Treatment of Hyperglycaemia in Type 2 Diabetic Patients in a Primary Care Population Database in a Mediterranean Area (Catalonia, Spain)

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Abstract

Aim: To analyse glycaemic control and antihyperglycaemic treatment in patients with varying duration of type 2 diabetes in a population-based database.

Methods: A cross-sectional survey of 286,791 patients with type 2 diabetes registered in the primary care centres of the Catalan Health Institute (Catalonia, Spain) in 2009. We analysed the effects of types of treatment, diabetes duration and renal function on glycaemic control, adjusting for other clinical variables.

Results: Twenty-four percent of patients were treated with lifestyle changes only, 35.5% with oral glucose-lowering monotherapy, 21% with oral combinations and 17.7% with insulin (alone or in combination). Insulin was more frequently used in patients with longer duration of diabetes or severe renal impairment. Fifty-six percent of patients achieved the optimal target of HbA1c ≤ 7% (≤ 53 mmol/mol), a result more frequently observed in patients older than 65, early in the course of the disease and at the lower steps of treatment (p<0.001). Impaired renal function was present in 18.4% of patients. A significant number of patients with severe renal impairment were taking metformin (16.2%) or sulfonylureas (12.1%), which are contraindicated at this stage. Multivariable analyses confirmed that lower steps of treatment, advanced age and lesser years of diabetes duration were the variables positively related to good glycaemic control.

Conclusions: Glycaemic control deteriorates with the progression of the disease despite the treatment intensification. Impaired renal function was frequent and a remarkable proportion of these patients were taking contraindicated drugs.

Keywords: Type 2 diabetes; Pharmacological treatment; Diabetes duration; Renal impairment

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly in most parts of the world, which is likely to increase the incidence of complications associated with the disease [1]. This calls for improved treatment of hyperglycaemia and other risk factors associated with T2DM to lower the risk of both micro- and macrovascular complications and their related economic costs [2,3].

The currently available treatment options for hyperglycaemia, apart from lifestyle changes and weight reduction, are non-insulin glucose-lowering drugs and insulin. It is important that these agents be used optimally, frequently combining different therapeutic strategies, in order to achieve the commonly accepted glycaemic target level of HbA1c <7% (<53 mmol/mol) [4-9]. Despite scientific evidence and the publication of international [3,8,9] and national guidelines [4-7], adequate control of these patients’ health remains beset with challenges. A number of observational studies performed in Spain [10-15] report a gap between recommendations and daily clinical practice.

The implementation of universal electronic medical records systems in Catalonia (Spain) allowed us to access the anonymized data of the entire diabetic population registered in the public healthcare system for our study, in contrast to previous studies based on population samples [10-14]. Our group recently published a first report on the general aspects of the management of patients with T2DM in Catalonia (Spain) [15]. Previous publications on population registers in other countries have confirmed the relevance of these data to pharmacological treatment [16-28], especially when some cohorts have been followed to show differences in the incidence of cardiovascular disease, cancer or even mortality [21-28].

We undertook this study in order to specifically analyse the pharmacological treatment patterns in T2DM patients in Catalonia (Spain), with the primary aim to analyse glycaemic control and
antihyperglycaemic treatment in T2DM patients with varying duration of type 2 diabetes. Secondary aims were to analyse the effects of types of treatment and renal function on glycaemic control, adjusting for other clinical variables.

Methods

Catalonia, a Mediterranean region in northeastern Spain, has a public health system in which every citizen is registered with a general practitioner and a nurse in a publicly funded primary care centre. At each centre, doctors and nurses work as a team caring for the total population of a determined geographic area. All centres use the same software, called ECAP (Primary Care Clinical Station), to record their patients' clinical information. Healthcare and all diagnostic procedures are free of charge to patients. Medications were completely free for retired, severely ill or handicapped people. For other patients, glucose-lowering and antihypertensive drugs were almost completely free of charge and they paid 40% for other treatments. Strips for blood glucose monitoring were provided free of charge for all patients following local guidelines.

