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ORIGINAL ARTICLE

Assessment of simple strategies for identifying undiagnosed diabetes and prediabetes in the general population

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Abstract

Background and aims The rising tide of diabetes mellitus (DM) and prediabetes (PDM) is urgently calling for strategies easily applicable to anticipate diagnosis. We assessed the effectiveness of random capillary blood glucose (RCBG), administration of a validated DM risk questionnaire, or the combination of both.

Materials and methods RCBG measurement and/or questionnaire administration were offered to all individuals presenting at gazebos organized during the World Diabetes Day or similar public initiatives on diabetes awareness. Subjects with suspicious DM or PDM were invited to the Diabetes Center (DC) for laboratory confirmation (fasting plasma glucose and HbA1c).

Results Among 8563 individuals without known diabetes undergoing RCBG measurement, 341 (4%) had suspicious values. Diagnosis of DM was confirmed in 36 (41.9%) of the 86 subjects who came to the DC and PDM was found in 40 (46.5%). Among 3351 subjects to whom the questionnaire was administered, 480 (14.3%) had suspicious scores. Diagnosis of DM was confirmed in 40 (10.1%) of the 397 who came to the DC and PDM was found in 214 (53.9%). These 3351 subjects also had RCBG measurement and 30 out of them had both tests positive. Among them, 27 subjects came to DC and DM was diagnosed in 17 (63.0%) and PDM was found in 9 (33.3%).

Conclusions These data suggest that RCBG definitely outperforms the questionnaire to identify unknown DM and PDM. RCBG measurement, with questionnaire as an adjunctive tool, appears to be a simple, fast, and feasible opportunistic strategy in detecting undiagnosed DM and PDM.

Keywords Diabetes mellitus · Prediabetes · Capillary blood glucose · Diabetes risk questionnaire

Introduction

The World Health Organization recognized diabetes mellitus (DM) as a global health emergency [1]. In many European countries, the prevalence of known DM is around 6–7% and that of prediabetes (PDM) is around 4–5% [2]. In accordance with WHO definition, the United Nations adopted a resolution in 2006 which recommended all nations to promote and implement education and information programs on diabetes as well as campaigns for an earlier diagnosis of the disease [3].

It was estimated that the prevalence of undiagnosed DM is high also in affluent countries [4–7]. It is known that the diagnosis of DM often occurs with a delay of several years [8–10], so that as many as 50% of diabetic patients already have chronic complications at the time of DM diagnosis [11–13]. It is, therefore, essential to develop effective strategies to detect undiagnosed DM. Although many scientific societies recommend screening for diabetes, strategies to adopt are different and sometimes inconsistent or controversial [14–18]. On the other hand, in some studies, it was observed that screened positive subjects have a better outcome than diabetic subjects in the no-screening group [19–21]. Yet, preventive interventions in subjects with PDM

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seem to be cost-effective [22], and therefore, also the identification of PDM could be recommended. This condition is strongly associated with an increased risk of diabetes [23] as well as atherosclerosis progression [24] and eventually cardiovascular disease [25].

In the last decades, especially on the occasion of the World Diabetes Day (November 14th), many individuals are offered a measurement of a random capillary blood glucose (RCBG) as part of public awareness events promoted worldwide by institutions or associations of people with DM. Alternatively, or concomitantly, it is offered to people attending these events the possibility to fill in or to be administered a questionnaire set to establish the individual risk of developing DM. Every year, worldwide, high RCBG levels and/or high scores at the diabetes risk questionnaire raise the suspect of the presence of DM or PDM in a substantial proportion of people participating into these events. However, a few investigations were carried out so far to understand to what extent the suspect of DM or PDM is actually associated with its undiagnosed presence.

The present study aimed at exploring the reliability of RCBG measurement and/or risk questionnaire administration in the process of identification of undiagnosed DM and PDM.

Research design and methods

Experimental design

In a study conducted in the metropolitan areas of Verona and Padua, three different procedures were tested: (a) meal contextualized RCBG measurement; (b) administration of a structured DM risk questionnaire; (c) both RCBG and questionnaire.

