One-Hour Plasma Glucose Compared With Two-Hour Plasma Glucose in Relation to Diabetic Retinopathy in American Indians

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

We compared the ability of 1- and 2-h plasma glucose concentrations (1h-PG and 2h-PG, respectively), derived from a 75-g oral glucose tolerance test (OGTT), to predict retinopathy. 1h-PG and 2h-PG concentrations, measured in a longitudinal study of an American Indian community in the southwestern U.S., a population at high risk for type 2 diabetes, were analyzed to assess the usefulness of the 1h-PG to identify risk of diabetic retinopathy (DR).

RESEARCH DESIGN AND METHODS

Cross-sectional (*n* = 2,895) and longitudinal (*n* = 1,703) cohorts were assessed for the prevalence and incidence of DR, respectively, in relation to deciles of 1h-PG and 2h-PG concentrations. Areas under the receiver operating characteristic (ROC) curves for 1h-PG and 2h-PG were compared with regard to predicting DR, as assessed by direct ophthalmoscopy.

RESULTS

Prevalence and incidence of DR, based on direct ophthalmoscopy, changed in a similar manner across the distributions of 1h-PG and 2h-PG concentrations. ROC analysis showed that 1h-PG and 2h-PG were of similar value in identifying prevalent and incident DR using direct ophthalmoscopy. 1h-PG cut points of 230 and 173 mg/dL were comparable to 2h-PG cut points of 200 mg/dL (type 2 diabetes) and 140 mg/dL (impaired glucose tolerance), respectively.

CONCLUSIONS

1h-PG is a useful predictor of retinopathy risk, has a predictive value similar to that of 2h-PG, and may be considered as an alternative glucose time point during an OGTT.

Hyperglycemia assessed by the oral glucose tolerance test (OGTT) is a well-accepted method for identifying individuals with type 2 diabetes and those at risk of developing type 2 diabetes (1). Current World Health Organization (WHO) (2) or American Diabetes Association (ADA) criteria (1) do not use 1-h plasma glucose (1h-PG) to identify those at elevated risk for a diagnosis of type 2 diabetes. However, the potential contribution of 1h-PG was previously appreciated, as shown by inclusion of 1h-PG in the 1979 National Diabetes Data Group criteria for identifying impaired glucose tolerance (IGT) and diabetes (3). Although some investigators preferred using 1h-PG

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over 2-h plasma glucose (2h-PG) for convenience and because of the high correlation between the two values (4), WHO criteria deemed it unnecessary in 1980, as did later ADA criteria that considered 2h-PG as the only postchallenge time point required (5,6). Though some evidence has indicated better reproducibility of the 2h-PG than the 1h-PG (4), the recommendation by WHO (5) was not based on evidence that the 1h-PG was inferior in predicting a relevant clinical end point such as diabetic retinopathy (DR), which may be a better judge of its value.

Four separate groups have previously reported that 1h-PG is a comparable or even better predictor of type 2 diabetes than 2h-PG (7–10), perhaps because it is more closely associated with insulin secretion (7,8,10), indicating that 1h-PG might also be a better predictor of DR than 2h-PG. In our report from a longitudinal study of American Indians living in the southwestern U.S., 1h-PG was more closely associated with insulin secretion, less closely associated with insulin action, but similarly able to predict future type 2 diabetes when compared with 2h-PG in individuals without type 2 diabetes (11). In a recently published Swedish longitudinal population study, 1h-PG was reported to be a better predictor of diabetes and a better predictor of complications of diabetes, including retinopathy, than 2h-PG (12). Many previous studies, including studies involving an American Indian community in the southwestern U.S., examined glycemic cutoffs for diabetes using fasting plasma glucose (FPG), 2h-PG, and hemoglobin A_{1c} (A1C) and their associations with DR (13–16). To our knowledge, the ability of 1h-PG to predict DR has only been recently evaluated, and not in this closely followed American Indian cohort.

We sought to investigate the hypothesis that the ability of 1h-PG to predict DR is superior to that of 2h-PG. Accordingly, in an American Indian community in the southwestern U.S., the associations between postload glucose concentrations (1h-PG and 2h-PG) and DR were evaluated in both cross-sectional and prospective manners.

