ORIGINAL ARTICLE

Is diabetes mellitus correctly registered and classified in primary care? A population-based study in Catalonia, Spain

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KEYWORDS
Diabetes;
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Classification;
Coding

Abstract
Objective: To assess the prevalence of miscoding, misclassification, misdiagnosis and under-registration of diabetes mellitus (DM) in primary health care in Catalonia (Spain), and to explore use of automated algorithms to identify them.

Methods: In this cross-sectional, retrospective study using an anonymized electronic general practice database, data were collected from patients or users with a diabetes-related code or from patients with no DM or prediabetes code but treated with antidiabetic drugs (unregistered DM). Decision algorithms were designed to classify the true diagnosis of type 1 DM (T1DM), type 2 DM (T2DM), and undetermined DM (UDM), and to classify unregistered DM patients treated with antidiabetic drugs.

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Introduction

Clinical guidelines classify diabetes mellitus based on the pathogenesis of hyperglycaemia, broadly into type 1 (T1DM; due to β-cell destruction), type 2 (T2DM; due to a progressive insulin secretory deficit), and other types (e.g., genetic forms, gestational diabetes, drug- or chemically-induced, or other causes). Moreover, guidelines give distinct recommendations for management and treatment based on classification, but they do not give clear guidance to assist physicians in classifying the condition. However, the distinction between T1DM and T2DM in clinical practice is not always obvious based on initial history, physical examination and laboratory values at first presentation. The difficulties in the distinction between diabetes types may result in errors in patients' registries in primary care records. Incorrect coding is categorised as misclassification (when the patient is falsely classified as a given type of DM), misdiagnosis (when the patient does not have diabetes), and miscoding (when a non-specific code – undetermined – is used and it is not possible to determine the type of diabetes).

The prevalence of incorrect and incomplete coding and classification of diabetes in routinely collected data is difficult to quantify because of the heterogeneity among available studies, as a systematic review noted. Still, the article highlighted the potential implications and impact, which includes inappropriate or delayed pharmacological management (e.g., prescription of insulin at T2DM onset,

Results: Data were collected from a total of 376,278 subjects with a DM ICD-10 code, and from 8707 patients with no DM or prediabetes code but treated with antidiabetic drugs. After application of the algorithms, 13.9% of patients with T1DM were identified as misclassified, and were probably T2DM; 80.9% of patients with UDM were reclassified as T2DM, and 19.1% of them were misdiagnosed as DM when they probably had prediabetes. The overall prevalence of miscoding (multiple codes or UDM) was 2.2%. Finally, 55.2% of subjects with unregistered DM were classified as prediabetes, 35.7% as T2DM, 8.5% as UDM treated with insulin, and 0.6% as T1DM.

Conclusions: The prevalence of inappropriate codification or classification and under-registration of DM is relevant in primary care. Implementation of algorithms could automatically flag cases that need review and would substantially decrease the risk of inappropriate registration or coding.

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or non-insulin antidiabetic drugs [NIADs] before insulin in T1DM; incorrect risk management (e.g., risk of ketoacidosis in T1DM incorrectly classified as T2DM); implications for family members (e.g., need for genetic counselling); and dubious validity and quality of care findings for researchers (e.g., inaccurate incidence and prevalence rates of DM and prescribing practices). Particularly, the inaccuracy of raw electronic data has a greater impact among patients attended in primary care, where most of them are diagnosed and managed, and where incorrect coding is known to be an issue. Finally, some patients are treated with antidiabetic drugs without any registered diabetes-related diagnosis code. This may reflect a lack of motivation, heavy workload, time constraints, or negligence in relation to a physician's responsibilities and duties with the institution in terms of a patient's health needs. These are well-known professional-related barriers to the delivery of optimal clinical practice and health care.

Different record-based algorithms applied to raw electronically collected data have been applied and proved useful to detect and classify patients with diabetes. The aim of the present study was to assess the quality of diabetes diagnostic data recorded electronically in primary care centres in Catalonia (Spain), and to develop and apply diagnostic algorithms to identify miscoded, misclassified and misdiagnosed diabetic records.

Methods

Design

This was a cross-sectional, retrospective study using an anonymised electronic general practice database (Information System for the Development of Research in Primary Care [SIDIAP]). Briefly, the database contains data from all electronic medical records available since 2001 obtained through specific software (Electronic Clinical station in Primary Care; eCAP), and includes data from all of the 274 primary care centres of the Catalan Health Institute (ICS), which attends 80% of the total population (about 5.835 million patients) in Catalonia.

Data extraction and variables

Data were obtained from patients who, during 2014, had a diagnosis code for diabetes mellitus by means of the International Classification of Diseases [ICD-10] codes, namely E10 (T1DM), E11 (T2DM), and E14 (undetermined DM; UDM). Moreover, we obtained data from patients receiving antidiabetic treatment but who did not have a DM or prediabetes (code R73.0; abnormal glucose) diagnosis recorded. Patients with only a code for gestational or secondary diabetes were excluded. Primary variables included were: age at time of diagnosis; HbA1c in 2014; and first HbA1c at the time of diagnosis. Secondary variables included were: age, gender, time since diagnosis; body mass index (BMI) in 2014; and BMI at the time of diagnosis. The prescribed antidiabetic treatments were extracted from prescription- and pharmacy-invoicing databases provided by the CatSalut (Catalan Health Service), which are yearly incorporated into the SIDIAP database.