Subjects with high risk (i.e., positive) according to RCBG or questionnaire were invited to the local Diabetes Center (DC) for a standard laboratory testing of fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c).

Subjects

RCBG measurement and questionnaire administration, supervised by healthcare professionals, were offered to all individuals presenting to receive information on DM at gazebos organized during the World Diabetes Day or similar public initiatives on diabetes awareness. Inclusion criteria were age ≥ 18 years and the signature of an informed consent prior to participation in the study. Exclusion criteria were: age < 18 years; known DM (self-reported, diagnosis ascertained by medical professionals); ongoing pregnancy; breastfeeding; severe illness; ongoing steroid therapy.

Written informed consent was obtained from all study subjects before participating in the study. The protocol was approved by the local Institutional Review Boards.

Random capillary blood glucose

RCBG measurements were made from 8.30 in the morning to 18.30 in the afternoon. Glucose level reading was contextualized according to last meal (see below for details). Devices (glucose meters) for RCBG measurement were selected among top models available on the market according to their accuracy and precision.

Risk questionnaire

The questionnaire for the determination of individual DM and PDM risk is the Finnish Diabetes Risk Score Calculator (FINDRISC) [26], previously validated in the Italian language. The FINDRISC is based on a scoring system exploring the following domains: age, physical activity, family history of diabetes, body mass index, waist circumference, personal history of hyperglycaemia, anti-hypertensive drug use, and dietary habits. The FINDRISC is structured to assign a specific score to each item. The algebraic sum of the score obtained in each item returns an overall score ranging from 0 to 27. Thus, individuals may fall in one of the following pre-specified categories: < 7, low risk; 7–11, slightly elevated risk; 12–14 moderate risk; 15–20 high-risk; > 20 very high risk of developing DM in 10 years. This questionnaire was used also for diabetes and dysglycemia identification [27, 28].

Definition of diabetes or prediabetes risk

The cut-off for referring the screened individuals to the DC for a laboratory confirmation of a suspect DM or PDM was an FINDRISC score ≥ 15 points. The RCBG reading cut-off considered suggestive of DM or PDM, after contextualizing from last meal, were arbitrarily set as follows: RCBG ≥ 200 mg/dl within 2-h after last meal/sugar drink; ≥ 150 mg/dl within 2–5 h; ≥ 125 mg/dl over 5 h.

Laboratory confirmation

Each participating DC performed the FPG and HbA1c testing to confirm the diagnosis of DM or to identify PDM according to the standard laboratory procedures. Hemoglobin A1c was measured by a IFCC standardized method, with an automated high-performance liquid chromatography method on Tosoh G7 automated 26 analyzers (Tosoh Bioscience Inc., San Francisco, CA; USA); the upper limit of normal was 5.6% (38 mmol/mol). Plasma glucose was measured by a glucose oxidase method. DM and PDM were

diagnosed according to the standard criteria. In particular, DM was diagnosed when FPG was ≥ 126 mg/dl (7 mmol/l) and/or HbA1c was equal or above 6.5% (48 mmol/mol), whereas PDM was diagnosed when FPG was in the range 100–125 mg/dl (5.55–6.9 mmol/l) and/or HbA1c was in the interval 5.7–6.4% (39–47 mmol/mol).

Statistical analysis

Primary outcome was the confirmed diagnosis of DM and/or PDM. Statistical analyses were carried out with standard techniques (Chi-square and Kruskal–Wallis).

Data are presented as mean ± standard deviation (SD) or median and interquartile range [IQR] or as percentage of total.

Results

As many as 8563 individuals underwent RCBG measurement and 341 out of them had glucose readings compatible with the presence of DM. FPG and HbA1c testing were offered to all of them, but only 86 (25%) eventually came to the DC for laboratory testing. DM diagnosis was confirmed in 36 of these individuals and PDM was found in 40 (Table 1).

As many as 3351 subjects were administered the FINDRISC questionnaire and 480 reported high-risk scores. Out of them, 397 (82.7%) came to the DC and DM diagnosis was confirmed by laboratory testing in 40 of these subjects and PDM was found in 213 (Table 1).

