



Original Research

Diagnostic values of glycated haemoglobin and diagnosis of diabetes: Results of a cross-sectional survey among general practitioners in the province of Reggio Emilia, Italy



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ABSTRACT

Aims: The aim of this study was to investigate whether subjects included in the diabetes register solely because their HbA1c was over the diagnostic threshold received a diagnosis of diabetes from their general practitioner (GP).

Methods: The study included all registered cases in 2009–2010 aged 18 or over that were identified only by the laboratory database because they had one or more HbA1c over the 6.5% threshold and for whom we did not find any information in the search of full electronic clinical records. Multilevel logistic regression was used to examine the influence of GP and patient characteristics.

Results: There were 228 participating GPs (76.3% of those invited) and 832 assessed subjects (68.8% of study population). There was a strong clustering among the GPs (residual intraclass correlation = 0.52, 95% CI 0.40–0.64). About one in two (55.5%) subjects with two or more HbA1c >=6.5% has been diagnosed as diabetic and the percentage declined – unless zeroing – in case the abnormal value was only one (28.3%). The likelihood of being labelled ‘no diabetes’ was greater in subjects aged less than 65 or over 74 with respect to the reference age group (OR 1.89, 95% CI 1.13–3.15; OR 1.55 95% CI 0.94–2.53). The same likelihood consistently decreased when HbA1c test was accompanied by abnormal fasting plasma glucose (FPG) assay (OR 0.20, 95% CI 0.12–0.32).

Conclusions: A permanent exchange of information between the diabetes register and GPs should be maintained to improve the care of patients and the awareness of criteria for diabetes diagnosis among GPs.

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Introduction

The onset of type 2 diabetes (T2DM) is slow, and the disease is often asymptomatic for a long time, as glucose levels increase only gradually over time. Diabetes may remain undetected for many years, thus leading to severe complications [1–4]. Therefore, diabetes must be diagnosed as early as possible, so that appropriate action can be taken to prevent or delay the development of complications. In 2011, a high level of glycated haemoglobin (HbA1c) was endorsed by the

World Health Organisation (WHO) as a sufficient criterion for T2DM using a diagnosis threshold of $\geq 6.5\%$ (48 mmol/mol) [5]. The WHO states that diagnosis can be based on either glucose tests or HbA1c, although in asymptomatic patients, elevated HbA1c or fasting glucose should be confirmed by repeating the same test [6].

The utility of HbA1c in diabetes screening is under discussion [7], especially because of its low sensitivity (42–44%), although its specificity is 99.6% [8].

Despite its low sensitivity, a threshold of 6.5% for HbA1c (48 mmol/mol) has a strong clinical rationale, since this is the level at which the risk of complications has been shown to rise and, indeed, at which measures should be taken to control glycaemia [6].

Given these considerations, the diabetes register for the province of Reggio Emilia includes the HbA1c measurement database

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among the sources, using 'having at least one HbA1c value of $\geq 6.5\%$ (48 mmol/mol) as an inclusion criterion' [9].

The aim of this study was to investigate whether the subjects included in the diabetes register solely because they have an HbA1c over the threshold did in fact receive a diagnosis of diabetes from their general practitioner (GP).

Material and methods

Setting

The diabetes register catchment area is the province of Reggio Emilia, which is situated in Northern Italy and has a population of approx. 550,000. It includes all resident patients who are identified by one or more of the following sources: hospital discharge, drug dispensation, HbA1c values from the biochemistry laboratory, disease-specific exemption, diabetes outpatient clinics, and mortality databases [9]. Women with gestational diabetes or who were receiving treatment for polycystic ovarian syndrome are excluded from the register. Furthermore, the applied algorithm is able to ascertain cases and to distinguish types of diabetes and care settings. Currently, the diabetes register contains both incident and prevalent cases of diabetes from 2009 to 2013.

For patients identified by one or more sources that do not specify the type of diabetes, full electronic clinical records are searched to complete the records. As per other disease registers based on routinely collected databases, the data collection and search in the electronic clinical record are delayed with respect to the reference period, and for the 2009–2010 data, both procedures were carried out during 2013. Once the uploading process is finished, a small group of subjects belongs to the register solely because they have of one or more HbA1c values over the threshold; these subjects are the population included in this study.