Glucose lowering agents included insulin and NIADs marketed in Spain up to 2014, namely metformin, sulfonylureas, glinides, glitazones, dipeptidyl peptidase-4 inhibitors (DPP-4I), glucagon-like peptide-1 receptor agonists (GLP-1ra), alpha-glycosidase inhibitors (AGI), and sodium-glucose co-transporter 2 inhibitors (SGLT2i). Antidiabetic treatments were grouped as insulin in monotherapy, insulin plus metformin, NIADs other than metformin (alone or in combination with insulin or metformin or both), and metformin alone.

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

Decision algorithm development and output

Three different algorithms were designed and applied to sort diagnostic codes into T1DM, T2DM, prediabetes or unspecified DM treated with insulin. To establish a definite diagnosis, each algorithm started with the original code(s) recorded in the clinical history (or treatment received if no code was recorded), and further applied filters based on compatibility of prescribed antihyperglycaemic treatment, age at diagnosis, fasting plasma glucose, and HbA1c.

Incorrect coding was categorised as follows: (a) misclassification, when the subject was falsely classified as one type of DM (e.g., T1DM instead of T2DM); (b) misdiagnosis, when the diagnosis of diabetes was inadequate because the patient probably did not have the condition (e.g., prediabetes); (c) miscoding, when there were multiple codes or the code was non-specific (e.g., undetermined diabetes; UDM), not allowing to discriminate precisely the type of diabetes; and (d) unregistered diabetes (UnrDM), when there was no diabetes-related code recorded but the patient was being treated with antidiabetic drugs.

T1DM algorithm

This algorithm was used for subjects with a single specific code for T1DM with and without multiple codes (miscoding): T1DM and T2DM and/or UDM (Fig. 1). Those subjects initially coded as T1DM but not treated with insulin or treated with insulin and also a NIAD other than metformin were considered misclassified and reclassified to T2DM. A definite diagnosis of T1DM was applied if the subject was treated with insulin, but not with a NIAD other than metformin (which can be prescribed with insulin in T1DM), and was younger than 30 years at the time of diagnosis. In subjects with the same pattern but older than 30 years at the time of diagnosis, T1DM was considered probable because insulin-treated T2DM patients could not be completely excluded.

T2DM and UDM algorithm

This algorithm was used for subjects with a single specific code for T2DM with and without multiple codes (T2DM plus UDM), and for subjects with a single code for UDM (Fig. 2). Within subjects coded as UDM, those not treated with a NIAD other than metformin and with glycaemic values below the threshold for diabetes diagnosis (fasting plasma glucose <126 mg/dl and/or HbA1c <6.5%) at any time (after or before the diagnosis) were considered misdiagnosed of diabetes and were classified as prediabetes. Conversely, subjects treated
Figure 1  Algorithm for the validation of T1DM diagnosis. Footnote: NIADs, non-insulin antidiabetic drugs; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Figure 2  Algorithm for the validation of T2DM diagnosis. Footnotes: BG, basal plasma glucose; DM, diabetes mellitus; NIAD, non-insulin antidiabetic drugs; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. *At any time (before or after onset).

Figure 3  Algorithm for the detection of undiagnosed diabetes in patients without a code for diabetes or prediabetes who were treated with antidiabetic drugs. Footnotes: BG, basal plasma glucose; DM, diabetes mellitus; NIAD, non-insulin antidiabetic drugs; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. *Includes 904 patients on only NIADs other than metformin, 320 in combination with metformin, 25 in combination with insulin, and 23 on triple therapy. ** At any time (before or after onset).

Pharmacologically treated algorithm for subjects without a DM or prediabetes code (unregistered DM) taking antidiabetics

This algorithm considered that subjects on insulin as monotherapy and younger than 30 years at the time of diagnosis were T1DM cases (Fig. 3). Those on insulin as monotherapy who were older than 30 years at the time of diagnosis or those on insulin combined with metformin could be either T1DM or T2DM, and were therefore classified as UDM treated with insulin. Subjects treated with a NIAD other than metformin (alone or in combination with insulin or metformin or both) and subjects on metformin alone or who fulfilled diabetes diagnosis criteria at any time were classified as T2DM, while subjects on metformin alone with glycaemic values always below the threshold for diabetes diagnosis were categorised as prediabetes.

