributor statements:

N.P. wrote the initial draft, edited the manuscript and contributed to data analysis and interpretation. J.S., A.D., M.D.D., P.F., P.M.J., S.M., S.M., U.P., A.S., A.Z. researched data and reviewed/edited the manuscript. R.W.H. conceptualized the study in collaboration with J.S., reviewed and edited the manuscript, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version to be published.

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Table 1 - Baseline characteristics of study population, classified by sex and presence/absence of dementia.

	T2D patients			Female T2D patients		Male T2D patients	
	All	No dementia	Dementia	No dementia	Dementia	No dementia	Dementia
N	215,932	209,162	6,770	100,936	3,862	108,226	2,908
Female sex, %	48.5	48.3	57.0	100.0	100.0	0.0	0.0
Age, years	70.4 [61.2; 77.7]	70.1 [60.9; 77.4]	79.9 [74.2; 85.2]	72.1 [63.1; 79.4]	82.2 [76.5; 86.9]	68.1 [59.2; 75.3]	77.2 [71.5; 82.1]
Age at diabetes diagnosis, years	59.0 [49.5; 68.3]	58.6 [49.3; 68.0]	69.1 [60.4; 76.1]	60.3 [50.7; 69.8]	71.0 [62.7; 77.8]	57.1 [48.2; 66.1]	66.4 [57.7; 73.3]
Diabetes duration, years	8.6 [3.1; 15.1]	8.6 [3.1; 15.1]	10.3 [5.7; 14.8]	9.1 [3.4; 15.6]	10.5 [6.0; 14.9]	8.0 [2.7; 14.6]	10.1 [5.4; 14.7]
Duration of pharmacological diabetes therapy, years	4.4 [0.2; 10.3] (n=186,118)	4.4 [0.2; 10.3] (n=180,088)	5.1 [0.3; 10.5] (n=6,030)	4.7 [0.3; 10.7] (n=86,418)	5.2 [0.3; 10.6] (n=3,447)	4.0 [0.1; 10.1] (n=93,670)	5.0 [0.2; 10.5] (n=2,583)
Body weight, kg	84.7 [73.3; 98.0] (n=191,015)	85.0 [73.8; 98.0] (n=185,936)	76.0 [66.7; 87.0] (n=5,079)	79.2 [68.4; 92.0] (n=89,427)	70.8 [62.1; 80.5] (n=2,847)	90.0 [79.4; 102.8] (n=96,508)	82.0 [74.0; 93.0] (n=2,232)
BMI, kg/m²	29.6 [26.2; 33.9]	29.7 [26.2; 33.9]	27.4 [24.4; 30.9]	30.1 [26.1; 34.8]	27.2 [24.0; 30.9]	29.4 [26.3; 33.2]	27.6 [24.8; 31.0]

Median with quartiles unless otherwise indicated. Except for duration of pharmacological diabetes therapy, all p-values were <0.01 for the comparison between patients with or without dementia. *BMI* body mass index, *T2D* type 2 diabetes.

Table 2 - Metabolic control and diabetes therapy in type 2 diabetes with or without comorbid dementia.

Adjusted estimates	Type 2 diabetes		P-value
	No dementia	Dementia	
N	209,162	6,770	-
HbA1c, %	7.7±0.1 (n=189,372)	7.7±0.1 (n=6,030)	ns
HbA1c, mmol/mol	61±1	61±1	ns
No pharmaceuticals, %	19.7	18.7	ns
OAD/GLP-1, %	46.6	42.6	<0.001
Metformin, %	33.2	28.5	<0.001
Sulfonylureas, %	13.8	13.1	ns
Glibenclamide, %	4.1	3.9	ns
Glimepiride, %	8.2	8.1	ns
Others[†], %	1.6	1.6	ns
Insulin, %	54.7	59.3	<0.001
Insulin dose[*], IU/kg	0.60±0.01 (n=102,169)	0.58±0.01 (n=3,399)	0.004

Adjusted means±SE or proportions. To adjust for the confounders age, sex and duration of diabetes, hierarchic multiple regression modeling was applied. For variables not documented in all patients, the number in parentheses indicates the patients studied. ^{*}insulin-treated patients only. [†]includes e.g. chlorpropramide, gliclazide, gliquidone. *GLP-1* glucagon-like peptide-1 agonists, *HbA1c* hemoglobin A1c, *ns* not significant, *OAD* oral anti-diabetic drugs.