RESEARCH DESIGN AND METHODS

Study Population

Briefly, participants were enrolled in a longitudinal epidemiological study that began in 1965 among an American Indian community in Arizona (17). Written informed consent was obtained from all participants, and the study was approved by the scientific director of the National Institute of Arthritis and Metabolic Diseases and, beginning in 1976, by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases. Individuals aged 5 years and older were invited, regardless of health, for standardized outpatient research examinations approximately every 2 years. These exams included a medical history, a physical examination, an OGTT, and an assessment of DR by direct ophthalmoscopy (4,14,18). BMI (kilograms per meter squared) was calculated based on measured height and weight with the volunteer wearing light clothing and no shoes.

Participants underwent a 75-g OGTT with venous plasma glucose measurements. Participants with visits before 1980 had both 1h-PG and 2h-PG (4); after that year 1h-PG was not collected. Plasma glucose concentrations were measured by the modified Hoffman method (Technicon Instruments Corporation, Tarrytown, NY), the hexokinase method (Ciba Corning Express 550 analyzer; Ciba Corning, Oberlin, OH), or the glucose oxidase method (Vital Diagnostics Envoy). Type 2 diabetes was diagnosed and classified according to the 2003 ADA criteria (19).

This study included only men and nonpregnant women (age $\geq$18 years) with baseline 1h-PG and 2h-PG measurements (milligrams per deciliter). Participants taking oral or injectable hypoglycemic medications (i.e., insulin) were excluded from the main analysis but included in the sensitivity analysis. The risk for DR in relation to 1h-PG and 2h-PG was evaluated in cross-sectional and longitudinal analyses. In cross-sectional analysis, the prevalence of retinopathy was determined from participants' last outpatient exam with 1h-PG and 2h-PG measurements and at which DR was also assessed by dilated pupillary exam via direct ophthalmoscopy. For the longitudinal analysis, the first visit when both 1h-PG and 2h-PG were available and retinopathy was absent, as evaluated by direct ophthalmoscopy, was chosen as the baseline visit.

Direct Ophthalmoscopy

Direct fundoscopic examinations were preformed after pupil dilation by physicians who were unaware of each individual's diabetes status. The physicians were not ophthalmologists by training, but all underwent an initial training period. On the basis of the worse eye at each exam, DR was classified into three groups: *1*) normal, *2*) nonsevere, and *3*) severe. The normal group included eyes with hard exudates only, as this was previously shown to be a common finding in American Indians without type 2 diabetes (18). The nonsevere group involved at least a single microaneurysm in one eye in the absence of proliferative retinopathy. Those with proliferative changes or scars from prior laser therapy in at least one eye were considered to have severe DR.

Retinal Photography

Beginning in 1982, retinal photographs of two standard fields for both eyes were taken at the same visit using a Canon CR4–45NM fundus camera, as previously described (20). Therefore, we do not have retinal photography data from exams where 1h-PG was measured, but we have retinal photographs available for subsequent exams. As an additional objective assessment of DR, another analysis compared the association of 1h-PG and 2h-PG at the baseline visit (before 1980) with DR in a subgroup of participants who were later evaluated by fundus photography at a second visit (between 1982 and 2007). These photographs were graded in a standardized manner, without knowledge of clinical details, using the modified Airlie House classification system (20,21). DR was classified based on the worse eye. Similar to the direct ophthalmoscopy exams, "normal" eyes included isolated hard exudates but no other sign of retinopathy or retinal hemorrhage without microaneurysms, nonsevere DR included the presence of microaneurysms (level 20 or higher but below level 51), and severe DR was based on proliferative changes, hemorrhages, and/or intraretinal microvascular abnormalities present (level $\geq$51) (22).

Statistical Analyses

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC) and SPSS (version 23; IBM, Armonk, NY). In cross-sectional analysis, the prevalence of any DR on direct ophthalmoscopy was examined by 10ths of the distributions of 1h-PG and 2h-PG. In longitudinal analysis of participants without DR at baseline, participants were followed until DR developed, as observed on direct ophthalmoscopy. Cumulative incidence of DR on direct

ophthalmoscopy was estimated using the Kaplan-Meier method and plotted by deciles of 1h-PG and 2h-PG. On the basis of predicted cumulative incidence of DR at 15 years (any DR on direct ophthalmoscopy) and 25 years (severe DR on direct ophthalmoscopy), receiver operating characteristic (ROC) curves were derived for 1h-PG and 2h-PG by modeling the survival probability with PROC PHREG in SAS software, using successive detection thresholds for 1h-PG and 2h-PG, in increments of 1 mg/dL, as previously described (23). Cutoffs to classify IGT and type 2 diabetes using 1h-PG values were identified based on the point on the ROC curve closest to the well-established 2h-PG cutoffs of 140 and 200 mg/dL. Kappa statistics (24) were used to assess agreement between 1h-PG and 2h-PG when categorizing normal glucose tolerance, IGT, and type 2 diabetes and to assess agreement between direct ophthalmoscopy and retinal photography for classifying DR.