In accordance with regional guidelines [10], patients first see their GP and, if diabetes is suspect on the strength of glycaemic tests, they should be referred by the GP to diabetes clinics (DCs) to confirm the diagnosis and stage their diabetes. The patients included in this study were unknown to the DCs; therefore, they were not referred to specialised clinics for the initial assessment and are not included in any structured diagnostic and therapeutic pathway. Possibly, they could be diagnosed as T2DM and cared exclusively by their GP through diet and lifestyle advice, or they could be undiagnosed or they could have one abnormal HbA1c value due to being affected by pre-diabetes or by one of other conditions artificially increasing HbA1c values, carbamylated haemoglobin (renal failure), hypertriglyceridaemia, hyperbilirubinaemia, or iron deficiency [6,11].

To better understand if these subjects were diagnosed as having diabetes or not, and if not why, a survey of GPs was carried out.

Study design

This was a cross-sectional study conducted by surveying GPs. The study included all registered cases in 2009–2010 aged 18 or over that were identified only by the laboratory database because they had one or more HbA1c over the 6.5% threshold and for whom we did not find any information in the search of full electronic clinical records (Fig. 1). For this group of cases, there is no mention of diabetes anywhere in the available electronic sources; therefore, to know if they received a diagnosis or not we had to ask to their GPs.

Each GP received a list of his/her patients showing the date(s) and the value(s) of HbA1c assay(s), along with additional information about the fasting plasma glucose (FPG) assay, if this test was performed. The survey was conducted in the first six months of 2014;

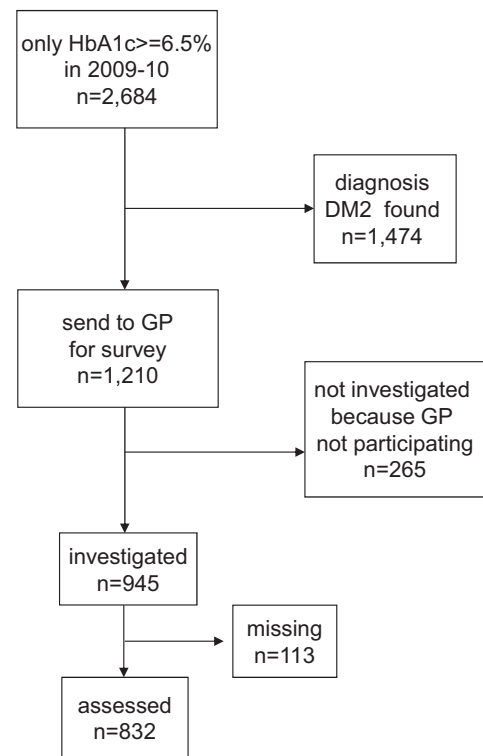


Figure 1. Study population selection flow.

hence, allowing the GP to answer according to the medical charts updates in 2014.

Outcome and covariates

The outcome of interest was confirmation of diabetes diagnosis by the GP (yes or no).

Independent variables included in the analyses are listed below:

GP level: sex, age (years).

Patient level: sex, age (years), foreign status (determined as per citizenship), first HbA1c value equal or over the threshold, number of HbA1c assays, value of FPG closest to first diagnostic HbA1c, all measures performed in 2009–2010. Additionally, for patients with only one HbA1c value over the threshold in the reference period, we retrieved information about further HbA1c tests done in 2011–2013, and we classified this variable in three categories: "further HbA1c $\geq 6.5\%$ in 2011–13"; "further HbA1c $< 6.5\%$ in 2011–13"; "not retested in 2011–13".

Statistical methods

We compared the demographic and clinical characteristics of the study population, stratified based on whether the GP answered or not. Afterwards, the subjects for whom a response was obtained were stratified by type of response. Chi square tests were performed to highlight possible differences in the probability to be assessed and to be diagnosed among the different categories of each of the considered variables.

Multilevel logistic regression was used to examine the influence of GP (level 2) and patient (level 1) characteristics on GP diagnosis in the assessed patients and separately in subjects with two or more HbA1c and in those not retested. The fixed effects are presented as odds ratios (ORs) with 95% confidence intervals (95%

CI). An intra-GP intraclass correlation coefficient (ICC) was calculated. Analyses were carried out using the STATA statistical package, Version 11.