The data in this cross-sectional study were obtained from the SIDIAP (Information System for the Development of Research in Primary Care) database of electronic medical records of all patients attending the 274 primary care practices of the Catalan Health Institute, covering a population of about 5.8 million patients (80% of the total population for the region). SIDIAP (www.sidiap.org) started in 2006 and contains anonymized longitudinal patient information including sociodemographic characteristics, morbidity (International Classification of Diseases; ICD-10), clinical and lifestyle variables, specialist referrals, laboratory tests and treatments (prescription and corresponding pharmacy invoicing data) [29]. Clinical data before 2006 were transferred from paper-based records to electronic medical records by doctors and nurses.

All patients aged 31 to 90 years with a diagnosis of type 2 diabetes [ICD (International Classification of Diseases)-10 codes E11, E14] before 1/7/2009 were included. All variables registered at the end of 2009 were collected. Patients younger than 31 years were excluded to avoid the inclusion of type 1 diabetic patients. The following data were available for each patient: age, sex, time since diagnosis, estimated glomerular filtration rate (eGFR) using the MDRD (Modified Diet in Renal Disease) formula and standardized HbA1c values, using the most recent value of the preceding 15 months. Variables related to glycaemic control were analysed by age group (<55, 55-74 and ≥ 75 years-old) and by diabetes duration (<2 years, 2-5 years, 6-10 years and >10 years). Data pertaining to other cardiovascular risk factors and chronic complications were also available and have been extensively described elsewhere [15].

Data on glucose-lowering medication were obtained from the drug pharmacy prescription invoices database. A subject was considered to receive glucose-lowering medication when he/she had obtained the medication to cover at least 80% of the total theoretical dose needed from the first to the last prescription during 2009. Patients were considered untreated if they had not obtained any drugs. Patients were categorized as undergoing double or triple glucose-lowering therapy when (i) criteria for continuous treatment were met for each of the components and (ii) either a combination of two or three glucose-lowering drugs or a fixed-dose combined medication was given at least for two months, according to the prescription drug pharmacy invoices.

This study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol.

Statistical methods

Descriptive analysis consisted of summary statistics, mean and standard deviation for continuous variables, and percentages for categorical variables. Comparisons by age group, sex, diabetes duration, glycaemic-lowering step of treatment, and renal function were performed with Pearson chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables. We applied multilevel logistic regression models (considering the primary care centres as random) to identify the factors associated with good glycaemic control (HbA1c ≤ 7%, ≤ 53 mmol/mol). Only those variables with a statistically significant effect at the 0.05 level in the univariable analyses remained in the multivariable model. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95%CI) were presented. Statistical calculations were performed using StataCorp 2009 (Stata Statistical Software: Release 11. College Station, TX: StataCorp, LP).

Results

Data from 286,791 patients were analysed regarding proportions of different glucose-lowering treatments, age groups and duration of diabetes (Table 1 and Figure 1). Treatment with diet only or oral monotherapy decreased sharply with increasing diabetes duration from <2 years to >10 years (37.8% to 12.7% and 43.2% to 23.5%, respectively). The use of insulin therapy alone or combined with oral agents increased, from 7.5% to 34.4%. As shown in Table 1, the mean HbA1c value increased slightly with longer diabetes duration, especially in patients treated with insulin alone or in combination with oral agents. There was a slight decrease in mean BMI in all groups of patients with longer diabetes duration, although changes were smaller in patients treated with insulin alone. However, the frequency of obesity remained high, around 40% to 55%, in all patients. Interestingly, clinical characteristics clearly differed between younger and older patients: patients under 55 years of age were more often smokers and considerably more obese. They also had higher mean HbA1c, but lesser complications.

Glucose-lowering treatment

Table 2 shows patient characteristics according to the glucose-lowering step of treatment. Data on the use of specific glucose-lowering drugs by age group, sex, diabetes duration and renal function are shown in Table 3.