Statistical analysis

Demographic and clinical characteristics are presented as mean and standard deviation (SD) for continuous variables, and percentages for categorical variables. The Chi-squared test and t-test were used to compare qualitative and quantitative variables, respectively, with Bonferroni correction as a post hoc test to determine the significance of differences between groups at a level of $\alpha = 0.05$ for all tests. Statistical analyses were performed using the Stata Statistical Software, release 11 (StataCorp, College Station, TX, USA). Statistical significance was set at two-tailed $p < 0.05$. 
Table 1 Demographic and clinical characteristics of 376,278 included patients who had a DM code recorded.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1DM</th>
<th>T2DM</th>
<th>UDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male, n (%)</td>
<td>10,535 (56.9)</td>
<td>194,224 (54.9)</td>
<td>1744 (50.9)</td>
</tr>
<tr>
<td>Age in 2014, years, mean (SD)</td>
<td>44.8 (18.2)</td>
<td>69.7 (12.3)</td>
<td>71.2 (13.5)</td>
</tr>
<tr>
<td>Age at diagnosis, years, mean (SD)</td>
<td>32.4 (18.2)</td>
<td>60.81 (12.1)</td>
<td>58.9 (13.1)</td>
</tr>
<tr>
<td>Age &lt;30 years at diagnosis, n (%)</td>
<td>9105 (49.2)</td>
<td>2800 (8.0)</td>
<td>92 (2.7)</td>
</tr>
<tr>
<td>Duration of diabetes, years, mean (SD)</td>
<td>12.3 (9.5)†</td>
<td>8.9 (6.0)</td>
<td>12.3 (5.5)†</td>
</tr>
<tr>
<td>HbA1c in 2014, %, mean (SD)</td>
<td>8.1 (1.5) (n = 8279)</td>
<td>7.1 (1.2)† (n = 272,641)</td>
<td>7.1 (1.3)† (n = 2223)</td>
</tr>
<tr>
<td>HbA1c at diagnosis, %, mean (SD)</td>
<td>9.1 (2.6) (n = 1948)</td>
<td>7.1 (1.7)† (n = 106,034)</td>
<td>6.9 (1.9)† (n = 319)</td>
</tr>
<tr>
<td>BMI in 2014, kg/m², mean (SD)</td>
<td>26.5 (5.3) (n = 9100)</td>
<td>30.2 (5.2) (n = 235,629)</td>
<td>29.7 (5.2) (n = 2155)</td>
</tr>
<tr>
<td>Obesity (BMI ³30 kg/m²) in 2014, n (%)</td>
<td>2019 (22.4) (n = 9100)</td>
<td>117,615 (49.9) (n = 235,629)</td>
<td>926 (43.0) (n = 2155)</td>
</tr>
<tr>
<td>BMI at diagnosis, kg/m², mean (SD)</td>
<td>24.6 (6.3) (n = 3083)</td>
<td>31.5 (5.3) (n = 113,886)</td>
<td>30.8 (5.3) (n = 780)</td>
</tr>
<tr>
<td>Obesity (BMI ³30 kg/m²) at diagnosis, n (%)</td>
<td>578 (18.7) (n = 3083)</td>
<td>64,837 (56.9) (n = 113,886)</td>
<td>396 (50.8) (n = 780)</td>
</tr>
</tbody>
</table>

Antidiabetic treatment (N = 384,985)

- No pharmacologic treatment, n (%) 1346 (7.3) 62,929 (17.7) 834 (24.4)
- Metformin, n (%) 298 (1.6) 125,623 (35.3) 822 (24.0)
- Any NIAD other than metformin, n (%) 87 (0.5) 20,993 (5.9)† 186 (5.4)†
- Metformin + other NIADs, n (%) 206 (1.1) 71,962 (20.2) 656 (19.2)
- Insulin as monotherapy, n (%) 14,129 (76.4) 19,982 (5.6) 314 (9.2)
- Insulin + metformin, n (%) 1804 (9.8) 31,395 (8.8) 362 (10.6)
- Insulin + any NIAD other than metformin, n (%) 250 (1.4) 7134 (2.0) 81 (2.4)
- Insulin + metformin + other NIADs, n (%) 381 (2.1) 16,155 (4.5)† 169 (4.9)†

† Not statistically significant differences (p > 0.05) between the means or percentages in the same row. Bonferroni correction was used to perform the multiple comparisons test. BMI, body mass index; NIAD, non-insulin antidiabetic drug; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UDM, undetermined diabetes mellitus.

a The sample number is given between parenthesis and italics if different form the total population corresponding population.

Results

Out of the initial 5,432,691 patients’ records, we retrieved data from a total of 376,278 subjects with an ICD-10 code for DM (Table 1): 18,501 (4.9%) had at least one code for T1DM, of which 16,414 were single codes; 356,173 (94.7%) had at least one code for T2DM, of which 351,591 were single codes; 3424 (0.9%) had a single code for UDM. Overall, 2.2% of subjects were potential miscoding errors if we take into account 4849 patients with multiple codes and 3424 with UDM code. Patients in the UDM group were older than in the T1DM and T2DM groups (71.2 years vs. 44.8 and 69.7 years, respectively; p < 0.001), and there was a lower proportion of males in the UDM group than in the other groups (50.5% vs. 56.9% and 54.9% in the T1DM and T2DM groups, respectively; p < 0.001). The most frequent treatments were insulin alone in the T1DM group (76.4% of cases), metformin alone in the T2DM group (35.3%), and no pharmacological treatment or metformin alone in the UDM group (24% in both cases). Subsequently, we retrieved data from a total of 8707 patients who did not have any DM or prediabetes code recorded but were treated with antidiabetic drugs (UnrDM; Table 2): metformin was the most frequent treatment (n = 6650; 76.3%), followed by any NIAD other than metformin (alone or in association with metformin or insulin) (n = 1272; 14.6%), insulin as monotherapy (n = 691; 7.9%), and insulin with metformin (n = 94; 1.1%).