In these 3351 subjects also the RCBG measurement was performed and 30 of them were at high risk according to both procedures. Out of these subjects, 27 (90%) came to the DC and DM was confirmed by laboratory testing in 17 of these subjects and PDM was found in 9 (Table 1).

In subjects undergoing laboratory testing at the DC ($n = 456$), a number of clinical information were collected. Table 2 illustrates data from subjects without or with PDM or DM. Significant differences were observed in gender, age, BMI, waist circumference, systolic blood pressure, and use of lipid-lowering drugs (Table 2).

FINDRISC revealed a significantly greater proportion of subjects resulting positive to case finding as compared to

Table 1 Number of subjects undergoing initial assessment with different tools and subsequent laboratory testing

Assessment tool	Examined with the tool (*n*)	High risk of having DM or PDM (*n*)	Undergoing laboratory testing (*n*)	PDM confirmed (*n*)	DM confirmed (*n*)	DM or PDM confirmed (*n*)
RCBG	8563	341	86	40	36	76
FINDRISC	3351	480	397	213	40	253
RCBG or FINDRISC	8563	791*	456	253	59	312
RCBG and FINDRISC	3351	30**	27	9	17	26

DM diabetes mellitus, *PDM* prediabetes, *RCBG* random capillary blood glucose

*Positive to one or other assessment tool; **positive to both assessment tools

Table 2 Clinical features of 456 subjects undergoing laboratory testing

Variable	All subjects ($n = 456$)	No DM or PDM ($n = 144$)	PDM ($n = 253$)	DM ($n = 59$)	*p* value
Men (%)	48.9	42.1	49.6	61.0	0.018
Age (years)	63 [55–70]	59 [53–68]	64 [57–71]	59 [56–72]	< 0.001
Body mass index (kg/m^2)	27.4 [24–30]	26.9 [23–30]	27.4 [25–30]	28.4 [26–32]	0.021
Waist circumference (cm)	100.0 [91–107]	96.0 [88–104]	100.0 [92–107]	101.5 [95–114]	< 0.001
HbA1c (%)	5.7 [5.4–5.9]	5.4 [5.2–5.5]	5.9 [5.7–6.1]	6.8 [6.4–7.5]	< 0.001
FPG (mg/dl)	99 [88–104]	90.0 [84–94]	101.5 [94–108]	134.5 [126–152]	< 0.001
Systolic BP (mmHg)	130 [120–140]	125 [120–138]	130 [120–140]	132.5 [125–150]	0.024
Family history of DM (%)	66.0	68.6	67.4	54.5	NS
Current smokers (%)	8.9	11.0	8.5	6.3	NS
Anti-hypertensive drugs (%)	56.9	48.3	61.9	56.5	NS
Lipid lowering drugs (%)	16.3	4.5	23.1	15.2	< 0.001

Percentage or median [IQR]. Comparisons between three categories of glucose tolerance by Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables

DM diabetes mellitus, *PDM* prediabetes, *FPG* fasting plasma glucose, *BP* blood pressure

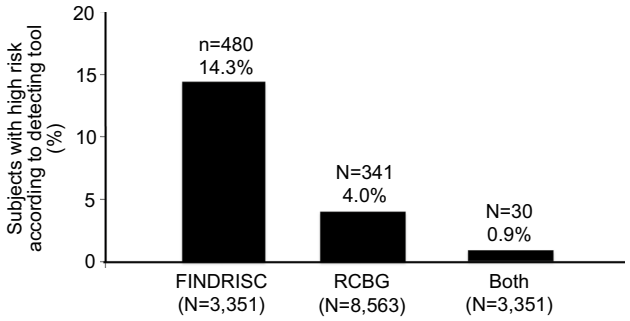

Fig. 1 Proportions of individuals at high risk according to the different detecting tools. All comparisons $p < 0.001$