A quarter of all patients were managed only by lifestyle changes (24.4%) with respect to oral glucose-lowering treatments: 46.9%, 22.9% and 2.8% were taking one, two and three glucose-lowering drugs, respectively. In total, 17.7% of the patients on continuous glucose-lowering drug therapy received insulin, 7.7% as monotherapy, while the frequency of obesity remained high, around 40% to 55%, in all patients. Interestingly, clinical characteristics clearly differed between younger and older patients: patients under 55 years of age were more often smokers and considerably more obese. They also had higher mean HbA1c, but lesser complications.
Pharmacological treatment in patients with chronic renal impairment

Steps of treatment according to oral function are shown in Table 2. Mild renal impairment increased from 15% in patients treated only with lifestyle modifications to 29.4% in patients treated with insulin. Severe renal impairment was more frequent in patients treated with insulin monotherapy (6.8%) than other steps of treatment (from 0.6% to 1.5%). Data about drugs used in patients with chronic renal impairment are shown in Table 3. It is to be noted that some of these individuals were treated with drugs completely contraindicated in patients with eGFR<30 ml/min. A remarkable proportion (12.1%) of patients with severe renal impairment were taking sultoluyloace, mainly glitazone (41%), gliclazone (33%) and glibempire (17%), and 366 (16.2%) on metformin. On the other hand, 42.6% of those patients were treated with insulin (alone or in combination).

Glycaemic control according to patient characteristics

Good glycaemic control (HbA1c ≤ 7%, ≤ 53 mmol/mol) was associated mostly with older age groups (49.3% among patients younger than 55 years and 60% of those >75 years old). By contrast, the significance of the gender variable has no clinical relevance (57% of women vs. 56% of men). Likewise, better glycaemic control was associated with patients who were not obese, did not smoke, and were receiving dietary treatment. Thus, the prevalence of patients with good glycaemic control ranges from 24% of those treated in combination with oral agents up to 85% of patients with

### Table 1: Patient characteristics, according to age groups, steps of treatment and diabetes duration

| Age, mean years ± SD | Diabetes duration, mean years ± SD | HbA1c, mean, % ± SD | BMI, mean Kg/m² ± SD | eGFR ≥ 60 mL/min/1.73 m², % | eGFR 30-59 mL/min/1.73 m², % | eGFR <30 mL/min/1.73 m³, % |
|----------------------|-----------------------------------|--------------------|----------------------|---------------------------|-----------------------------|-----------------------------|
| 60 ± 11.4            | 6.5 ± 5.1                         | 7.1 ± 1.5          | 37.6 ± 5.4           | 80.9 ± 1.7                | 54.6 ± 16.0                 | 16.6 ± 1.5                  |
| 65 ± 11.4            | 6.8 ± 4.9                         | 7.3 ± 1.9          | 35.7 ± 5.5           | 77.2 ± 1.4                | 54.9 ± 15.7                 | 15.1 ± 1.5                  |
| 70 ± 11.4            | 7.1 ± 4.7                         | 7.5 ± 1.2          | 34.7 ± 5.5           | 77.2 ± 1.4                | 55.1 ± 15.7                 | 14.8 ± 1.5                  |
| 75 ± 11.4            | 7.6 ± 4.3                         | 7.7 ± 1.1          | 33.7 ± 5.5           | 77.2 ± 1.4                | 55.3 ± 15.7                 | 14.6 ± 1.5                  |
| 80 ± 11.4            | 8.1 ± 3.9                         | 7.9 ± 1.0          | 32.7 ± 5.5           | 77.2 ± 1.4                | 55.5 ± 15.7                 | 14.4 ± 1.5                  |
| 85 ± 11.4            | 8.6 ± 3.5                         | 8.1 ± 0.9          | 31.7 ± 5.5           | 77.2 ± 1.4                | 55.7 ± 15.7                 | 14.2 ± 1.5                  |
| 90 ± 11.4            | 9.1 ± 3.1                         | 8.3 ± 0.8          | 30.7 ± 5.5           | 77.2 ± 1.4                | 55.9 ± 15.7                 | 14.0 ± 1.5                  |
| 95 ± 11.4            | 9.6 ± 2.7                         | 8.5 ± 0.7          | 29.7 ± 5.5           | 77.2 ± 1.4                | 56.1 ± 15.7                 | 13.8 ± 1.5                  |
| 100 ± 11.4           | 10.1 ± 2.3                        | 8.7 ± 0.6          | 28.7 ± 5.5           | 77.2 ± 1.4                | 56.3 ± 15.7                 | 13.6 ± 1.5                  |
| 105 ± 11.4           | 10.6 ± 1.9                        | 8.9 ± 0.5          | 27.7 ± 5.5           | 77.2 ± 1.4                | 56.5 ± 15.7                 | 13.4 ± 1.5                  |
| 110 ± 11.4           | 11.1 ± 1.5                        | 9.1 ± 0.4          | 26.7 ± 5.5           | 77.2 ± 1.4                | 56.7 ± 15.7                 | 13.2 ± 1.5                  |