Algorithm application for T1DM, T2DM and UDM codes

When the 18,501 patients initially having at least one code for T1DM were categorised based on the proposed T1DM algorithm (Fig. 1), 42.5% (n = 7871) of the cases were classified as definite T1DM. Moreover, 43.6% (n = 8062) of cases were on insulin, not taking any NIADs other than metformin and were >30 years at the time of diagnosis, and were considered as a probable T1DM since it cannot be discarded that the group included insulin-treated T2DM patients. Finally, 13.9% of cases (n = 2568) were found to be misclassified because they were not on insulin or they were on insulin in combination with NIADs other than metformin, and were thus reclassified as T2DM.

The proposed T2DM algorithm included 351,591 patients with only a code for T2DM, 3424 subjects with a single code
for UDM, and 2762 patients with both codes (Fig. 2). After applying the algorithm to subjects with a single code of UDM diabetes, 80.9% of them (n = 2770) were classified as T2DM because they were treated with a NIA other than metformin (31.9% of cases), or because although they were treated only with metformin, their glycaemic values were above the threshold for diabetes diagnosis (fasting plasma glucose ≥126 mg/dl and/or HbA1c ≥6.5%; 49% of cases). Finally, 19.1% of cases were considered misdiagnosed because they were not pharmacologically treated and their glycaemic values were always under the diagnosis threshold for diabetes and were therefore reclassified as prediabetes.

Algorithm application for subjects pharmacologically treated without a DM or prediabetes code (UnRDM)

Among patients on insulin as monotherapy (n = 691), 49 of them (7%) were younger than 30 years at the time of diagnosis, and were considered as a definite T1DM diagnosis, but the remaining ones (>30 years at the time of diagnosis), together with subjects on insulin and metformin, could also be patients with T2DM, and were therefore classified as UDM treated with insulin (Fig. 3). Among 6650 subjects treated with metformin alone, 72.3% of them did not have abnormal glycaemic values, and were thus classified as prediabetes. Finally, a total of 3112 patients were classified as T2DM, and these included 27.7% of patients on metformin alone but with high glycaemic values (n = 1840), and 1272 patients treated with NIA other than metformin (904 patients on only NIA other than metformin, 320 in combination with metformin, 25 with insulin, and 23 on triple therapy).

In summary, after the application of the designed algorithms to all subsets, 13.9% of patients with T1DM were found to be misclassified and to actually be T2DM cases, 80.9% of patients with UDM were reclassified as T2DM, and 19.1% of them were classified as probably having prediabetes (Fig. 4). Overall, the prevalence of miscoding because of patients with multiple codes or initially coded as UDM in our sample was 2.2%. Finally, 55.2% of subjects with UnRDM (i.e., lacking a DM code but pharmacologically treated with antidiabetic drugs) could be classified as prediabetes, 35.7% as T2DM, 0.6% as T1DM, and in 8.5% of cases the DM type could not be discriminated and were coded as UDM treated with insulin.

Discussion

This study showed the application of automated algorithms to flag and reclassify cases inappropriately coded in electronic records from primary care. The overall prevalence of coding errors in our database was 5.2%. The most common errors were under-registration (no DM-related code but treated with antidiabetic drugs; 43.1% of all errors) and miscoding (i.e., multiple DM codes or UDM code; 41% of all errors). Misclassification was less frequent (i.e., T1DM instead of T2DM; 12.7% of all errors), and misdiagnosis (i.e., UDM probably prediabetes) was the least frequent error (2.2% of them).

Clinical features that have been shown to be the most discriminatory to differentiate T1DM and T2DM are age at diagnosis and time to insulin, while BMI, usually used in

| Table 2 | Demographic and clinical characteristics of 8707 patients who were on an antidiabetic treatment but no code for DM or prediabetes recorded (unregistered diabetes). |
|-----------------|---------------------------------|-----------------|-----------------|-----------------|
|                | Metformin alone | Any NIA other than metformin | Insulin plus metformin | Insulin alone |
| Gender, male, n (%) | 2838 (42.7) | 532 (41.8) | 42 (44.7) | 182 (26.3) |
| Age in 2014, years, mean (SD) | 60.1 (7.7) | 65.7 (16.9) | 61.4 (16.8) | 50.0 (19.8) |
| Age <30 in 2014, years, n (%) | 472 (7.1) | 36 (2.8) | 2 (2.1) | 49 (7.1) |
| HbA1c in 2014, %, mean (SD) | 6.2 (0.8) | 6.5 (1.5) | 7.1 (1.9) | 6.2 (1.3) |
| HbA1c, ≤7%, n (%) | 2747 (90.3) | 358 (77.2) | 28 (60.9) | 157 (78.5) |
| HbA1c 7.1–8%, n (%) | 182 (6.0) | 48 (10.3) | 8 (17.4) | 20 (10.0) |
| HbA1c >8%, n (%) | 87 (2.9) | 37 (8.0) | 6 (13.0) | 19 (9.5) |
| BMI in 2014, kg/m², mean (SD) | 32.0 (6.4) | 30.4 (5.9) | 30.6 (7.1) | 28.8 (5.1) |
| BMI <25 kg/m², n (%) | 374 (11.1) | 116 (18.8) | 10 (23.8) | 92 (25.0) |
| Normal weight (BMI <25 kg/m²), n (%) | 1012 (29.9) | 196 (31.7) | 13 (31.0) | 134 (36.4) |
| Overweight (BMI 25.0–29.9 kg/m²), n (%) | 1988 (59.0) | 306 (49.5) | 19 (45.2) | 142 (38.6) |

BMI, body mass index, NIA, non-insulin antidiabetic drug, SD, standard deviation.

