In-hospital screening for diabetes mellitus with HbA1c in an internal medicine department was not useful; a prospective pilot study

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Background. Screening inpatients for diabetes mellitus may be a good opportunity to detect undiagnosed cases and several studies have demonstrated the feasibility and usefulness of this practice. HbA1c has been suggested as the method of choice due to the effects of acute illness on glucose. The aim of this study was to evaluate a screening protocol based on HbA1c to identify inpatients with undiagnosed diabetes mellitus in an internal medicine department.

Methods. We conducted a prospective study of all admissions in the internal medicine department of a 412-bed community hospital in Greece during a 6-month period. Candidates for screening based on the American Diabetes Association's recommendations were screened with HbA1c. Patients with very poor health status and patients with conditions that may interfere with HbA1c measurement or interpretation were excluded.

Results. Of 463 patients (median age 74) only a small proportion (14.9%) were candidates for screening with HbA1c. Known diabetes mellitus, a low admission glucose, severe anemia or blood loss and poor health status were the most common reasons of exclusion. Among the 55 screened patients, 7 had diabetes (based on $\text{HbA1c} \geq 6.5\%$). However, in only 1 of them HbA1c was above target considering the patients' health status. Categorical agreement (no diabetes, prediabetes, diabetes) between morning glucose and HbA1c was low. However, the concordance between a morning glucose $< 125 \text{ mg/dl}$ and $\text{HbA1c} < 6.5\%$ was $> 90\%$.

Conclusions. In settings similar to ours (very elderly patients, high rate of conditions that confound the use of HbA1c and high rate of patients with poor health status), untargeted screening of inpatients with HbA1c is unlikely to be cost-effective. A morning glucose during hospitalization may be a better first step for screening.

Key words: diabetes mellitus, screening, inpatients, glycated hemoglobin A, glucose.

INTRODUCTION

The prevalence of undiagnosed diabetes mellitus remains significant in many countries [1], including Greece [2]. Considering the high prevalence of diabetes mellitus, the relative long asymptomatic period, the availability of screening tests and the availability of effective therapies that improve long-term outcomes several expert groups recommend screening of the general population either above a certain age or targeted screening of high-risk individuals [3–5]. Inpatients may represent a high-risk group as the prevalence of diabetes mellitus in hospitalized patients is higher compared to the prevalence in the community [6]. Therefore, screening patients at the time of presentation or admission to the hospital may be a good opportunity to detect patients with undiagnosed diabetes mellitus.

However, glucose-based methods (such as fasting or random blood glucose, or the oral glucose

tolerance test) may be impractical to perform in inpatients and are problematic considering the effects of acute illness on glucose. The main confounding factor is stress hyperglycemia, i.e. transient hyperglycemia that occurs during acute illness even in patients without diabetes mellitus or pre-diabetes [7]. The use of dextrose-containing intravenous solutions, administration of corticosteroids [8], and the use of insulin for treatment of stress hyperglycemia are other confounding factors to consider among inpatients. Furthermore, hospitalized patients are at risk for both iatrogenic and “spontaneous” hypoglycemia [7].

An alternative to glucose-based diagnosis is the measurement of glycated hemoglobin (HbA1c), which has been adopted as an acceptable diagnostic criterion ($\text{HbA1c} \geq 6.5\%$) [3]. In contrast to glucose-based methods, HbA1c is not substantially affected by acute illness [3, 9]. Several previous studies have screened acute medical admissions or patients presenting to the emergency department with HbA1c to identify

patients with undiagnosed or poorly controlled diabetes mellitus and most studies have demonstrated a high prevalence of undiagnosed diabetes mellitus [6, 10–18]. A disadvantage of HbA1c is that some conditions may interfere with the measurement (e.g. hemoglobinopathies) or interpretation of HbA1c (e.g. conditions associated with altered red blood cell turnover) [3, 19, 20].

Despite the availability of several studies demonstrating the feasibility and usefulness of HbA1c screening in inpatients, we believe that these data may not be generalizable to other countries/settings. Our aim was to examine the usefulness of HbA1c screening in patients admitted to the internal medicine department of a community hospital in Greece.

MATERIALS AND METHODS

Study design and setting

The study was conducted prospectively in the Internal Medicine department of a 412-bed community hospital located in Heraklion, Greece. All acute medical admissions from October 2017 to April 2018 were evaluated for the inclusion/exclusion criteria described below. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the hospital's Scientific Council. An informed consent was not required as this was a non-interventional study (the criteria used for obtaining HbA1c are in agreement with the indications for screening for diabetes mellitus according to standard guidelines [3]). Furthermore, many prior studies have validated the use of HbA1c measurement among hospitalized patients [6, 10–18]. Patients were informed about the results and if diabetes was detected were referred to the diabetology unit.