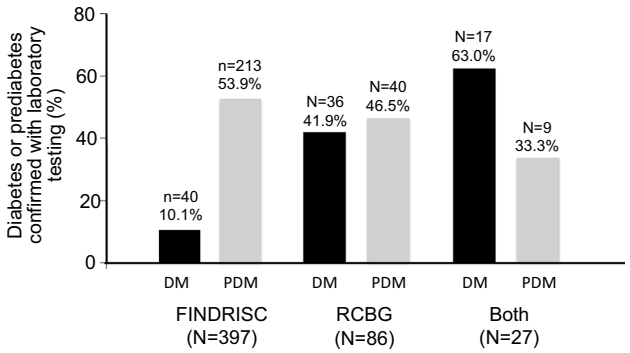

Fig. 2 Diabetes (DM) or prediabetes (PDM) confirmation according to detecting tool. DM detection: FINDRISC vs. RCBG $p < 0.001$; FINDRISC vs. Both $p < 0.001$; RCBG vs. Both $p < 0.005$. PDM detection: FINDRISC vs. RCBG $p =$ NS; FINDRISC vs. Both $p < 0.05$; RCBG vs. Both $p =$ NS

RCBG, with a small percentage of subjects being positive to both procedures (Fig. 1).

Among the 397 subjects with high FINDRISC score undergoing laboratory testing, 40 (10.1%) had diabetes and 213 (53.9%) had PDM. Overall, 64% of these subjects had DM or PDM. Among the 86 subjects with high RCBG level, who came to the DC for laboratory testing, 36 (41.9%) had DM and 40 (46.5%) had PDM. Overall 88.4% of these subjects had DM or PDM. Among the 27 subjects with high RCBG level and also high FINDRISC score who underwent laboratory testing, 17 (63%) had DM and 9 (33.3%) had PDM. Overall, 96.3% of these subjects had DM or PDM (Fig. 2).

Discussion

Detecting undiagnosed DM is extremely important, because anticipating the diagnosis would allow a more precocious and timely control of hyperglycemia and, therefore, the prevention of chronic complications. Unfortunately, several subjects with newly diagnosed DM have target organ damage (retinopathy, nephropathy, neuropathy, cardiovascular disease, and foot problems) due to a late diagnosis [8–13]. Anticipating the diagnosis of DM would substantially diminish this proportion with a consequent reduction in complication-related cost. In this regard, it should be remarked that cost of complications represents the majority of the overall economic burden of the disease for health systems [29–32]. Anticipating DM diagnosis with RCBG measurement and/or with the administration of a structured questionnaire (e.g., FINDRISC) followed by a confirmation with laboratory testing of fasting glucose and/or HbA1c might be a simple, fast, cheap, and opportunistic strategy. Its reliability, however, is still poorly defined.

In the present study, we measured RCBG and/or administered FINDRISC questionnaire in several thousand unselected subjects from the general population. We found that subjects positive (high-risk score) to the questionnaire were ~ threefold more common in the population than subjects positive to RCBG measurement (high-risk level) and that only a minimal portion of subjects undergoing both procedures were at high risk with RCBG and also FINDRISC. However, as many as 96% of subjects who had a double positivity actually had DM or PDM. In those positive to FINDRISC, most had PDM (~ 54%) but not DM (~ 10%), whereas in subjects positive to RCGB measurement, there was a similar proportion of DM (~ 42%) and PDM (~ 46%). In those positive to both procedures, we found a definite predominance of DM vs. PDM (63 vs. 33%).

Our results are quite original, because they are based upon RCBG measurement without a single predefined cut-off prompting to laboratory confirmation. In fact, we have contextualized RCBG according to time elapsed from previous meal. In other studies, a single fixed RCBG cut-off was used (e.g., RCBG ≥ 100 mg/dl or ≥ 140 mg/dl) [14–17, 21, 33–36]. Toscano et al. [36] analyzed 22 million of random fasting or non-fasting capillary blood glucose tests carried out in Brazil and found 3.5 million screened positive subjects of whom only about 10% were confirmed new cases of diabetes. In this monumental study, RCBG cut-off was set at ≥ 100 mg/dl in the fasting state and at ≥ 140 mg/dl in the non-fasting state. Their performance is definitely lower than ours in terms of case finding.