- The sample number is given between parenthesis and italics if different form the corresponding total number.
- Includes 904 patients on only NIA other than metformin, 320 in combination with metformin, 25 in combination with insulin, and 23 on triple therapy.
- Statistically significant differences (p < 0.05) in comparison to the remaining results in the same row. Bonferroni correction was used to perform the multiple comparisons test.
clinical practice as a surrogate marker, does not seem to add much to these 2 other criteria. Moreover, the use of algorithms that include surrogate markers to confirm or refute the diagnosis of diabetes, and to help differentiate between diabetes types has been proved useful when used with data from electronic records in primary care. One study reported that HbA1c levels $>6.5\%$ have a high positive predictive value (PPV) to confirm a DM diagnosis; the combination of age $<30$ years, insulin treatment, and BMI $<30$ kg/m$^2$ had a high PPV for T1DM; and age $>45$ years, BMI $>30$ kg/m$^2$ and hypertension a high PPV for T2DM. Another study, conducted in insulin-treated diabetic patients, reported that the most discriminative variables to predict diabetes type were time from diagnosis to insulin treatment (optimal cut-off 12 months), and age at diagnosis (optimal cut-off $<39$ years), while BMI (optimal cut-off $<23.1$ kg/m$^2$) was less discriminatory. Following the same scheme, the discriminative variables that we included in our algorithms were therapy, age at onset, and glycaemic levels, but not BMI.

The prevalence of T2DM incorrectly labelled as T1DM (misclassified diabetes) in our study was 13.9%. This is in line with the previous 10–30% prevalence of misclassifications reported in the UK primary care setting through the use of algorithms, and also in line with the 22.7% reported in a Medicaid paediatric T1DM population misclassified as T2DM in the US, predominantly in primary care settings. Contributing factors to this high rate of T1DM misclassification may be the increasing prevalence of obesity in children and adolescents, and the decreasing age of onset for T2DM, which during the last decades tends to overlap with age at onset of T1DM, all together blurring the differential diagnosis.

From previous studies, people with T2DM misclassified as T1DM tend to be older than those correctly classified, have lower HbA1c levels, are more likely to achieve good glycaemic control, and have a higher BMI at diagnosis. The rate of misdiagnosed patients in our study, namely subjects coded as UDM but actually more likely to have prediabetes than T2DM was 19.1%, which is line within the wide range of observed misdiagnoses reported in other studies (6.1–34.5%). Misdiagnosed patients have been reported to have similar age or BMI at diagnosis than actual T2DM patients, but tend to have lower HbA1c values at diagnosis, levels that remain lower over time, and thus they essentially mimic good glycaemic control. Moreover, we found that 72.3% of subjects without a code for DM but treated with metformin alone were recategorised as prediabetes, which is of concern and emphasises the fact that those subjects might be receiving unnecessary medication, and although they should be closely followed in case of changes in their glycaemic levels, they could be managed with lifestyle modification as the first option. In fact, neither metformin nor other antidiabetic drugs are currently authorised for the treatment of prediabetes in Europe, so its use in these patients is off-label.

The prevalence of miscoded diabetes (i.e., patients with multiple codes or UDM) was 2.2% in our study, which is lower than the rates observed in other studies, ranging from 4.9% to 10%, and much lower than the 47.8% reported in another study. However, if we also consider subjects uncoded for DM but treated with antidiabetics because they are not registered as having the disease, then the rate of miscoding in our study would rise up to 4.4%. It has been reported that patients with vague or non-specific codes have poorer glycaemic control, which may indicate that they are at risk of suboptimal management because of the lack of a clear identification that would otherwise allow the adoption of specific clinical guidelines or recommendations for their DM type. Finally, in 8.5% of patients without a code

![Figure 4](image-url) Distribution of diagnoses before and after the application of the algorithms. Footnotes: DM, diabetes mellitus; NIAD, non-insulin antidiabetic drugs; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. *Includes codes for only T1DM, and multiple codes: T1DM + undetermined DM, T1DM + T2DM, and T1DM + T2DM + undetermined DM. †Includes 904 patients on only NIADs other than metformin, 320 in combination with metformin, 25 in combination with insulin, and 23 on triple therapy.
for DM but treated with insulin alone or insulin with NIADS
and who were older than 30 years, it was not possible to
discriminate between T1DM and T2DM, and patients were
labelled as UDM treated with insulin. This group may include
real T1DM patients, insulin-treated T2DM patients, and even
latent autoimmune diabetes of the adult (LADA), although
for the latter type there are no current specific interna-
tional guidelines for management and treatment. Time to
insulin treatment since diagnosis would have been helpful in
the SDIAP database started in 2006 and this criterion
could not be included in the algorithms for people diagnosed
before this year. Some have suggested that, when facing
diagnostic ambiguity, the diagnosis should be reviewed, the
patient should be referred to a specialist, or complementa-
tory tests such as measurement of insulin secretion should be
performed (C-peptide and islet autoantibody levels). However,
these are expensive techniques and not routinely
performed in some primary care settings.