Screening protocol

The patients were considered as candidates for screening based on the recommendations of the American Diabetes Association if they met one of the following criteria [3]: 1) age ≥ 45 or 2) overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) adults with ≥ 1 additional risk factor. Patients with in-hospital hyperglycemia (defined here as glucose $>140 \text{ mg/dl}$ [21]) were also candidates for screening with HbA1c even if none of the above 2 criteria was fulfilled. However, no additional patients were candidates based on this criterion alone.

The following patients were excluded from our screening protocol: 1) Patients with known diabetes

mellitus. 2) Patients without a prior diagnosis of diabetes mellitus but a low admission glucose ($<100 \text{ mg/dl}$), as such patients are unlikely to have diabetes mellitus [10]. Measurement of glucose at admission was not required but represents routine practice in our hospital. 3) Patients with factors that may interfere with the HbA1c measurement. More specifically, we excluded patients with known homozygous or compound heterozygous hemoglobinopathies. 3) Patients with conditions that may affect the interpretation of the HbA1c results. More specifically we excluded patients with recent blood loss (e.g. gastrointestinal bleeding or acute hemolysis), patients with significant anemia (hemoglobin $<10 \text{ mg/dl}$), patients that had received red blood cell transfusion within 6 months before admission, patients with significant kidney disease ($\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$, calculated with the MDRD equation [22]) and patients on erythropoietin. 4) Elderly (>65 years old) patients with very poor health status (unable to perform any activity of daily living) or patients with poor prognosis, such as end-stage malignancy or other end-stage disease on palliative care. We excluded such patients because treatment of hyperglycemia would be indicated only if severe and symptomatic [23], and therefore an HbA1c measurement would be unnecessary. 5) Pregnant women were excluded because HbA1c is not recommended for the diagnosis of diabetes mellitus in pregnancy [3]. 6) Patients admitted due to diabetic ketoacidosis or hyperglycemic hyperosmolar state. The diagnosis of diabetes mellitus is evident in such patients and therefore such patients were irrelevant to the aims of this study. 7) Patients with HbA1c measurement within 3 months before admission. 8) Patients admitted to our clinic more than one time during the study period were included only in their first admission.

For patients fulfilling the inclusion criteria and without any of the exclusion criteria, HbA1c was sent with the next morning labs. HbA1c was measured with high-performance liquid chromatography using the Tosoh Automated Glycohemoglobin Analyzer G8. External quality control is conducted every 15 days by ESEAP, the national External Quality Assessment Scheme for clinical chemistry in Greece [24]. As part of the study's protocol glucose measurements during hospital stay were also evaluated. Although measurement of blood glucose was not required, it represents common practice in our hospital. Patients were not required to fast. A morning blood glucose was considered as fasting if both of the following conditions were satisfied: 1) Fasting for at least 8 hours and 2) No receipt of intravenous dextrose-containing solutions for at least 8 hours. We also recorded administration of corticosteroids during the prior 24 hours.

Data analysis

Analysis of the data was conducted in Microsoft Excel. Among screened patients we examined the frequency of undiagnosed diabetes mellitus and pre-diabetes. In patients with newly diagnosed diabetes mellitus, especially older (≥ 65 years old) adults, we examined whether HbA1c was above glycemic targets taking into account the patients' health status (target HbA1c: $<7.5\%$ for healthy older adults, $<8\%$ for complex/intermediate health status, $<8.5\%$ for very complex/poor health status) [23, 25]. We also examined the rate of categorical agreement between morning plasma glucose and HbA1c. The following categories were considered based on the definitions of the American Diabetes Association [3]: no diabetes (HbA1c $< 5.7\%$, fasting glucose < 100 mg/dl), prediabetes (HbA1c $5.7\text{--}6.4\%$, fasting glucose $100\text{--}125$ mg/dl) and diabetes (HbA1c $\geq 6.5\%$, fasting glucose > 125 mg/dl).

RESULTS

Description of the study population

A total of 463 patients admitted between October 2017 and May 2018 were evaluated. The median age of medical admissions at our department was 78 (interquartile range 65–85). Only 69 (14.9%) were candidates for screening according to our inclusion and exclusion criteria. Most patients were excluded from screening based on a low admission glucose (<100 mg/dl, $n = 129$) or an already established diagnosis of diabetes mellitus ($n = 128$, 28%). The most common reasons for exclusion among the rest of the patients were anemia/acute blood loss ($n = 60$) and very poor health status or poor prognosis ($n = 55$). The rest of the exclusion criteria resulted in small number of additional patients excluded. A flow chart of our study is depicted in Figure 1.

eGFR= estimated glomerular filtration rate (MDRD equation) ^a Excluding patients that were admitted more than one time during the study period ^b Some patients had more than one reasons of exclusion. The numbers in the figure indicate the number of additional patients excluded for each reason of exclusion.

