Comparison of five different risk scores to predict incident type 2 diabetes in the Swiss HIV cohort study

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Abstract: OBJECTIVE People with HIV (PWH) have a higher risk of type 2 diabetes (T2D) than HIV-negative individuals. In the general population, diabetes risk scores are used to identify persons at risk of developing T2D, but little is known regarding their performance in PWH. DESIGN Assessment of the capacity of five diabetes risk scores to predict T2D in PWH. METHODS A prospective study including all Swiss HIV cohort study (SHCS) participants followed between 2009 and 2019. Five diabetes risk scores were assessed: FINDRISC versions 1 and 2, Balkau, Swiss Diabetes Association (SDA), and Kraege. RESULTS Three thousand eight hundred fifty-three T2D-free PWH (78.5% men, 39.9 ± 11.3 years) were included. After a median follow-up of 4.8 years (interquartile range 2.2-7.8), 62 participants (1.6%) developed T2D, corresponding to an incidence rate of 3.18 per 1000 person-years (95% confidence interval = 2.47-4.08). Participants who developed T2D were older (48.7 ± 12.4 vs. 39.8 ± 11.2 years), more likely to be obese (22.6% vs. 7.4%), abdominally obese (9.7% vs. 1.5%), and to have a family history of diabetes (32.3% vs. 19.1%) than those without T2D. The AUC for incident T2D ranged between 0.72 (Kraege 16) and 0.81 (SDA, FINDRISC2 and Balkau). Sensitivity ranged between 3.2% (Balkau) and 67.7% (FINDRISC1) and specificity between 80.9% (FINDRISC1) and 98.3% (Balkau). Positive predictive values of all scores were below 20%, while negative predictive values were above 98%. CONCLUSION Our study shows that the performance of conventional diabetes risk scores in PWH is promising, especially for Balkau and FINDRISC2, which showed good discriminatory power. These scores may help identify patients at a low risk of T2D in whom careful assessment of modifiable T2D risk factors can be spared.

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CONCISE COMMUNICATION

Comparison of five different risk scores to predict incident type 2 diabetes in the Swiss HIV cohort study

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Objective: People with HIV (PWH) have a higher risk of type 2 diabetes (T2D) than HIV-negative individuals. In the general population, diabetes risk scores are used to identify persons at risk of developing T2D, but little is known regarding their performance in PWH.

Design: Assessment of the capacity of five diabetes risk scores to predict T2D in PWH.

Methods: A prospective study including all Swiss HIV cohort study (SHCS) participants followed between 2009 and 2019. Five diabetes risk scores were assessed: FINDRISC versions 1 and 2, Balkau, Swiss Diabetes Association (SDA), and Kraege.

Results: Three thousand eight hundred fifty-three T2D-free PWH (78.5% men, 39.9 ± 11.3 years) were included. After a median follow-up of 4.8 years (interquartile range 2.2–7.8), 62 participants (1.6%) developed T2D, corresponding to an incidence rate of 3.18 per 1000 person-years (95% confidence interval = 2.47–4.08). Participants who developed T2D were older (48.7 ± 12.4 vs. 39.8 ± 11.2 years), more likely to be obese (22.6% vs. 7.4%), abdominally obese (9.7% vs. 1.5%), and to have a family history of diabetes (32.3% vs. 19.1%) than those without T2D. The AUC for incident T2D ranged between 0.72 (Kraege 16) and 0.81 (SDA, FINDRISC2 and Balkau). Sensitivity ranged between 3.2% (Balkau) and 67.7% (FINDRISC1) and specificity between 80.9% (FINDRISC1) and 98.3% (Balkau). Positive predictive values of all scores were below 20%, while negative predictive values were above 98%.

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Conclusion: Our study shows that the performance of conventional diabetes risk scores in PWH is promising, especially for Balkau and FINDRISC2, which showed good discriminatory power. These scores may help identify patients at a low risk of T2D in whom careful assessment of modifiable T2D risk factors can be spared.

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Keywords: diabetes mellitus, HIV, prospective study, risk score, validation

Introduction

Over the last decade, the number of people with HIV (PWH) on antiretroviral therapy (ART) has increased remarkably worldwide. In December 2020, about 27.5 million PWH in developing countries were taking ART, compared with only 7.8 million in 2010 [1]. Consequently, overall mortality due to HIV has decreased and PWH suffer increasingly from the additional burden of noncommunicable diseases [2]. Indeed, PWH are two to four times more likely to develop diabetes mellitus type 2 (T2D) [3] compared with the general population [4].