Ethical approval

The diabetes register was approved by the provincial Ethics Committee in July 2014. Direct contact with GPs to confirm information from register data sources was included in the protocols for registration approved by the Ethics Committee. According to the Italian privacy law, no patient or parental consent is required for large retrospective population-based studies approved by an Ethics Committee when data are published in aggregate form only.

Results

At the end of 2010, there were 27,525 residents aged 18 or over included in the diabetes register (6.3% of the general population), of whom 2684 (9.8%) were acquired solely by the HbA1c criterion (Fig. 1). For 1474 patients, we found a T2DM diagnosis in supplementary sources, along with discharge and medical reports; thus, the remaining 1210 subjects (4.3% of the population included in the register) comprised the target population of this study.

Out of the 299 GPs invited, 228 (76.3%) participated. There was no difference in sex or age between participating and non-participating GPs ($p = 0.380$ and $p = 0.331$, respectively).

Among surveyed subjects (Table 1), 265 (21.9%) were not investigated because the GP did not participate, and 113 (9.3%) were not assessed by the GP (i.e. missing) because the subjects were deceased (62) or had emigrated (14), or the GP simply did not evaluate that patient (37).

Comparing not investigated vs. assessed subjects, the former seemed to have higher HbA1c and FPG values (% of having HbA1c $> 7\%$: 35.5% vs 25.1, $p = 0.004$; % of having FPG > 126 mg/dL:

43.4% vs 31.7%, $p = 0.001$). Moreover, the percentage of not retested was higher in not investigated patients with respect to the assessed (48.5% vs 40.0%, $p = 0.020$).

When missing vs. assessed subjects were compared, the former seemed to be older (% aged 75+ : 60.2 vs 34.7, $p < 0.001$) and were more likely not to be retested during 2011–2013 (62.4% vs 40.0, $p < 0.001$).

More than half of the assessed patients (461/832 = 55.4%) had two or more HbA1c values $\geq 6.5\%$ (i.e. for 185 the two values were obtained in the study period and for 276 the second one was obtained during 2011–2013). One in three (259/832 = 31.1%) had only one HbA1c value over the 6.5% threshold during the study period and they were not retested in 2011–2013 and the remaining (112/832 = 13.5%) had only one HbA1c value in $> 6.5\%$ followed by further values in 2011–2013 below the threshold. In each of the above-mentioned groups, we found patients diagnosed as diabetic and patients who were not, although with different percentages.

When the whole study population was analysed, the intraclass correlation (Table 2) showed a strong clustering among the GPs, with almost 50% of total variance accounted for by the GP clustering. The likelihood of having a 'no DM' label was higher in subjects aged less than 65 or over 74, with respect to the reference age group (65–74 years), and in people who are not confirmed diabetics, either without any repeated test or with a repeated test below the diagnostic threshold, compared to those having at least two abnormal results. Conversely, the likelihood of having a 'no DM' label significantly decreased when the HbA1c test was associated with FPG values ≥ 126 mg/dL.

When we restricted the analysis to subjects with two or more HbA1c values over the 6.5% threshold (Table 3), the residual intraclass correlation has lower than in the overall population. The risk to be undiagnosed was double for those aged below 65 and seemed higher also for those aged over 74. Conversely, the risk was very low when the glycaemia alteration was confirmed by the FPG test.