Figure 1. Flow chart of the study.

Results of screening based on HbA1c

Among screened patients, the frequency of undiagnosed diabetes mellitus (HbA1c $\geq 6.5\%$) and prediabetes (HbA1c 5.7–6.4%) was 12.7% ($n = 7$) and 67.3% ($n = 37$), respectively. Of note is that based on the age and health status of the patients only 1 patient (1.8% of screened patients) had HbA1c above glycemic targets as recommended by the American Diabetes Association [23, 25]. Of the 7 patients with HbA1c $\geq 6.5\%$, 6 had an HbA1c $< 7\%$.

Screening based on morning blood glucose

Although daily blood glucose monitoring was not a requirement of the study protocol, all screened patients had at least one morning blood glucose measurement as a result of routine practice. Furthermore, although patients were not asked to fast, blood sampling takes place early in the morning and a fasting plasma

glucose measurement was available for 46 of the 55 screened patients. Among those 46 patients only 4 had been administered corticosteroids during the prior 24 hours.

Categorical agreement (“no diabetes”, prediabetes, diabetes) between fasting morning plasma glucose and HbA1c was observed in only 22 of the 46 patients (47.8%) (Table 1). Among patients with a fasting morning glucose < 100 mg/dl only 27.8% had an HbA1c $< 5.7\%$. Among patients with a fasting morning glucose 100–125 mg/dl 71.4% had an HbA1c 5.7–6.4%. Finally, among patients with a fasting morning glucose > 125 mg/dl only 28.6% had an HbA1c $\geq 6.5\%$. Nevertheless, the agreement between a morning glucose < 125 mg/dl and HbA1c $< 6.5\%$ was high (92.3%). The results were similar using the WHO/IDF criteria [26] (cut-off for normal fasting glucose 110 mg/dl instead of 100 mg/dl); categorical agreement was 32.1% for “no diabetes” and 81.8% for pre-diabetes.

Table 1

Categorical agreement between morning glucose and HbA1c

HbA1c		First available morning glucose†			
		< 100 mg/dl	100–125 mg/dl	> 125 mg/dl	≤ 125 mg/dl
HbA1c	$< 5.7\%$	4 (27%)	4 (19%)	3 (16%)	8 (22%)
	5.7–6.4%	10 (67%)	15 (71%)	12 (63%)	25 (69%)
	$\geq 6.5\%$	1 (7%) ‡	2 (10%) ‡	4 (21%)	3 (8%) ‡
	$< 6.5\%$	14 (93%)	19 (91%)	15 (79%)	33 (92%)
HbA1c		Fasting morning glucose ($n = 46$ of the 55 patients)			
		$< 5.7\%$	4 (19%)	1 (14%)	9 (23%)
		5.7–6.4%	12 (67%)	15 (71%)	4 (57%)
		$\geq 6.5\%$	1 (6%)	2 (10%) ‡	2 (29%)
		$< 6.5\%$	17 (94%)	19 (91%)	5 (71%)
					36 (92%)

Cell numbers represent the number of patients. Percentages represent column percentages. In bold are cases of categorical agreement: i.e. cases with morning glucose < 100 mg/dl and HbA1c $< 5.7\%$, cases with morning glucose 100–125 mg/dl and HbA1c 5.7–6.4%, cases with morning glucose > 125 mg/dl and HbA1c $\geq 6.5\%$, and cases with morning glucose ≤ 125 mg/dl and HbA1c $< 6.5\%$. † The first available morning glucose represented a fasting glucose in 34 of the 55 patients. ‡ Two patients had a fasting morning blood glucose of 124 mg/dl and 125 mg/dl, with an HbA1c of 6.5%. One patient (75 years-old) had a fasting morning glucose of 95 mg/dl and HbA1c 6.8%.

DISCUSSION

Applying strict inclusion and exclusion criteria only a small percentage (about 15%) of acute medical admissions in a typical Greek Internal Medicine department were candidates for in-hospital screening for diabetes mellitus with HbA1c. Most patients could be excluded from screening based on an already established diagnosis of diabetes mellitus (27.6%) or an admission glucose < 100 mg/dl (27.8%), and an additional 13.8% could be excluded due to significant anemia, acute blood loss or recent transfusion (i.e., factors that complicate the interpretation of HbA1c measurement due to altered red blood cell turnover). Furthermore, many elderly patients were poor candidates for screening due to very poor health status,

resulting in exclusion of an additional 11.9% of all patients. In such patients glycemic goals are relaxed and avoiding severe/symptomatic hyperglycemia is the main goal [23].