Incidence of diabetes in PWH varies geographically. For instance, in 2008, incidence of T2D was estimated at 5.72 per 1000 person-year follow-up [5] (PYFU) in the Data collection on Adverse events of Anti-HIV Drugs (D:A:D cohort), which encompasses several worldwide HIV cohorts. In Switzerland, estimated incidence of diabetes in PWH was 4.4 per 1000 PYFU [6] in 2007, whereas in a recent study in men with treated HIV in Australia, incident T2D was estimated at 10.2 per 1000 PYFU [7]. In the Netherlands, T2D incidence is foreseen to reach 17% of PWH by 2030 [8] and to become the second most frequent noncommunicable disease after cardiovascular illnesses.

A review conducted in 2011 [9] identified as many as 145 T2D risk models or scores. However, little is known about T2D score performance in PWH. Recently, two T2D predicting scores, the Finnish Diabetes Risk Score (FINDRISC) [10] and one adapted from the American Diabetes Association (ADA) [11], were specifically evaluated among women living in the USA, with either confirmed HIV or at risk of being infected [12]. They showed suboptimal performance for predicting T2D risk over 3 years (AUROC=0.68 and 0.64, respectively) [12] highlighting the fact that HIV-specific risk factors for diabetes may need to be considered in diabetes risk models [13].

Our aim was to assess the capacity of five diabetes risk scores (the Kraege score [14], the FINDRISC [10] versions 1 and 2, the Swiss Diabetes Association (SDA) score [15], and the Balkau clinical risk score [16]) in predicting incident T2D in PWH.

Materials and methods

Participants

The Swiss HIV Cohort Study (SHCS) [17] (www.shcs.ch) is an ongoing, prospective, clinic-based study, established in 1988. It continuously enrolls HIV-1 and HIV-2 infected individuals aged at least 18 years from five university hospital outpatient clinics, two large district hospitals, affiliated regional hospitals and private practices. Prior to SHCS enrolment, written informed consent is required from all patients. Participants are followed every 6 months. For this analysis, we included all participants with visits from January 1, 2009, and December 31, 2019, as the SHCS collects physical activity since 2009.

Diabetes risk scores

The FINDRISC [10] diabetes score was developed for the Finnish population, and it combines two versions: one originally including seven variables (FINDRISC1) and a second also including history of familial diabetes (FINDRISC2). For the purpose of the study, we included both versions. The Swiss Diabetes Association score (SDA) [15] is derived from the FINDRISC2 with a scoring system adapted for the Swiss population. As vegetables and fruit consumption are not systematically collected in the SHCS, we adapted the FINDRISC1, FINDRISC2, and SDA scores as previously indicated [18], and the thresholds were reduced by one unit. The Balkau [16] score was derived from the French population. The Kraege score [14] was developed in a Swiss general population cohort; two different thresholds were used to define high risk, 13 (Kraege 13) and 16 (Kraege 16). Information regarding scores and thresholds is summarized in Table 1.

Incident diabetes mellitus

Incident T2D was defined as two consecutive plasma glucose levels suggestive of diabetes (either a fasting glucose level >7 mmol/l or a random glucose level >11.1 mmol/l) and/or the presence of an oral antidiabetic or insulin treatment. The date of the second elevated plasma glucose level corresponded to the date of the incident diabetes diagnosis.

Inclusion and exclusion criteria

We included all SHCS participants followed between January 1, 2009, and December 31, 2019. Exclusion

Table 1. Design and characteristics of the diabetes risk scores used in this study.

	Kraege [11]	SDA [12]	Balkau [13]	FINDRISC1 [7]	FINDRISC2 [7]
Country	Switzerland	Switzerland	France	Finland	Finland
Population size	5277	NA	3817	4435	4435
Follow-up (years)	10.9	NA	9	5	5
Age	X	X		X	X
Sex	X		X		
BMI, weight		X		X	X
Waist	X	X[a]	X	X[a]	X[a]
Hypertension	HM or MH	HM	HM or MH	HM	HM
Family history of diabetes	X	X	X		X
History of hyperglycemia		X		X	X
Physical activity	X	X		X	X
Smoking			X		
Number of variables	6	7	5	6	7
Threshold	13 or 16	15	5	8	12

HM, hypertension medication; MH, measured hypertension; X = variable used in the score; SDA, Swiss Diabetes Association risk score. As vegetable and fruit consumption were not collected in the SCHS, they were not included in the computation of the FINDRISC1, FINDRISC2 and SDAS scores; hence, the corresponding thresholds to define high risk of diabetes were reduced by one unit as reported in the study by Schmid *et al.* [15].
[a]Sex-dependent waist value.

criteria were presence of type 1 diabetes or T2D at baseline, missing data for one or more variables used in the scores, or absence of outcome data. Familial history of diabetes was the predominant missing variable (6% of the total sample).