The main advantage of the present study is the use of
a large database of computerised data collected auto-
matically from primary care centres representative of the
health care practices in our country. The main limitation
is the data source itself, which is subject to errors in data
recording, missing values, or incomplete clinical histories.
For instance, the number of patients with recorded HbA1c
values was in some cases low. Since this variable was used
to establish a definite diagnosis in the algorithms for T2DM
and/or UDM codes and unregistered diabetes, we cannot
discard that some patients with diabetes have been actu-
ally classified as prediabetes. Moreover, and as previously
pointed out, the algorithms rely upon clinicians coding and
prescribing decisions, and it cannot minimise the future risk
of incorrect coding if a wrong diagnosis is made and the
patient is treated accordingly. Conversely, we cannot
discard that in some cases of miscoding (T1DM instead of
T2DM for patients treated only with insulin) both the patient
and the physician know the correct diagnosis and treatment
is actually appropriate. In addition, we did not consider
the possibility that patients coded as T2DM or T2DM+UDM
could be miscoded. This is because more than 95% of
diabetic patients are T2DM, and the objective of the algo-
rithms is to help clinicians classify infrequent cases, namely
a T1DM code, a doubtful code (i.e., only UDM code), mul-
tiple codes or antidiabetic treatment without a diabetes or
prediabetes code. Finally, we did not explore the presence
of false negative cases, namely subjects likely to have undi-
agnosed diabetes based on existing altered blood glucose
recordings, and estimated to be around 1% in studies using
algorithms to primary care electronic registries in the
US and the UK, or subjects who do not have a diabetes
code nor diabetes-related treatment recorded. Therefore, it is probable that the overall prevalence of cod-
ing errors in our study was underestimated.

In conclusion, we detected a high prevalence of problems
with misclassification, misdiagnosis, miscoding and under-
registration of DM in primary care in Catalonia. This may
be in part due to patients who were difficult to charac-
terise at the time of diagnosis, but it also points to a lack
of accuracy in distinguishing diabetes from no diabetes, and
incomplete coding when only treatment but not disease is
recorded. This has consequences at the level of quality of
disease management, but also at the epidemiological level
when the database is used for research on the epidemi-
ology and natural history of the disease. The embedment
of algorithms in the primary care centre’s computer sys-
tems could automatically flag cases that would need review
because of potential miscoding (i.e., absent, vague, unspe-
sific or multiple DM codes), misclassification (T2DM instead
of T1DM or vice versa), under-registration (patients treated
with antidiabetic drugs but without diagnosis) and misdiag-
nosis (no current criteria for DM), and largely reduce the risk
of inappropriate coding.

Authors’ contributions

MM-C and DM wrote the manuscript and contributed equally
to this study; JR managed the database, performed the
statistical analyses and contributed to the discussion; and
JF-N, MM-C, BB and DM designed and conducted the study,
reviewed/edited the manuscript and contributed to the dis-
cussion. MM-C had full access to all data in the study and
takes responsibility for the integrity of data and the accu-
racity of the data analysis.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Association AD. 2. Classification and diagnosis of diabetes. Dia-
March 2016. Available at: http://www.who.int/mediacentre/
factsheets/fs312/en/ [accessed May 2016].
3. Rollason W, Khunti K, de Lusignan S. Variation in the recording
of diabetes diagnostic data in primary care computer sys-
tems: implications for the quality of care. Inform Prim Care.
4. de Lusignan S, Khunti K, Belsey J, Hattersley A, van Vlymen J,
Gallagher H, et al. A method of identifying and correcting mis-
coding, misclassification and misdiagnosis in diabetes: a pilot
and validation study of routinely collected data. Diabetes Med.
5. Stone MA, Camosso-Stefinovic J, Wilkinson J, de Lusignan S,
Hattersley AT, Khunti K. Incorrect and incomplete coding and
2010;27:491–7.
6. Khunti K, Ganguli S. Who looks after people with diabetes: pri-
7. de Lusignan S, van Weel C. The use of routinely collected
computer data for research in primary care: opportunities and

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Cuando Metformina no es suficiente, que nada te pare.
Empieza con Jentadueto

- Disminución de HbA1c de hasta 1,7% en pacientes con DM2 mal controlados\(^1\)*
- Eficacia sostenida durante 2 años, con un 76% de los pacientes que alcanzaron el control (HbA1c<7\%)\(^2\)
- La combinación en pastilla en que uno de sus componentes no tiene como vía primaria de excreción el riñón\(^1\)

*Sigue con Trajenta\(^\circledR\) aunque la función renal empeore\(^3\)

Cuando Metformina no es suficiente, elige Jentadueto\(^\circledR\)