Therefore, admissions to our department are characterized by a high median age (> 70), a high rate of patients with very poor health status (i.e. patients unlikely to benefit from screening with HbA1c), and high rate of diagnoses that may complicate interpretation of HbA1c measurement. This is important to consider when designing screening algorithms for inpatients, especially in settings like ours, where many patients are not candidates for HbA1c screening. Furthermore, it is important to consider whether an HbA1c measurement is likely to alter patient management. In our study, taking into account the

patients' health status only 1 of the 7 patients (corresponding to 1.8% of screened patients and 0.2% of all admissions) with undiagnosed diabetes mellitus had an HbA1c value above glycemic targets [23, 25].

Despite the confounding effects of acute illness, a morning glucose may still be a useful screening test for undiagnosed diabetes mellitus among inpatients. Although categorical agreement (no diabetes, prediabetes, diabetes) between morning plasma glucose and HbA1c was low in our study, most

patients (92%) with a morning glucose <125 mg/dl had an HbA1c value <6.5%. Other studies have also described the use of fasting or random plasma glucose as a first step for screening inpatients for diabetes mellitus [10, 27–29]. Although the requirement of fasting for several hours (typically 8 hours) may be impractical in acutely ill hospitalized patients, in our setting we found that morning blood sampling results in most samples being fasting. Furthermore, fasting for less than 8 hours (but at least 3 hours) may also be acceptable [30].

¹ According to American Diabetes Association guidelines [3, 21]. ² The ideal cut-off might be different in other departments with different patient characteristics or different timing of blood-sampling. ³ Glycemic targets are more relaxed in elderly patients or patients with poor health status [23]. In palliative care patients, management of severe symptomatic hyperglycemia is the main goal (therefore HbA1c measurement is not helpful).

Figure 2. Suggested algorithm for screening inpatients for undiagnosed diabetes mellitus.

Our study has some limitations. The most important limitation is the small number of screened patients. Despite an initial plan to include a larger number of patients the study was stopped earlier because based on an interim analysis, systematic screening of patients admitted to our department with HbA1c was unlikely to be cost-effective. A low morning plasma glucose was sufficient to rule out a high HbA1c in most patients and therefore represents a more cost-effective first step for screening. Another limitation is that patients were not followed after discharge with repeat fasting glucose or HbA1c measurements in order to evaluate the correlation between inpatient measurements and measurements after resolution of acute illness. Finally, our study was single-center involving only one hospital department. Therefore, our findings may not be generalizable to other hospital departments, with different patient characteristics.

CONCLUSION

In conclusion, although in-hospital diagnosis of diabetes mellitus is feasible and several studies have recommended the use of HbA1c for this purpose, in departments with similar characteristics to ours, where most patients are elderly, of poor health status and many have concurrent conditions that may interfere with HbA1c measurement or interpretation, untargeted screening of inpatients with HbA1c is unlikely to be cost-effective. A morning (which is often fasting) glucose measurement, commonly available among hospitalized patients as a result of routine practice, may be a more cost-effective first step for screening hospitalized patients for undiagnosed diabetes mellitus. Most patients can be excluded from further screening with HbA1c based on a low morning glucose. A suggested algorithm for inpatient screening for diabetes mellitus is provided in Figure 2.

Introducere. Screening-ul pentru diabetul zaharat poate fi o oportunitate de a detecta cazurile nediagnosticate, mai multe studii demonstrează beneficiul și fezabilitatea unui astfel de demers. Analiza HbA1c a fost aplicată. Scopul studiului este de a evalua un protocol de screening bazat pe analiza HbA1c pentru a diagnostica pacienții cu diabet zaharat care se prezintă pentru alte afecțiuni în Secția de medicină internă.

Materiale și metode. A fost realizat un studiu prospectiv într-un spital comunitar din Grecia cu 412 paturi, în cadrul Secției de medicină internă. Pacienții au fost examinați conform recomandărilor Societății Americane de Diabetologie. Au fost excluși pacienții cu status socio-economic precar.

Rezultate. Din 413 pacienți eligibili (vârsta medie de 74 ani) numai o mică parte au fost candidați pentru screening cu analiza HbA1c (14,9%). Principalele motive de excludere au fost reprezentate de nivelul scăzut al glicemiei la internare, anemia severă sau hemoragia cronică. Din 55 de pacienți examinați, 7 pacienți au fost diagnosticați cu diabet (considerând $HbA1c \geq 6,5\%$). Concordanța dintre glicemia à jeun <125 mg/dl și $HbA1c <6,5\%$ a fost de $>90\%$.

Concluzii. Screening-ul s-a dovedit a nu fi economic. Primul pas pentru screening ar fi mai degrabă glicemia à jeun.

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