*N=214,867 patients with HbA1c available. °202,451 with body mass index (BMI) available. Micro- or Macroalbuminuria. °N= 202,938 with plasma creatinine available for calculating estimated glomerular filtration rate.
dietary treatment (Table 2): the greater the diabetes duration and/or complexity of treatment, the fewer patients with good glycaemic control. Patients with severe renal impairment (eGFR <30 ml/min) also had better glycaemic control than those with eGFR ≥ 60 ml/min (62% vs. 56%, respectively). On the other hand, figures on very poor control, defined as HbA1c>10% (>86 mmol/mol), (5% of the total population), increased with the duration of diabetes: 4.2% of subjects with ≤ 2 years duration and 5.8% in those with >10 years. The presence of microvascular complications also increased these figures, from 4.2% in patients with none to 9.1% among those with 2 complications. Regarding treatment, the group of subjects receiving insulin alone or combined with oral agents had the worst control (10.2% and 11.2% with HbA1c>10% (>86 mmol/mol), respectively) while in patients treated with lifestyle changes, oral monotherapy or combined oral agents, figures were notably better (1.4%, 3.1% and 6.7%, respectively).

**Multivariable analysis of good glycaemic control**

After adjusting the multivariable analysis for age, sex, BMI, hypertension, low-density lipoprotein cholesterol control, macrovascular disease, heart failure, renal function, presence of nephropathy and current smoking habit (Table 4), increased diabetes duration and antihyperglycaemic step of treatment were the most relevant variables related to good glycaemic control. Patients with the lowest adjusted Odds Ratios (aOR) were those treated with insulin plus oral agents compared to metformin in model 1 (glycaemic lowering agents) and to lifestyle changes in model 2 (steps of treatment) (aOR 0.33 and 0.05 respectively), and those with longer diabetes duration (aOR 0.44 in model 1 and 0.58 in model 2). In comparison with patients on metformin as a reference (model 1), lifestyle changes were positively related to good glycaemic control (aOR 4.48) while the rest of pharmacological treatments, especially insulin, were negatively related (aOR between 0.86 and 0.33).

In relation to glycaemic control by age groups, an aOR of 1.89 was observed between patients older than 75 years and those younger than 55 years. Finally, an aOR of 2.17 was observed in patients with severe renal impairment (eGFR <30 ml/min) vs. patients with eGFR >60 ml/min.

**Discussion**

This population-based study shows that glycaemic control deteriorates with the duration of the disease and the more complex steps of treatment, particularly among insulin-treated patients. The major strength of our study is the inclusion of every patient with T2DM from a total population database of 3,755,038 persons over age 30, providing data from 286,791 diabetic patients. Moreover, 96% of the patients with T2DM had contacted the healthcare system during the year of study at least once. With regard to methodology, the accuracy of the results is strengthened by the existing link between primary care clinical records and prescriptions obtained from the pharmacy database. The diabetes literature about the treatment of T2DM is enormous, and a lot of database studies have been done in North and central Europe and in Northern America [16-28], but this is the first one that provides data from a Mediterranean area. Further, this study is based on the whole population.