* Cambio de HbA\(_{1c}\) frente placebo (media ajustada) en pacientes tratados con Linagliptina 2,5 mg 2v/d + Metformina 1000 mg 2v/d durante 24 semanas
\(^*\) Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas
1. NOMBRE DEL MEDICAMENTO. Trajenta® 5 mg comprimidos recubiertos con película. 2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA. Cada comprimido contiene 5 mg de linagliptina. Para la consulta de la lista completa de excipientes ver sección 6.1. 
3. FORMA FARMACÉUTICA. Trajenta® 5 mg es un comprimido recubierto con película de color rojo claro, redondo, de 8 mm de diámetro, grabado con la inscripción "5" en una cara y el logotipo de Boehringer Ingelheim en la otra. 4. DATOS CLÍNICOS. 4.1. Género, edad, características de la enfermedad. Linagliptina sola se ha utilizado en pacientes con insuficiencia renal o hepática pero no se dispone de experiencia clínica en estos pacientes. 4.2. Administración y manejo. Linagliptina se toma una vez al día, en general sin relación con las comidas. 4.3. Contraindicaciones. No se ha establecido todavía la seguridad y la eficacia de linagliptina en niños menores de 18 años. 4.4. Advertencias y precauciones de uso. General. No debe utilizarse Trajenta® en pacientes con diabetes tipo 1 ni para la tratamiento del estado hipoglucémico diabético. 4.5. Interacciones medicamentosas. Potenciales interacciones con linagliptina en terapia combinada con medicamentos con un efecto hipoglucémico no conocido (metformina), los índices de hipoglucemia notificados con linagliptina fueron similares a los índices de los pacientes observados en ensayos clínicos. 4.6. Fertilidad, embarazo y lactancia. No se ha estudiado el uso de linagliptina en mujeres embarazadas. 4.7. Efectos sobre la capacidad para conducir y utilizar máquinas. Este medicamento no requiere condiciones especiales de conservación. 4.8. Reacciones adversas. Trajenta® es un medicamento que puede causar reacciones adversas en pacientes sanos. Se ha notificado a los profesionales sanitarios reacciones adversas de pancreatitis aguda. Se debe informar a los profesionales de salud de cualquier reacción adversa que se dé durante el tratamiento con este medicamento. No hay datos sobre reacciones alérgicas de hipersensibilidad. El tratamiento con linagliptina debe ser suspendido si se sospecha un caso de reacción alérgica. Frente a un 7,6% en el placebo. En los ensayos controlados con placebo, un 4,9% de los pacientes experimentaron "hipoglucemia como reacción adversa de la linagliptina". 
4.9. Sobredosis. Síntomas. Durante los ensayos clínicos controlados en sujetos sanos, dosis únicas de hasta 600 mg de linagliptina (equivalentes a 120 veces la dosis recomendada) se toleraron bien en general. No hay experiencia con dosis superiores a 600 mg en humanos. Tratamiento. En caso de sobredosis, es razonable emplear las medidas de soporte habituales, p. ej. eliminar en el caso de sobredosis oral a través del Sistema Español de Farmacovigilancia de medicamentos de Uso Humano: www.notificalARM.es. 5. PROPIEDADES FARMACOLÓGICAS (ver ficha técnica completa). 6. DATOS FARMACOLÓGICOS, farmacocinéticos y farmacodinámicos. Linagliptina está indicado en el tratamiento de la diabetes mellitus tipo 2 en monoterapia o en combinación (frecuencias identificadas a partir de un análisis conjunto de ensayos controlados con placebo) en ensayos clínicos y a partir de la experiencia post-comercialización. 
6.1. Preparación del medicamento. Trajenta® está indicado en el tratamiento de la diabetes mellitus tipo 2 en monoterapia o en combinación (frecuencias identificadas a partir de un análisis conjunto de ensayos controlados con placebo) en ensayos clínicos y a partir de la experiencia post-comercialización.
Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas. Ver la sección 4.8 del capítulo sobre reacciones adversas en "Cómo tomar Jentadueto®". El medicamento se debe administrar a pacientes con diabetes mellitus tipo 2. Jentadueto® 2,5 mg/850 mg comprimidos recubiertos con película y Jentadueto® 2,5 mg/1.000 mg comprimidos recubiertos con película. 2. COMPOSICION CUALITATIVA Y CUANTITATIVA. Cada comprimido contiene 2,5 mg de hidrocloruro de metformina y 850 mg de linagliptina. Evaluaciones de equivalencia a su producto de referencia han demostrado que Jentadueto® contiene los principios activos, esto es linagliptina y metformina, respectivamente. Para consultar la lista completa de excipientes, ver sección 6.1. 