Table 1
Demographic and clinical characteristics of study population

Characteristics	Diagnosed as DM (n = 361)	Not diagnosed as DM (n = 471)	p	Assessed (n = 832)	Missing ^a (n = 113)	Not investigated ^b (n = 265)
Sex: n(%)			0.127			
Males	174 (46.3)	202 (53.7)		376	68	133
Females	187 (41.0)	269 (59.0)		456	45	132
Age groups: n (%)			0.089			
<35	2 (66.7)	1 (33.3)		3	-	-
35–44	7 (30.4)	16 (69.6)		23	-	11
45–54	32 (38.1)	52 (61.9)		84	11	25
55–64	70 (42.2)	96 (57.8)		166	9	51
65–74	134 (50.2)	133 (49.8)		267	25	65
75 +	116 (40.1)	173 (59.9)		289	68	113
Citizenship: n (%)			0.258			
Italian	351 (43.8)	451 (56.2)		802	109	252
Foreign	10 (33.3)	20 (66.7)		30	4	13
HbA1c value: n (%)			<0.001			
48 mmol/mol (6.5%)	65 (30.2)	150 (69.8)		215	21	55
49–52 mmol/mol (6.6–6.9%)	184 (45.1)	224 (54.9)		408	58	116
53 + mmol/mol (7 + %)	112 (53.6)	97 (46.4)		209	34	94
# HbA1c test: n (%)			<0.001			
2 or more	101 (54.6)	84 (45.4)		185	20	59
Only 1	260 (40.2)	387 (59.8)		647	93	206
Further HbA1c $\geq 6.5\%$ in 2011–13	155 (56.2)	121 (43.8)		276	26	85
Further HbA1c $< 6.5\%$ in 2011–13	25 (22.3)	87 (77.7)		112	9	21
Not tested in 2011–13	80 (30.9)	179 (69.1)		259	58	100
FPG value: n (%)			<0.001			
<126 mg/dL	192 (33.8)	376 (66.2)		568	77	150
≥ 126 mg/dL	169 (64.0)	95 (36.0)		264	36	115

^a Patients for whom the participating GP not provided a response.

^b Patients assigned to not participating GP.

Table 2

Odds ratios (OR) for subjects no diagnosed as DM vs diagnosed as DM and 95% confidence intervals (95% CI), patients and GP variables, whole study population

Variables	OR	95%CI
Individual level		
Sex		
Male	1	
Female	1.10	0.73–1.66
Age group ^a (years):		
<65	1.89	1.13–3.15
65–74	1	
75 +	1.55	0.94–2.53
Foreign status		
Italian	1	
Foreign	0.80	0.24–2.63
HbA1c value (%):		
48 mmol/mol (6.5%)	1	
49–52 mmol/mol (6.6%–6.9%)	0.61	0.37–1.00
53 + mmol/mol (7 + %)	0.61	0.33–1.14
# HbA1c test		
2 or more in 2009–2013 ^b >=6.5%	1	
Only 1 >=6.5% in 2009–10 repeated in 2011–13, but < 6.5%	5.73	2.91–11.30
Only 1 >=6.5% in 2009–10 not retested in 2011–13	4.43	2.68–7.32
FPG value (mg/dL)		
<126	1	
>= 126	0.20	0.12–0.32
GP level		
Sex		
Male	1	
Female	1.19	0.54–2.63
Age group (years)		
<55	1	
55 +	0.54	0.25–1.11
Residual intraclass correlation	0.52	0.40–0.64

LR test vs. logistic regression $p < 0.001$.

^a Subjects aged below 65 years were grouped in the same class.

^b This class includes subjects with 2 or more HbA1c >=6.5% in 2009–2010 (n = 185) and those with only one HbA1c >=6.5% in 2009–2010, but with further HbA1c in 2011–2013 (276).

In the group composed by subjects with only one HbA1c value over the threshold in 2009–2010 and not retested during the subsequent period, the likelihood to be labelled as “no diabetes” was inversely associated with higher HbA1c values and to the presence of a diagnostic FPG value.

Discussion

The number of subjects included in the diabetes register solely on the basis of diagnostic HbA1c test was quite small (4.3% of subjects with diabetes and 0.3% of the resident population aged 18 or over). Our results are consistent with those of a similar study [12] and may reflect the ability of the health system to direct people with diabetes diagnosed by HbA1c into an appropriate care model that includes specialised visits, medication (if needed) and/or exemption from costs related to the disease.

Nevertheless, the survey suggests that feedback to the GP may be an effective tool for improving the timeliness of diabetes diagnosis and at the same time to develop proactive medical initiatives. In fact, almost 45% of subjects with two or more HbA1c values over the threshold, i.e. with sufficient and very specific criteria to be diagnosed as diabetic, were not referred to DC or diagnosed as diabetes cases. Additionally, almost one in ten was not retested, while the guidelines recommend repeating the test in the event of one abnormal HbA1c value. Finally, one in four apparently with no diabetes

Table 3

Odds ratios (OR) for subjects no diagnosed as DM vs diagnosed as DM and 95% confidence intervals (95% CI), patients and GP variables, by number and type of HbA1c values^a