The degree of glycaemic control observed is similar to previously published studies [10-19]. The recommended HbA1c < 7% (53 mmol/mol) goal was reached by two thirds of the total population, but less than one-third of the insulin-treated patients with 6 or more years of diabetes duration. The percentage of patients on pharmacological treatment (75.6%) was high, taking into account that only patients who were receiving continuous treatment with glucose-lowering drugs were considered. Most patients receiving medication were managed with oral glucose-lowering treatment (56.5%), while 17.7% were treated with insulin, either alone or combined with oral agents. The percentage of non-medicated patients was similar to other studies carried out in Spain, but lower than reported in a recent study in Sweden (33.4%) [19]. It is to be noted that the percentage of patients who reached the objective of HbA1c ≤ 7% (53 mmol/mol) decreased dramatically with the progression of treatment (85.4% for lifestyle only to 24.3% for insulin combined with oral agents). These results are generally similar to the figures observed in a recently published study, with a similar methodology, by Ekström et al. in 163,121 T2DM patients from a Swedish population register for 2009 [19]. The degree of control by steps of treatment was very similar: 84.8% of patients treated with lifestyle changes reached the objective (HbA1c ≤ 7%, ≤ 53 mmol/mol), whereas this percentage was notably lower in patients treated with insulin in combination with oral agents (25%) [19]. Mean HbA1c values were also similar to that of our study, steadily increasing from 6.4% (46 mmol/mol) in patients treated only with lifestyle changes, 6.8% (51 mmol/mol) with oral monotherapy, 7.1% (54 mmol/mol) with two oral drugs and 7.4% (57 mmol/mol) to 7.9% (63 mmol/mol) with different patterns of insulin therapy (alone or in combination with oral drugs) [19].

We interpret these findings as a consequence of clinicians not prescribing drug treatment to well-controlled patients, while prescribing metformin to moderately well controlled patients and combined oral agents or insulin-based treatment to less-controlled patients. On the other hand, this disappointing result is probably related to the fact that therapeutic changes are sometimes introduced after several years of uncontrolled HbA1c, frequently above 8% (64 mmol/mol), or even 9% (75 mmol/mol) [29-33]. In some cases there is a delay in the intensification of treatment, or so-called therapeutic inertia that has been described to happen in 30% to 60% of patients with insufficient control [34]. In a recent study in a primary care centre in Catalonia, therapeutic inertia was observed in 40.6% of patients with HbA1c >7% (>53 mmol/mol) [35]. Moreover, a multicentre Spanish study reported a prescription change from oral monotherapy to bitherapy when HbA1c reached a mean of 8.1% (65 mmol/mol) in patients whose values had exceeded 7% (53 mmol/mol) for a mean period of 2 years [36]. Guidelines propose an early introduction and
progression in the combination of drugs [6-9] to prevent the worsening of glycaemic control when more complex therapies are delayed, but the benefit of this strategy has not been demonstrated.

The prevalence of impaired renal function in our study (18.4%) is inferior to that observed in two British studies, 25.5% [31] and 27.8% [32], and in one large database in the USA, 35.2% [30]. The National Institute for Health and Clinical Excellence (NICE) [9] and the Spanish local guidelines [6,7] propose that metformin should not be prescribed when severe renal impairment is established (eGFR <30 mL/min). It seems very reasonable considering the large number of older people who could be deprived of the benefits of metformin treatment. On the other hand, professionals should instruct the patient to immediately suspend metformin in any acute situation that predisposes to lactic acidosis (diarrhoea, infections with high fever, etc.). The surprisingly high percentage of patients with severe renal impairment taking metformin (16.2%) observed in our study was similar to an American study in which 19.6% of patients with severe impaired renal function (1,673 of 8,522 patients) were taking this drug [32]. This puts a high number of patients at high risk of medication-related severe adverse events. Our institution recently implemented a new aid for prescription, integrated with the electronic medical record system, that automatically alerts physicians of this contraindication.