Table 3 - Diabetes-related comorbidities in type 2 diabetes with or without comorbid dementia.

Adjusted estimates	Type 2 diabetes		P-value
	No dementia	Dementia	
N	209,162	6,770	-
Hypertension, %	72.2 (n=195,866)	74.7 (n=6,481)	<0.001
Anti-hypertensive drugs, %	57.7 (n=195,581)	61.0 (n=6,465)	<0.001
Severe hypoglycemia, per 100 pat.years			
Total			
All patients *	5.42±0.06	7.75±0.29	<0.001
Patients on insulin	10.39±0.11 (n=108,271)	14.77±0.58 (n=4,118)	<0.001
Patients on sulfonylureas	5.23±0.15 (n=30,406)	8.06±0.79 (n=1,123)	<0.001
With coma			
All patients *	2.20±0.04	4.29±0.21	<0.001
Patients on insulin	3.88±0.07 (n=108,271)	7.55±0.39 (n=4,118)	<0.001
Patients on sulfonylureas	2.56±0.10 (n=30,406)	4.78±0.59 (n=1,123)	<0.001
Depression, %	4.7	9.9	<0.001
Stroke, %	6.5	25.3	<0.001
Diabetic foot syndrome, %	5.2	6.0	0.004
Microalbuminuria, %	32.2 (n=146,002)	34.7 (n=4,775)	<0.001
Repeated inpatient care, %	13.6	19.0	<0.001
Hospital duration, days/year	5.83±0.01	7.09±0.03	<0.001

Adjusted means±SE or proportions. To adjust for the confounders age, sex and duration of diabetes, hierarchic multiple regression modeling was applied. For variables not documented in all patients, the number in parentheses indicates the patients studied. * model adjusted for demographics plus insulin therapy and use of sulfonylureas. *pat.years* patient-years.

Fig. 1 - Selection of study population.

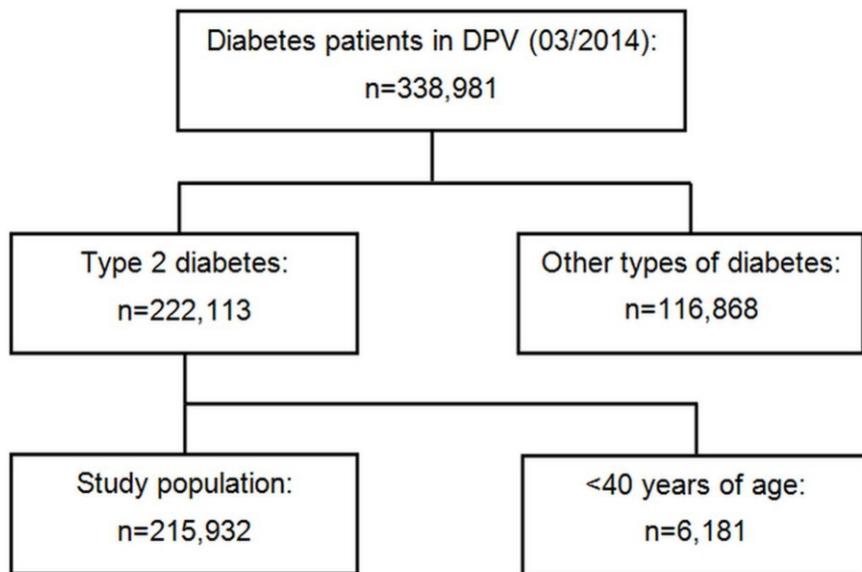


Fig. 2 - Comparison of sex distribution between type 2 diabetes patients with (DM+D) or without dementia (DM-D) and the general German population (GP [17]), specified by age classes. Sex distribution for the Austrian population is similar to those in the German population.