Statistical analysis

Statistical analyses were performed using Stata version 16.0 for windows (Stata Corp, College Station, Texas, USA). Descriptive results were expressed as number of participants (percentage) or as average ± standard deviation. Between-group comparisons were performed using chi-square or Fisher's exact test for qualitative variables, and Student's *t*-test, analysis of variance, or Kruskal–Wallis test for quantitative variables. The incidence of T2D was assessed as number of cases (percentage), and as number of cases per 1000 person-years of follow-up (PYFU) with corresponding 95% confidence intervals (95% CIs). The diagnostic capacity of each T2D prediction score was assessed by computing the area under the receiver operating curve (AUC), sensitivity, specificity, positive and negative predictive values, and their corresponding 95% CIs. Multivariable analysis was performed using logistic regression and the results were expressed as odds ratio (OR) and 95% CI.

Results

Characteristics of participants

Of the 5170 eligible SHCS participants, 3853 (74.5%) were included after removing diabetic participants and those with missing data. Of the 25.5% excluded, 18.8% had missing data, 3.5% no follow-up, and 3.2% diabetes at baseline. Excluded participants were more often more than 55 years old (14% vs. 10.2%), of black ethnicity (23.1% vs. 16.5%), obese (10% vs. 7.6%), and had higher waist circumference (87.7% vs. 85.8 cm) than included participants.

Incidence of diabetes and factors associated with incidence of diabetes

Over a median follow-up time of 4.8 years (interquartile range 2.2–7.8), 62 participants (1.6%) developed T2D, corresponding to an incidence rate of 3.18 per 1000 PYFU (95% CI = 2.47–4.08).

On bivariate analysis, participants who developed T2D were significantly ($P < 0.05$) older (>55 years old: 33.9% vs. 9.8%), of black ethnicity (27.4% vs. 16.4%), more frequently reported a familial history of diabetes (32.3% vs. 19.1%), had higher obesity markers (BMI $\geq$30 kg/m^2: 22.6% vs. 7.4%), had hypertension (72.6% vs. 46.1%), and longer ART duration (115 vs. 95 months) than participants who remained free of T2D (Supplemental Table 1). Multivariable analysis showed that age more than 55 years (OR = 6.44, 95% CI = 2.96–14.0), family history of diabetes (OR = 2.14, 95% CI = 1.23–3.71), ART duration (per 1-year increase) (OR = 1.04, 95% CI = 1.00–1.09), and obesity (OR = 2.93, 95% CI = 1.37–6.29) were significantly associated with incident T2D (Supplemental Table 2).

Performance of the diabetic risk scores

The AUCs (95% CI) and diagnostic capacity for incident T2D of the different diabetes risk scores are summarized in Table 2. The AUC for incident T2D ranged between 0.72 (Kraege 16) and 0.81 (Balkau, FINDRISC2, SDA). Sensitivity ranged between 3.2% (Balkau) and 67.7% (FINDRISC1) and specificity between 80.9% (FINDRISC1) and 98.3% (Balkau). Positive predictive values of all scores were below 20%, while negative predictive values were above 98%.

Table 2. Diagnostic capacity of the different diabetes risk equations, Swiss HIV cohort study, 2009–2019.

Equation	AUC	Sensitivity	Specificity	PPV	NPV	Positive LR
SDA	0.812 (0.761–0.864)	19.4 (10.4–31.4)	97.2 (96.7–97.7)	10.3 (5.4–17.2)	98.7 (98.2–99.0)	7.0 (4.1–12.0)
FINDRISC1	0.809 (0.752–0.865)	67.7 (54.7–79.1)	80.9 (79.6–82.1)	5.5 (4.0–7.3)	99.4 (99.0–99.6)	3.6 (3.0–4.3)
FINDRISC2	0.812 (0.761–0.864)	45.2 (32.5–58.3)	90.2 (89.3–91.2)	7.0 (4.7–10.0)	99.0 (98.6–99.3)	4.6 (3.5–6.2)
Kraege 13	0.783 (0.729–0.837)	59.7 (46.4–71.9)	82.3 (81.0–83.5)	5.2 (3.7–7.1)	99.2 (98.8–99.5)	3.4 (2.7–4.2)
Kraege 16	0.719 (0.656–0.782)	48.4 (35.5–61.4)	87.2 (86.1–88.3)	5.8 (4.0–8.2)	99.0 (98.6–99.3)	3.8 (2.9–5.0)
Balkau	0.812 (0.761–0.864)	3.2 (0.4–11.2)	98.3 (97.9–98.7)	3.1 (0.4–10.7)	98.4 (98.0–98.8)	1.9 (0.5–7.8)