A potential limitation of this study is the incomplete data for some of the studied variables. However, this is the first broad population-based study in Spain, the present results are comparable to previous publications by other authors, and the validity of the use of the SIDIAP database has been recently assessed by other studies [37-39]. Another limitation of the study, due to its retrospective design, is the lack of information about the exact timing of the HbA1c measurement in relation to possible changes in the steps of treatment: some values might have been measured just before the change and others later on.

In conclusion, in this study, patients of advanced age and those treated with only lifestyle changes show the best degree of control. Glycaemic control deteriorates with the progression of the disease.

### Table 2: Patient characteristics according to glycaemic-lowering step of treatment.

| Variable                  | Total (N=286791) | Lifestyle Only (N=153987) | Metformin (N=132804) | Sulphonylurea (N=153250) | Glitazone (N=96320) | GLP-1 analog (N=69924) | Lifestyle Only (N=153250) | Metformin (N=132804) | Sulphonylurea (N=96320) | Glitazone (N=69924) | Other (N=12804) |
|---------------------------|------------------|--------------------------|----------------------|--------------------------|---------------------|----------------------|--------------------------|----------------------|----------------------|---------------------|------------------|
| HbA1c, mmol/mol (SD)      | 7.1±1.5          | 6.3±1.0                  | 6.9±1.3              | 7.1±1.5                  | 6.8±1.3             | 6.1±1.3              | 6.3±1.0                  | 6.9±1.3              | 7.1±1.5              | 6.8±1.3             | 6.4±1.3          |
| BMI (Kg/m²), mean (SD)    | 29.6±5.0         | 29.4±4.8                 | 29.6±4.9             | 29.6±5.0                 | 29.6±4.9            | 29.6±5.0             | 29.6±4.8                 | 29.6±4.9             | 29.6±5.0             | 29.6±4.9            | 29.6±4.8         |
| eGFR <30 mL/min (SD)      | 81.6±8.3         | 83.7±6.2                 | 83.9±6.1             | 83.4±6.7                 | 83.4±6.1            | 83.4±6.0             | 82.4±6.2                 | 83.7±6.3             | 83.4±6.3             | 83.4±6.1            | 83.4±6.0         |
| OB (kg/m²), mean (SD)     | 17.4±13.5        | 17.6±13.5                | 17.5±13.7            | 17.6±13.7                | 17.6±13.7           | 17.6±13.7            | 17.6±13.5                | 17.6±13.7            | 17.6±13.7            | 17.6±13.7           | 17.6±13.5        |

*Other: Alphaglucosidase inhibitor, DPP4 inhibitor or GLP-1 analog (exenatide)

### Table 3: Use of glycaemic-lowering drugs by age, sex, diabetes duration and renal function.

| Drug          | <55 years (N=37221) | 55-74 years (N=64313) | >75 years (N=2266) | Women (N=132804) | Men (N=153887) | Total (N=286791) |
|---------------|---------------------|-----------------------|-------------------|-----------------|----------------|-----------------|
| Metformin     | 24.4±24.1           | 24.1±29.8             | 24.1±23.2         | 24.1±29.8       | 24.1±23.2       | 24.1±24.1       |
| Sulphonylurea | 41.2±41.7           | 40.6±44.3             | 41.4±34.9         | 40.6±44.3       | 40.6±34.9       | 40.6±41.7       |
| Glitazone     | 17.4±17.7           | 17.2±11.4             | 17.2±16.6         | 17.2±11.4       | 17.2±16.6       | 17.2±17.4       |
| Other *       | 12.4±11.5           | 13.5±10.7             | 14.4±14.5         | 14.5±14.5       | 14.5±14.5       | 14.5±12.4       |

*Other: Alphaglucosidase inhibitor, DPP4 inhibitor or GLP-1 analog (exenatide)

eGFR: Estimated Glomerular Filtration Rate
Take Home Messages

- As diabetes progresses, glycaemic control deteriorates despite the treatment intensification, particularly among insulin-treated patients.
- Lower steps of treatment, advanced age and fewer years of diabetes duration were positively related to good glycaemic control.
- Impaired renal function was frequent and a remarkable proportion of these patients were taking contraindicated drugs.

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