Variables	2 + HbA1c >= 6.5 (n = 461) ^b		Only 1 >=6.5% not retested (n = 259)	
	OR	95% CI	OR	95% CI
Individual level				
Sex				
Male	1		1	
Female	0.82	0.49–1.38	1.10	0.47–2.60
Age group ^c (years)				
<65	2.03	1.06–3.90	2.12	0.70–6.41
65–74	1		1	
75 +	1.42	0.77–2.59	1.84	0.64–5.30
Foreign status				
Italian	1		1	
Foreign	2.63	0.27–25.74	0.45	0.07–2.94
HbA1c value (%)				
48 mmol/mol (6.5%)	1		1	
49–52 mmol/mol (6.6%–6.9%)	0.74	0.38–1.43	0.28	0.10–0.81
53 + mmol/mol (7 + %)	0.98	0.45–2.13	0.17	0.04–0.61
FPG value (mg/dL)				
<126	1		1	
>= 126	0.19	0.10–0.35	0.24	0.08–0.66
GP level				
Sex				
Male	1		1	
Female	1.24	0.53–2.88	1.29	0.37–4.48
Age group (years)				
<55	1		1	
55 +	0.80	0.37–1.73	0.34	0.11–1.07
Residual intraclass correlation	0.44	0.27–0.63	0.53	0.28–0.77

LR test vs. logistic regression $p < 0.001$, $p = < 0.001$, respectively.

^a Due to a small number of patients with only one HbA1c >=6.5% (n = 112), the multilevel logistic regression was not computable.

^b This class includes subjects with 2 or more HbA1c >=6.5% in 2009–2010 (n = 185) and those with only one HbA1c >=6.5% in 2009–2010, but further HbA1c in 2011–2013 (276).

^c Subjects aged below 65 years were grouped in the same class.

because the second test was below the cut-off has been diagnosed as suffering from diabetes.

The multilevel analysis showed a strong GP clustering effect, which means that the latent characteristics of the practitioner other than those taken into account play a role in diagnostic decision-making process. This result, combined with the presence of undiagnosed and diagnosed among those not totally fulfilling the WHO criterion, suggests a lack of uniformity in the application of the guidelines.

People aged over 74 were more likely to be considered as ‘not having diabetes’ than those included in the reference class, which is consistent with several studies that call attention to increases in physiological HbA1c with ageing [13–16]. However, even subjects aged below 65 had a higher likelihood; in this case, the GP would have preferred a disglycaemia as the diagnosis. These two findings suggest that two different conditions may favour an absence of diabetes diagnosis: newly acquired diabetes in younger and older people who may be underserved or institutionalised. The latter usually lose contact with their GPs and have poor access to hospital or outpatient care.

Foreign status was not associated with undiagnosed diabetes, as some authors have found [17–19], although the small number of foreigners does not provide a sufficiently large statistical sample to exclude minor differences.

Furthermore, the reduced likelihood to be considered as ‘not having diabetes’ in presence of diagnostic FPG suggests an attitude

of traditional glucose criteria or at least of combining the two tests (i.e. HbA1c and FPG tests).

Strengths and limitations

This study accounts for physician-level variation by multilevel modelling and covers the entire province. Furthermore, overall participation was quite high compared with other physician surveys [20–22]

The main limitation was the lack of information on patient symptoms and comorbidities that artificially increases HbA1c values.

Additionally, the results could be affected by attrition bias, because older subjects dropped out of the study more frequently than others and were considered at higher risk of having undetected diabetes in an advanced age. In the target population, the proportion of subjects with a recognised diagnosis of diabetes by the GP may be lower than that found in the study population.

Finally, our survey may have been influenced both by GP awareness on diabetes achieved using the medical files up to 2014 and by a degree of desirability bias in answers; i.e. the diagnosis could be induced, consciously or not, by our survey. Nevertheless, a consistent number of patients are still undiagnosed.

Conclusion

The linkage of multiple electronic sources for compiling the diabetes register yielded only a small number of subjects with a sole diagnostic HbA1c value alone – a sign that the health care system detects diabetic subjects at an early stage. Nevertheless, certain actions should be planned, such as establishing a permanent exchange of information between GPs and the diabetes register, as well as further dissemination of the criteria used for diabetes diagnosis, particularly regarding the use of HbA1c as a diagnostic tool with high specificity.

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Conflicts of interest

The authors declare they have no conflicts of interest.

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