Prediction models for DR, accounting for the time to event, enabled calculation of C-statistics to compare predictive abilities of 1h-PG, 2h-PG, and both 1h-PG and 2h-PG combined (25). C-statistics were calculated by the method described by Pencina and D'Agostino (26) and compared with the use of the method developed by DeLong et al. (27). For these models, nonnormally distributed data, such as 1h-PG and 2h-PG, underwent ranked-based inverse normalization via Blom calculation (28). As an additional analysis, these analyses were repeated with severe DR based on direct ophthalmoscopy.

For an additional supportive analysis, 1h-PG and 2h-PG ROC curves were developed using PROC LOGISTIC for DR diagnosed by retinal photographs taken after the baseline longitudinal visit. Those with DR level ≥20 on retinal photography—a level that includes both nonsevere and severe DR—were compared with those with DR level <20 (22).

RESULTS

Baseline characteristics of participants included in the cross-sectional and longitudinal analyses are shown in Table 1. The cross-sectional analysis (n = 2,895) included 87 total cases of DR, of which 15 were severe. The prevalence of DR was examined by deciles of the distribution of 1h-PG and 2h-PG (Fig. 1*A* and Supplementary Table 1). The frequencies of DR were similar for each decile of 1h-PG and 2h-PG. The ROC curves for DR prevalence were also similar for 1h-PG and 2h-PG (Fig. 1*B*).

Longitudinal analysis (n = 1,703) included 498 incident cases of DR with a median follow-up of 22.7 years. When the 15-year cumulative incidence of DR was assessed by glucose decile, the curves for 1h-PG and 2h-PG were similar, showing a relative absence of retinopathy below the ninth decile (Fig. 1*C*). When the same data used for the graphs in Fig. 1*A* (prevalence) and Fig. 1*C* (15-year cumulative incidence) were alternatively plotted on a linear scale using the midpoint glucose concentration within each decile of 1h-PG and 2h-PG (Supplementary Fig. 4*A* and *B*, respectively), the prevalence and cumulative incidence appeared to increase more gradually, suggesting that the risk for retinopathy may gradually increase. The current 2h-PG threshold for type 2 diabetes (i.e., 200 mg/dL) falls within the ninth decile. The ninth decile range for 1h-PG was 186–261 mg/dL, indicating that an appropriate equivalent threshold for type 2 diabetes falls somewhere in this range. The 1h-PG concentration of 230 mg/dL has sensitivity and specificity for retinopathy almost identical to those of the 2h-PG concentration of 200 mg/dL (Fig. 1*D*), indicating that 1h-PG ≥230 mg/dL may be an equivalent threshold for type 2 diabetes diagnosis. Likewise, 1h-PG of 173 mg/dL has a sensitivity and specificity similar to those of the 2h-PG concentration of 140 mg/dL in analyses of both cumulative incidence (Fig. 1*D*) and prevalence (Fig. 1*B*), indicating that 173 mg/dL for 1h-PG may be equivalent for identifying those at intermediate risk for type 2 diabetes. Using this classification scheme for 1h-PG, three groups can be constructed that classify low, intermediate, and high risk for DR and provide similar prognostic information as the current 2h-PG classification (Table 2). The results did not change in cross-sectional and prospective analyses that included participants taking hypoglycemic medications (Supplementary Fig. 1). The results also did not change in additional analysis restricted to severe DR but excluding participants taking hypoglycemic medications at baseline (Supplementary Fig. 2; only prospective analysis because insufficient data were available for cross-sectional analysis). There was substantial agreement between 1h-PG and 2h-PG when categorizing into normal glucose