The approach of RCBG measurement and interpretation which we used in this study supports the possibility for healthcare professionals of taking advantage of an opportunistic case finding anytime during working hours. These professionals should be aware that a substantial proportion of RCBG positive subjects do not have DM but rather PDM, a condition that anyway deserves an effective preventive intervention. Overall, RCBG measurement contextualized according to time from previous meal seems to be able to identify up to ~ 88% of subjects with DM

or PDM. The adjunctive (subsequent) use of FINDRISC might increase this ability to ~ 96%. Accordingly, the number of false positive is trivial.

We feel that the contextualized cut-off points which we established for RCBG are consistent with the current diagnostic criteria for DM and PDM [2], also considering the well-established difference between plasma and blood glucose, the latter being 10–15% lower. A cut-off point of 200 mg/dl in subjects consuming the meal within the previous 2 h is consistent with the criteria of random plasma glucose or 2-h OGTT plasma glucose > 200 mg/dl for diagnosing DM. A cut-off point of 150 mg/dl for those consuming the previous meal 2–5 h before the test is consistent with the 2-h OGTT values between 140 and 199 mg/dl for diagnosing PDM. A cut-off point of 125 mg/dl for those who did not consume any food in the previous 5 h is consistent with the 126 mg/dl threshold for diagnosing DM after an 8 h fasting period as well as the threshold of 100 mg/dl for diagnosing PDM the same condition.

We found that approximately 4% of subjects tested with RCBG had a value compatible with DM or PDM. Subjects were adult, overweight, and often hypertensive, and two out of three of them had a family history of DM. Therefore, this finding is not surprising and is consistent with the prevalence of unknown DM and PDM in Western Countries [2]. Accordingly, in several similar experience during World Diabetes Day in the past 30 years, we found that glucose readings suspect for DM or PDM were generally around 5%. Under those circumstances, however, no laboratory follow-up was offered.

The use of FINDRISC alone for revealing unknown DM does not seem feasible because of the large number of false positive. In fact, only 10% of those at high risk by questionnaire had DM confirmed with laboratory testing. This is consistent with data obtained by others who used the same or other questionnaires [5, 15–17, 21, 27, 28, 33–35, 37]. However, a remarkable number of subjects with PDM was found with the questionnaire. Interestingly, FINDRISC was also able to substantially improve the detection power of unknown DM by RCBG, supporting the idea that in a two-step approach, RCBG might precede and not follow questionnaire administration, as done in most studies, and that the use of the latter could be restricted to RCBG positive subjects. In this regard, it is worth mentioning that RCBG measurement can be performed in about 1–2 min, whereas the administration of the questionnaire requires 5–10 min.

Strengths of this study include: large number of subjects examined; no selection of subjects under evaluation; RCBG interpretation contextualized according to time elapsed from last meal; use of two of the most popular approaches proposed to detect unknown diabetes in awareness campaigns; inclusion of PDM in analyses.

A limit of the study is the suboptimal definition of the time elapsed since the last meal before RCBG measurement and the assumption that the amount of carbohydrates ingested with the meal was not substantially different among subjects. Another limit is the impossibility to use a single model of glucose meter throughout the study period and under all circumstances. However, a remarkable proportion of subjects with suspect DM or PDM according to RCBG actually had a confirmation (~ 88%). A further concern might be that our experimental protocol does not allow to assess sensitivity and specificity. In fact, we did not make laboratory testing in subjects not at risk according to RCBG and/or questionnaire. However, this was beyond the scope of the present study which focused on DM or PDM confirmation in subjects at high risk. On the other hand, the literature data already provided detailed information on performance of the several screening strategies [38, 39].

In conclusion, our data suggest that RCBG definitely outperforms FINDRISC to identify unknown DM and PDM, but FINDRISC increases the predictive power of RCBG. The combined use of RCBG (step 1) and FINDRISC (step 2) appears to be a simple, fast, and cheap approach for an opportunistic detection of unknown DM as well as PDM in the general population.

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Author contributions EB designed the study. All authors collected the data. EB and MD written the paper. All authors reviewed and approved the manuscript.

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Compliance with ethical standards

Conflict of interest No conflict of interest was declared by any of the authors.

Ethical approval The protocol was approved by the local Institutional Review Boards.

Informed consent Written informed consent was obtained from all study subjects before participating in the study.

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