AUC, area under the receiver-operating curve; LR, likelihood ratio. Results are expressed as percentage and (95% confidence interval), except for AU, NPV, negative predictive value; PPV, positive predictive value; SDA, Swiss Diabetes Association.

Discussion

In our analysis of 3853 PWH, followed for an average of 5 years, the incidence rate of T2D was 3.18 per 1000 PYFU (95% CI = 2.47−4.08), lower than that reported in the same cohort in the early 2000 s [6]. This difference is probably attributable to the high number of participants at a high risk of T2D, that is, older and obese, excluded in our analysis.

Included participants were mostly white young men, with a mean age of 40 years. These characteristics are common in HIV populations of high-income countries as found in the D:A:D (Data Collection on Adverse events of Anti-HIV Drugs) study [19] or in the ATHENA cohort in the Netherlands [20]. Participants who developed T2D were significantly older, more often of black ethnicity, and more often reported a familial history of diabetes. They also had higher obesity markers, more often had hypertension, and a longer ART duration than participants who remained free of T2D. Therefore, as in the general population, modifiable T2D risk factors should be managed by implementing preventive measures at an early stage, even more so among PWH. Further, each additional year spent on ART significantly increased T2D risk, consistent with the acknowledged principle that HIV medications play an important role in T2D incidence [6,21]. We deliberately chose to avoid studying the relation between each therapeutic molecule and diabetes, as it has already been studied in the SHCS [6] and in larger cohorts [3,22].

The five clinical scores derived from general populations performed well in predicting T2D in the SHCS, with an AUC more than 0.7 and a negative predictive value above 98% (Table 2). Three scores (SDA, Balkau, and FINDRISC2) had an AUC more than 0.8 but a low sensitivity. As SDA has the same AUC as FINDRISC2, from which it is derived, we decided to remove it from our conclusion.

Our results are superior to those published by Galaviz *et al.* [12], who compared the ability of the ADA risk calculator and FINDRISC2 to predict 3-year occurrence of T2D in women with or at risk of HIV infection. In this relatively small sample (1111 participants) of mostly (61%) African−American women living with HIV, the AUC for FINDRISC2 was 0.68 (95% CI = 0.62−0.75) compared with 0.81 (95% CI = 0.76−0.86) in our study. More recently, the same author found that FINDRISC1 performance was suboptimal in PLWH in two U.S, cohorts [23].

Indeed, despite a low sensitivity, all five clinical diabetes risk scores studied had negative predictive values more than 98%. They could be used to rule out people at a low risk of developing diabetes, therefore allowing physicians to reduce time spent on implementing T2D preventive measures in these patients. An external validation in other PWH cohorts should be undertaken before broadly implementing one of these tools.

The strength of this investigation is that, to our knowledge and to this date, it is the first published study to compare five diabetes risk scores in a mixed sex population living with HIV, with a relatively long follow-up, along with the use of a confirmed value of hyperglycemia to define T2D.

The main limitation is the high percentage of excluded participants (25.5%), mostly due to the missing information of familial history of diabetes. This may have underestimated T2D incidence, as excluded participants were more frequently of black race and obese, two factors associated with a higher incidence of T2D [22].

In conclusion, our study shows that the performance of conventional diabetes risk scores in PWH is promising, especially for Balkau and FINDRISC2, which showed good discriminatory power. These scores may help identify patients at a low risk of T2D in whom careful assessment of modifiable T2D risk factors can be spared.

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F.B., V.K., M.C., M.M., and P.M.V. designed the study. F. B. wrote the article; V.K. was the instigator of the study and revised the article for important intellectual content. J.D. contributed to SHCS data extraction and cleaning. P. M.V. performed the statistical analyses and wrote part of

the article; M.M. revised the article for important intellectual content. P.M.V. had full access to the data and is the guarantor of the study. M.C. initiated collaboration with the SHCS and revised the article for important intellectual content. All authors reviewed and agreed on the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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