Table 1—Participant characteristics at baseline examination

	Cross-sectional cohort (n = 2,895)		Longitudinal cohort (n = 1,703)	
Variables	Values	Participants (n)	Values	Participants (n)
Age (years)	31.7 (23.7, 46.3)	2,895	26.3 (20.1, 37.4)	1,703
Male sex	1,331 (46)	2,895	648 (38)	1,703
American Indian	2,895 (100)	2,895	1,703 (100)	1,703
BMI (kg/m^2)	31.1 ± 6.8	2,895	30.7 ± 6.3	1,703
Smoking	946 (34)	2,794	557 (38)	1,471
Blood pressure (mmHg)				
Systolic	127 ± 21	2,889	126 ± 18	1,701
Diastolic	77 ± 13	2,888	75 ± 12	1,700
Hypertension	932 (32)	2,895	404 (24)	1,703
Total cholesterol (mg/dL)	174 ± 37	2,881	173 ± 38	1,687
Serum creatinine (mg/dL)	0.76 ± 0.44	2,880	0.69 ± 0.18	1,687
FPG (mg/dL)	97 (89, 115)	1,509	92 (86, 102)	436
1h-PG (mg/dL)	152 (114, 220)	2,895	127 (102, 169)	1,703
2h-PG (mg/dL)	123 (99, 185)	2,895	112 (94, 139)	1,703
Type 2 diabetes	663 (23)	2,895	204 (12)	1,703
Diagnosis of diabetes at baseline examination	227 (8)	2,895	108 (6)¥	1,703
Any retinopathy	87 (3)	2,895	498 (29)	1,703
Follow-up (years)	—	—	22.7 (16.3, 28.8)	1,703
Severe retinopathy	15 (0.5)	2,895	148 (9)	1,703
Follow-up (years)	—	—	24.6 (17.6, 29.9)	1,703

Data are mean ± SD, median (interquartile range [25th, 75th percentiles]), or n (%) unless otherwise indicated. ¥Retinopathy at a follow-up (or censored) exam.

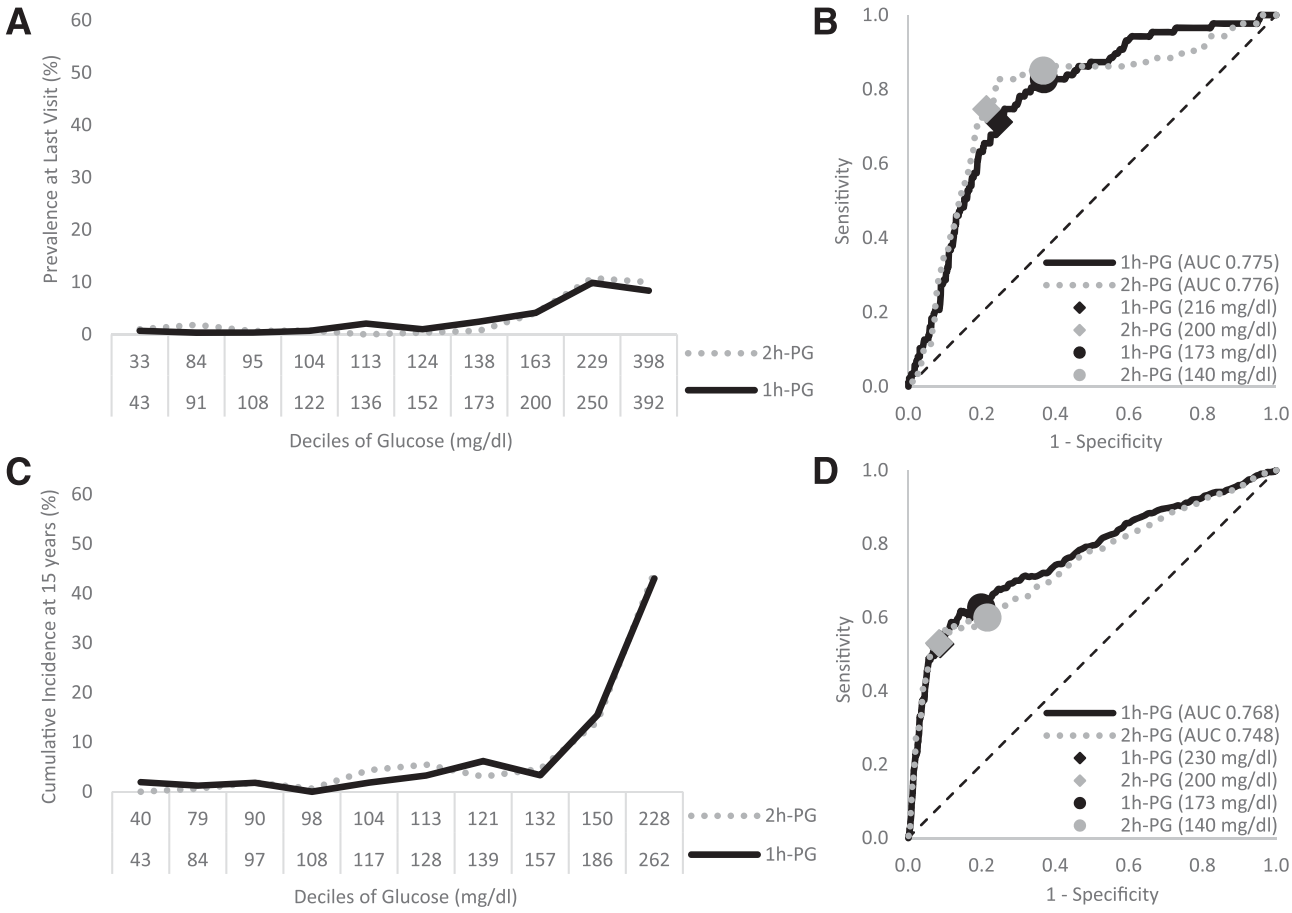

Figure 1—Prevalence (*A* and *B*) and predicted incidence at 15 years (*C* and *D*) of any retinopathy based on direct ophthalmoscopy. Retinopathy in relation to glucose deciles (*A* and *C*) and ROC curves (*B* and *D*) of 1h-PG and 2h-PG concentrations. The glucose values shown in *A* and *C* are the lower bounds for each decile.

tolerance, IGT, and type 2 diabetes when considering the cross-sectional (weighted κ 0.81; 95% CI 0.79–0.82) and longitudinal (weighted κ 0.77; 95% CI 0.74–0.80) groups (Supplementary Table 2).

Supplementary Table 3 provides the C-statistics for risk prediction models that involved 1h-PG and 2h-PG and accounted for the time to event. The model with 1h-PG (C-statistic 0.778; 95% CI 0.755–0.801) predicted risk statistically significantly better (P = 0.04) than the model with 2h-PG (C-statistic 0.759; 95% CI 0.735–0.784), though the difference was small and likely not clinically meaningful. Additional sensitivity analysis restricting events to severe DR showed that 1h-PG did not differ significantly from 2h-PG (Supplementary Table 3).

Table 2—Prevalence and cumulative incidence of DR by fundoscopy for risk groups based on 1h-PG and 2h-PG cutoffs for normal glucose tolerance, IGT, and type 2 diabetes

Retinopathy	Normal glucose tolerance (%)	IGT (%)*	Type 2 diabetes (%)†
Prevalence, any retinopathy (n = 2,895)			
1h-PG	0.9	3.1	8.6
2h-PG	0.7	2.0	9.8
15-year c.i., any retinopathy (n = 1,703)			
1h-PG	2.4	9.4	40.2
2h-PG	2.5	9.1	40.0
25-year c.i., severe retinopathy (n = 1,703)			
1h-PG	1.9	7.0	34.7
2h-PG	2.1	5.6	34.6

c.i., cumulative incidence. *IGT cutoffs for 1h-PG were ≥173 and <230 mg/dL, and for 2h-PG were ≥140 and <200 mg/dL. †Type 2 diabetes cutoff for 1h-PG was ≥230 mg/dL and for 2h-PG was ≥200 mg/dL.

In further supportive analyses, models were assessed involving DR diagnosed by retinal photography. Of the initial 2,895 participants, 1,361 (47%) had a later exam with a retinal photograph, and 360 of the 1,361 (26%) were diagnosed with any DR based on photography. With any DR diagnosed by retinal photography as the outcome measure, areas under the curve (AUCs) for 1h-PG (AUC 0.711; 95% CI 0.678–0.743) and 2h-PG (AUC 0.715; 95% CI 0.682–0.747) were similar (P = 0.72) (Supplementary Fig. 3*A*). Adjusting for follow-up time (median 23.0 years; interquartile range 18.0–27.4 years), the 1h-PG (AUC 0.741; 95% CI 0.717–0.764) and 2h-PG (AUC 0.725; 95% CI 0.700–0.748) were also similar (P = 0.08) (Supplementary Fig. 3*B*). Of the 1,361 participants with retinal photographs,

1,322 also had direct ophthalmoscopy performed during the same exam. There was moderate to substantial agreement between the two methods for evaluating any DR (unweighted κ 0.62; 95% CI 0.57–0.67) (Supplementary Table 4).

CONCLUSIONS

This study examined the prevalence and incidence of DR in relation to measurements of 1h-PG and 2h-PG concentrations during the OGTT. Complementary cross-sectional and longitudinal analyses indicated that 1h-PG and 2h-PG provide similar information about risk for DR. This study also identified that cutoffs for 1h-PG (≥230 mg/dL indicates type 2 diabetes; ≥173 and <230 mg/dL indicate IGT) provide information about DR risk similar to that provided by current 2h-PG criteria.

The relation between different glycemic measures (e.g., FPG, 2h-PG, and A1C) and retinopathy forms the basis for current diagnostic criteria for type 2 diabetes (2,29,30). The 2h-PG cutoff for type 2 diabetes (i.e., 2h-PG ≥200 mg/dL) was established to indicate a threshold above which subjects have a substantially elevated risk for type 2 diabetes–associated microvascular complications such as DR (30–32). The specific levels of A1C and FPG were adopted as diagnostic criteria for type 2 diabetes after 2h-PG, largely because they were shown to be equivalent to 2h-PG in predicting the development of DR (13). Although some groups previously favored 1h-PG for epidemiological studies (4), the routine clinical use of 1h-PG declined after the WHO recommendations in 1980 (5). Although at that time some evidence showed that 1h-PG was less reproducible than 2h-PG (4), investigators recognized that a superior arbiter between 1h-PG and 2h-PG should involve predictions of specific manifestations of type 2 diabetes, such as DR from longitudinal studies (4)—outcomes that had not been published to inform the 1980 WHO recommendations. Given the results of the current study, the choice of either 1h-PG or 2h-PG likely would have been satisfactory. Moreover, time and expense could be saved by choosing 1h-PG over 2h-PG.

Consistent with prior results for FPG and 2h-PG from this American Indian cohort (31) and other populations (30,32), 1h-PG also has an approximate threshold above which the prevalence and incidence of DR increase markedly, indicating that establishing a cutoff to define type 2 diabetes is appropriate. The prevalence and 15-year cumulative incidence of any DR below a 1h-PG cutoff of ~230 mg/dL were low (<5%). Although direct ophthalmoscopy has been shown to have high specificity for DR, use of retinal photographs could have resulted in greater prevalence and incidence in these low 1h-PG or 2h-PG deciles, because direct ophthalmoscopy is less sensitive than retinal photography (22,33). As previously reported, these "missed" cases of retinopathy were most often microaneurysms without other lesions (34). Although retinal photographs may identify isolated lesions such as microaneurysms or small retinal hemorrhages that are more difficult to identify through the use of direct ophthalmoscopy, such lesions have not been clearly shown to predict future type 2 diabetes and may be nonspecific markers of hypertension as opposed to DR (35). In addition, the moderate to substantial agreement between direct ophthalmoscopy and retinal photography in the subgroup of participants with these measures available and in the cohort at large (22) suggests that it is unlikely that the results would have changed with regard to the finding that 1h-PG and 2h-PG are similar predictors of DR; cases diagnosed by direct ophthalmoscopy likely represent true DR.

We could not compare the predictive ability of 1h-PG with that of FPG or A1C because these tests were not generally performed during the research exams where 1h-PG was also measured. On the other hand, if the basis for FPG and A1C to classify type 2 diabetes is largely from equivalence with 2h-PG in the prediction of DR, it is unlikely that 1h-PG would be inferior to those glycemic parameters. Nevertheless, a longitudinal comparison of all four glucose indices is needed.

We studied a specific population of American Indians at high risk for type 2 diabetes, so it is unknown how results would differ from other racial or ethnic groups. However, the association between 1h-PG and DR is unlikely to change because the underlying pathophysiology of type 2 diabetes, and the factors associated with and thresholds for predicting DR, have been shown to be shared by both American Indian and other populations (22,36,37). Similar studies in other populations would be needed to determine whether these relationships are universal.

Strengths of this study include the long follow-up time and the large number of individuals developing DR, including severe cases. In addition, detailed clinical data permitted the exclusion of individuals taking hypoglycemic medications, an exclusion criterion not necessarily used in our own earlier and other studies (32,38). Individuals taking hypoglycemic medications may have lower 1h-PG or 2h-PG concentrations, and prevalent or incident cases of DR could potentially be misattributed to low 1h-PG or low 2h-PG concentrations if diabetes medications were not excluded.

In conclusion, the ability of 1h-PG and 2h-PG to predict the prevalence and incidence of retinopathy was similar. Given that 1h-PG can shorten the OGTT and presents logistic and economic advantages over 2h-PG, 1h-PG should be considered as an alternative postload glucose time point to identify those at elevated risk for DR.

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