3. FORMA FARMACÉUTICA. Comprimido recubierto con película (comprimido). Dosis 850/2,5 mg: Comprimido recubierto con película de color roso claro, oválico, biconvexo, de 19,1 mm x 9,7 mm, grabado con la inscripción "D2/850" en una cara y el logotipo de la compañía en la otra. Dosis 1.000/2,5 mg: Comprimido recubierto con color de rosas claro, ovalado, bienpolido, de 21,1 mm x 9,7 mm, grabado con la inscripción "D3/1000" en una cara y el logotipo del fabricante en la otra. Jentadueto® contiene cuatro principios activos, el hidrocloruro de metformina y la linagliptina, respectivamente, que se unen a través de un mecanismo de acción dual. Jentadueto® contiene dos, tres, cuatro, seis o ocho comprimidos recubiertos con película por receta. En la batería de laboratorios se determinan los niveles de glicemia y, posteriormente, de forma regular: • al menos una vez al año en pacientes con función renal normal, • al menos de forma anual en pacientes con función renal disminuida (la dosis doble se debe suspender 48 horas antes de una cirugía programada con anestesia general, espinal o epidural). En general, el tratamiento debe reevaluarse regularmente, especialmente cuando se administran dosis concomitantes de metformina y riesgo de acidosis láctica. Por tanto, Jentadueto® se debe interrumpir antes o en el momento de la suspensión del tratamiento del otro medicamento y cuando éste se suprima. Jentadueto® con un índice comparable al de la metformina más placebo (2,4%). La hipoglucemia puede aparecer cuando se interrumpe el tratamiento con Jentadueto®. Si hay sospechas de pancreatitis, se debe interrumpir Jentadueto®. 4.5 Interacción con otros medicamentos y otras formas de interacción. No se han realizado estudios de interacciones farmacológicas con otros medicamentos. Se debe tener en cuenta que se han descrito en la farmacología de la metformina, glibenclamida, simvastatina, warfarina, digoxina o inhibidores de la proteasa. 4.6 Fertilidad, embarazo y lactancia. Embrazo. No se ha estudiado el uso de Jentadueto® en mujeres embarazadas. Los estudos en animales no indican efectos perjudiciales directos o indirecitos respecto a la toxicidad reproductiva (ver sección 5.3). Datos limitados sugieren que el uso de metformina en mujeres embarazadas no está asociado a un mayor riesgo de malformaciones congénitas. Los estudios con metformina en animales no indican efectos perjudiciales en el embrazo, el desarrollo embrionario o fetal, el parto o la lactancia. 4.8 Reacciones adversas. Resumen del perfil de seguridad. Combinación de dosis. No se cumple con el criterio de equivalencia. En comparación con el principio activo de la metformina, Jentadueto® contiene un sustrato sensible al CYP3A4, en voluntarios sanos. Después de la administración de una dosis de 5 mg de linagliptina no se vio modificada por la administración de dosis de metformina y riesgo de acidosis láctica. Por tanto, Jentadueto® se debe interrumpir antes o en el momento de la suspensión del tratamiento del otro medicamento y cuando éste se suprima. Jentadueto® con un índice comparable al de la metformina más placebo (2,4%). La hipoglucemia puede aparecer cuando se interrumpe el tratamiento con Jentadueto®. Si hay sospechas de pancreatitis, se debe interrumpir Jentadueto®. 4.5 Interacción con otros medicamentos y otras formas de interacción. No se han realizado estudios de interacciones farmacológicas con otros medicamentos. Se debe tener en cuenta que se han descrito en la farmacología de la metformina, glibenclamida, simvastatina, warfarina, digoxina o inhibidores de la proteasa.
añadida al tratamiento de metformina más sulfonylurina establecido. Cuando se administraron linagliptina y metformina en combinación con una sulfonylurina, la hiperglucemia fue el acontecimiento adverso notificado con más frecuencia (linagliptina más metformina más sulfonylurina 23,9% y 16,0% en placebo más metformina más sulfonylurina). Reacciones adversas notificadas cuando la linagliptina y la metformina se combinan con insulina. Cuando se administraron linagliptina y metformina en combinación con insulina, la hiperglucemia fue el acontecimiento adverso notificado con más frecuencia, pero se produjo con una incidencia comparable cuando se combinaron placebo y metformina con insulina con linagliptina más metformina más insulina 28,5% y 20,4% en el grupo de placebo con más metformina más insulina) con una baja incidencia de episodios graves (1,5 % y 0,9 %). Tabla de reacciones adversas. Reacciones adversas notificadas con una combinación a dosis fijas. A continuación se presentan las reacciones adversas notificadas en todos los ensayos clínicos realizados con Jentadueto® según la clasificación por órganos y sistemas. Durante el tratamiento con Jentadueto® pueden aparecer reacciones adversas que se conoce que aparecen con cada uno de los principales actores de manera individual pero que no se han observado en los ensayos clínicos con este medicamento. Estas reacciones adversas se clasifican por órgano y frecuencia. Las frecuencias se definen como muy frecuentes (≥ 1/10), frecuentes (≥ 1/100 a < 1/10), poco frecuentes (≥ 1/1.000 a < 1/100), raras (≥ 1/10.000 a < 1/100.000), muy raras (< 1/100.000) y frecuencia desconocida (no puede estimarse a partir de los datos disponibles).

**Tabla 1. Reacciones adversas notificadas en pacientes que recibieron Jentadueto® (frecuencias identificadas a partir de un análisis conjunto de ensayos controlados con placebo) en ensayos clínicos y a partir de la experiencia postcomercialización.**

**Tabla 2. Reacciones adversas notificadas adicionalmente en pacientes cuando la linagliptina y la metformina se combinan con una sulfonylurina.**

**Tabla 3. Reacciones adversas notificadas adicionalmente en pacientes cuando la linagliptina y la metformina se combinan con una insulina.**

**Tabla 4. Reacciones adversas notificadas en pacientes que recibieron metformina® en monoterapia y que no se observaron en pacientes que recibieron Jentadueto®.**

Referencias: