

Fasting Glucose and Retinopathy as a Diabetes Diagnosis

Results from three diverse population-based studies found no uniform fasting plasma glucose glycemic threshold for retinopathy.

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It is estimated that diabetes will affect 380 million people by 2025.¹ Both the World Health Organization (WHO)² and the American Diabetes Association (ADA)³ use a fasting plasma glucose (FPG) level of ≥ 126 mg/dL (7.0 mmol/L) to define diabetes. This criterion is based on an underlying assumption that there exists a clear glycemic threshold that separates individuals at high and low risk of diabetic complications.⁴ There is, however, increasing evidence that the relationship of increasing glucose levels and the risk of macrovascular complications like cardiovascular disease (CVD) is graded and continuous, with no suggestion of a threshold.⁵⁻¹⁰ Therefore, the argument for a glycemic threshold is largely built on the relationship of glucose and risk of retinopathy, the most specific microvascular complication of diabetes.

Approximately 2 decades ago, three pivotal epidemiologic studies among Pima Indians,¹¹ Egyptians,¹² and the NHANES (National Health and Nutrition Examination Survey) III population¹³ showed that retinopathy signs typical of diabetes (eg, microaneurysms, retinal hemorrhages) were rare below an FPG threshold located around 126 mg/dL, but their prevalence increased dramatically above it.¹³ A key observation from these studies was that the FPG cutoff of 126 mg/dL had high sensitivity and specificity for discriminating prevalent retinopathy, and hence this cutoff was used by the WHO and the ADA to diagnose diabetes.^{13,14}

These three studies, however, had a major limitation—a problematic and incomplete ascertainment of retinopathy. Retinopathy was assessed from a direct clinical ophthalmoscopic examination in one study¹¹ and from a single retinal photograph in the other two.^{12,13} These methods are less reliable, and because they capture only a small por-

tion of the retina they have been shown to underestimate retinopathy signs when compared with multiple-field retinal photographs, currently the gold standard in clinical trials.^{15,16} This limitation means that there is uncertainty regarding a clear glycemic threshold for retinopathy upon which the current diabetes diagnostic criteria are based. Early reports from the DPP (Diabetes Prevention Program) indicated a substantial prevalence of retinopathy signs in people with FPG below diabetic levels, casting further doubt on the validity of current diagnostic criteria.¹⁷

Here we discuss our study that sought to clarify the relation between FPG and retinopathy using data from three large contemporary populations, assessing retinopathy through a standardized, masked grading of multiple-field retinal photographs. Our objectives were (1) to provide updated data for the relation between FPG and retinopathy, (2) to assess the diagnostic accuracy of current FPG thresholds in identifying both prevalent and incident retinopathy, and (3) to verify the existence of a clear glycemic threshold for retinopathy in different populations.

STUDY DESCRIPTION

We analyzed cross-sectional data from three population-based cohorts: BMES (Blue Mountains Eye Study, $n=3,162$),^{18,19} AusDiab (Australian Diabetes, Obesity, and Lifestyle Study, $n=2,182$),^{20,21} and MESA (Multi-Ethnic Study of Atherosclerosis, $n=6,079$).^{22,23} We also analyzed prospective data from the BMES 5-year follow-up examination ($n=1,903$). Retinopathy grading followed the same protocol in all three studies. Details of participant characteristics and methods are shown in Table 1.

All three studies used multiple-field retinal photo-

TABLE 1. CHARACTERISTICS OF THREE POPULATION-BASED STUDIES

	Blue Mountains Eye Study ^{19,20}	Australian Diabetes, Obesity, and Lifestyle Study ^{21,22}	Multi-Ethnic Study of Atherosclerosis ^{23,24}
Location	Sydney, Australia	Australia-wide	Six US communities
Ethnicity	99% white	>95% white	White (39.6%), Black (27.0%), Hispanic (21.6%), Chinese (11.8%)
Eligibility	Adults aged ≥ 49 years living in two postcode areas in a region of mainly white individuals, with low migration in and out of the area	Adults aged ≥ 25 living in 42 randomly selected urban and rural areas	Adults aged 45–84 years living in six US counties chosen as being representative of the US population
Total sample size	3,654	2,773	6,814
Sample size (% of total eligible) in analysis	3,162 (71.3)	2,182 (78.7)	6,079 (89.2)
Date of survey	1992–2004	1999–2000	2002–2004
Mean age, years (SD)	65.9 (9.4)	57.5 (13.8)	63.5 (9.5)
Age range, years	49–97	25–90	45–84
Men (%)	1,360 (43.0)	964 (44.2)	2,895 (47.6)
Diabetes* (%)	253 (8.0)	733 (33.6)	778 (12.8)
Hypertension [†] (%)	2,256 (71.3)	17.8 (52.2)	2,974 (48.9)
Current cigarette smoker (%)	464 (14.7)	261 (12.2)	763 (12.6)
Fasting plasma glucose, mmol/L (mean[SD])	5.3 (1.6)	6.5 (2.2)	5.9 (1.4)
Systolic blood pressure, mm Hg (mean[SD])	146.4 (21.5)	137.2 (19.8)	124.3 (20.2)
Diastolic blood pressure, mm Hg (mean[SD])	83.4 (10.0)	72.1 (12.2)	70.4 (10.0)
Measurement of fasting glucose	Hitachi 747 biochemistry analyzer (Tokyo)	Olympus AU600 analyzer, Olympus Diagnostic Systems (Eastleigh, UK)	Vitros analyzer, Johnson & Johnson Clinical Diagnostics (New Brunswick, NJ)
Retinal photographs	Six 30°	Two 45°	Two 45°
Retinopathy grading scale used	Modified Airlie House classification scheme in ETDRS ^{21–23}	Modified Airlie House classification scheme in ETDRS ^{21–23}	Modified Airlie House classification scheme in ETDRS ^{21–23}
Definition of retinopathy	ETDRS level ≥ 15	ETDRS level ≥ 20	ETDRS level ≥ 20
Definition of moderate retinopathy ²⁴	ETDRS ≥ 31	ETDRS ≥ 31	ETDRS ≥ 31
Grading center	Sydney, NSW, Australia	Melbourne, VIC, Australia	Madison, MI, USA
Intragrader reliability kappa	0.82–0.98	0.73	0.84–0.95
Intergrader reliability kappa	0.90	NA (one grader)	0.89
Number (%) with retinopathy	364 (11.5)	210 (9.3)	959 (15.8)

*Diabetes defined as previous medical diagnosis of diabetes, or use of diabetic medications, or fasting plasma glucose ≥ 7.0 mmol/L.

[†]Hypertension defined according to WHO criteria.

SD = standard deviation; ETDRS = Early Treatment of Diabetic Retinopathy Study.^{25,26}

TABLE 2. SENSITIVITY, SPECIFICITY, POSITIVE, AND NEGATIVE PREDICTIVE VALUE FOR RETINOPATHY AT VARYING FASTING PLASMA GLUCOSE CUTOFFS*

Fasting Plasma Glucose Threshold	No of Retinopathy Cases/ Total No. of Participants (%)		Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio	Negative Likelihood Ratio
	Below the Cutoff	Above the Cutoff						
The Blue Mountains Eye Study								
≥7.8 mmol/L	314/3,030 (10.4)	50/132 (37.9)	13.7	97.1	37.9	89.6	4.7	0.9
≥7.0 mmol/L	310/2,990 (10.4)	54/172 (31.4)	14.8	95.8	31.4	89.6	3.5	0.9
	262/2,568 (10.2)	102/594 (17.2)	28	82.4	17.2	89.8	1.6	0.9
The Australian Diabetes, Obesity, and Lifestyle Study								
≥7.8 mmol/L	144/1,884 (7.6)	66/298 (22.2)	31.4	88.2	22.2	92.4	2.7	0.8
≥7.0 mmol/L	128/1,722 (7.4)	82/460 (17.8)	39.1	80.8	17.8	92.6	2	0.8
	57/773 (7.4)	153/1,409 (10.9)	72.9	36.3	10.9	92.6	1.1	0.7
The Multi-Ethnic Study of Atherosclerosis								
≥7.8 mmol/L	772/5,611 (13.8)	187/468 (40.0)	19.5	94.5	40	86.2	3.5	0.9
≥7.0 mmol/L	725/5,404 (13.4)	234/675 (34.7)	24.4	91.4	34.7	86.6	2.8	0.8
≥5.6 mmol/L	450/3,524 (12.8)	509/2,555 (19.9)	53.1	60	19.9	87.2	1.3	0.8
*To convert from mmol/L to mg/dL, multiply by 18.								

graphs and standardized protocols to assess retinopathy. At each site, trained graders masked to diabetes status assessed photographs for presence of retinopathy lesions.

In the BMES, 124 participants without gradable retinal photographs¹⁸ and 368 without FPG data were excluded; 3,162 participants contributed data toward the cross-sectional analyses. After further exclusions, 1,903 were left with follow-up data. The AusDiab study included 2,182 participants eligible for analysis.²¹ For MESA, 6,079 participants provided data for the analysis.

The overall prevalence of retinopathy was 11.5% (95% confidence interval [CI], 10.4–12.6; n=364/3,162) in BMES, 9.6% (8.4–10.9; n=210/2,182) in AusDiab, and 15.8% (14.9–16.7; n=959/6,079) in MESA (Figure 1). In BMES, the prevalence of retinopathy, even at low concentrations of FPG, was around 10% and increased above the 6.3- to 7.0-mmol/L category. Moderate retinopathy in BMES occurred in around 1% of the population with low FPG and started increasing above the same threshold (6.3–7.0 mmol/L). In the AusDiab population, the prevalence of retinopathy was roughly 8% in participants with low FPG concentrations and increased above 7.1 to 7.8 mmol/L, whereas the prevalence of moderate retinopathy showed a continuous relation with increasing FPG. In MESA, the prevalence of retinopathy, even at low FPG, was above 10% and increased continuously with FPG. Moderate retinopathy was also present at low FPG and also increased continuously with FPG.

Below 7.0 mmol/L, a substantial proportion (7.4%–13.4%) of participants in all three studies had retinopathy, whereas 17.8% to 34.7% had retinopathy above the cutoff. The sensitivity of this cutoff was low (14.8%–39.1%), with specificity

above 80% (80.8%–95.8%) for detecting retinopathy.

We examined the relationship between baseline FPG and incident retinopathy in BMES (Figure 2). On visual inspection, the incidence of retinopathy increased continuously with FPG. Change-point models indicated no thresholds. At a baseline 7.0 mmol/L cutoff, sensitivity for incident retinopathy was low at 10.2%, specificity was 97.4%, positive predictive value was 30.8%, negative predictive value was 90.4%, positive likelihood ratio was 3.9, negative likelihood ratio was 0.9, and area under the curve (AUC) was 0.59. A similar continuous relation between prevalent retinopathy and AUC was seen in MESA (Figure 3). Finally, we examined the relation between 2-hour postload glucose and retinopathy in AusDiab. The performance of an 11.1 mmol/L 2-hour postload glucose cutoff in identifying prevalent retinopathy in this population was poorer than for FPG; sensitivity was 24.8%, specificity was 81.1%, positive predictive value was 8.9%, negative predictive value was 93.5%, positive likelihood ratio was 1.3, negative likelihood ratio was 0.9, and AUC was 0.54 (Table 2).

DISCUSSION

Our study highlights several important findings. First, we found little evidence of a consistent glycemic threshold for retinopathy across populations, in contrast to the findings of the three previous studies on which the current diabetes diagnostic criteria are based. Our results show a more gradual increase of retinopathy prevalence with FPG and strongly suggest a continuous relationship. Our findings might differ from the three previous studies because they were able to detect only more severe retinopathy. We did not, howev-

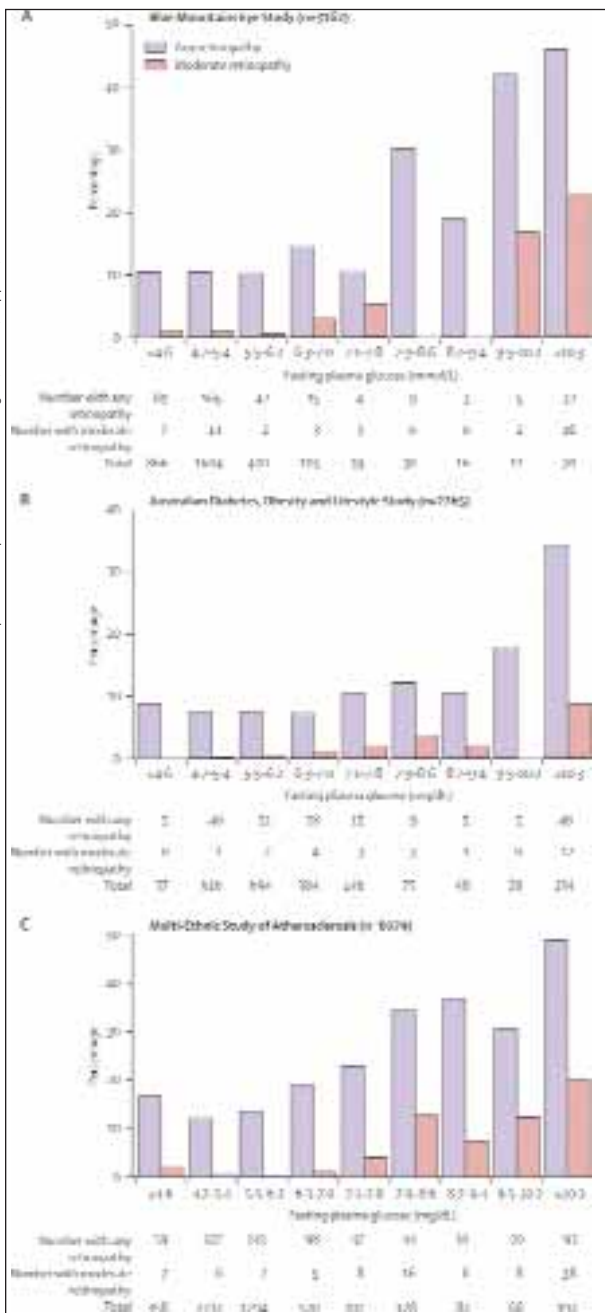


Figure 1. Relationship between FPG and retinopathy.

er, find any clearer evidence of a glycemic threshold with moderate retinopathy, with the data again suggesting a continuous relationship. These results of FPG and retinopathy are therefore consistent with observations that the relationship between glucose and macrovascular complications such as CVD is continuous with no threshold,^{5,6,8,24} and is analogous to that of end-organ damage found with other cardiovascular risk factors such as blood pressure and serum cholesterol levels.

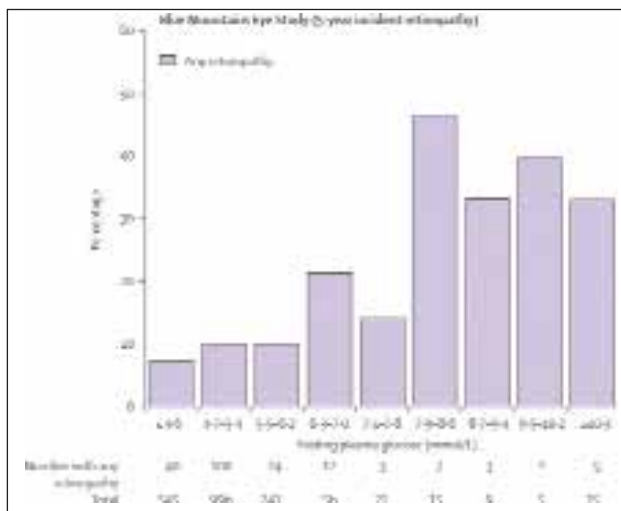


Figure 2. Relationship between baseline FPG and incident retinopathy, BMES.

A second major finding from our work is the poor performance of current and past cutoffs used to diagnose diabetes at separating individuals with and without retinopathy. This finding is largely a result of the much higher prevalence of retinopathy at low or normal concentrations of FPG than reported in the three previous studies, despite using the same or similar definitions of retinopathy. Earlier studies suggested a retinopathy prevalence of 2% to 4%¹¹⁻¹³ at concentrations of FPG <5.6 mmol/L. We now show that retinopathy signs actually occur in 7% to 13% of the population below this FPG concentration, indicating that earlier studies had underestimated retinopathy prevalence by two to five times. At a ≥ 7.0 mmol/L FPG cutoff, we observed sensitivities of <40%, compared with >80% from the earlier studies.^{11,12} We further report a considerably smaller AUC for FPG and retinopathy (<0.60) compared with previous reports.

In BMES, we also showed that FPG poorly predicted incident retinopathy after 5 years, with most incident retinopathy cases occurring in people with FPG below the 7.0 mmol/L cutoff. This finding contrasts with the previous study in Pima Indians,⁵ which showed little incident retinopathy below the 7.0 mmol/L cutoff, but it is consistent with newer studies showing that, numerically, more incident retinopathy lesions occur in people with FPG below this cutoff than above it.^{25,26}

New data from the DPP¹¹ and other studies^{27,28} support our findings of a higher prevalence of retinopathy at low and normal FPG. In fact, there is now evidence that retinopathy signs in these individuals are only weakly related to hyperglycemia^{29,30} and are probably the result of other vascular processes such as hypertension,¹⁸ rather than being specific to hyperglycemia. More advanced retinopathy lesions could be more strongly related to hyperglycemia, suggesting that

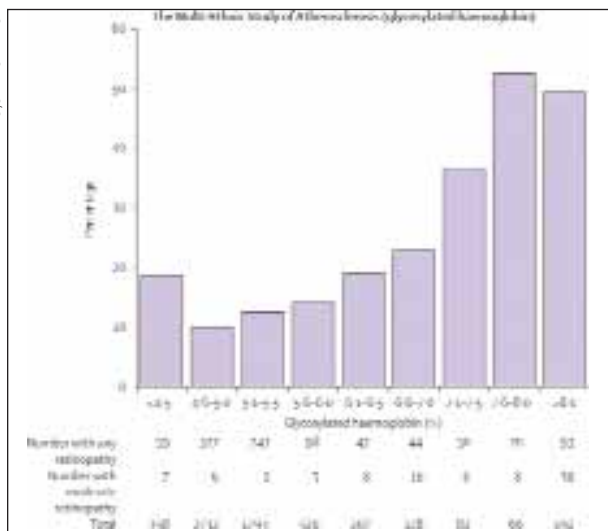


Figure 3. Relationship between AUC and retinopathy, MESA.

examining the relationship of these lesions to FPG might be more useful in deriving diagnostic thresholds for diabetes. This area remains to be explored.

Retinopathy proportion in nondiabetic (<7.0 mmol/L) individuals in our populations ranged from 7.4% to 13.4%. This range of prevalence is probably attributable to different population age and race structures, different distribution of hypertension and other vascular diseases, different numbers of retinal photographs taken, and the short-term variability in FPG measurements that might cause variation in prevalence estimates.³¹ After adjusting for age, race, and hypertension, these differences in retinopathy prevalence were not significant. Regardless of the source of this variability, our study does not support the existence of a clear glycemic threshold but rather suggests a continuous relationship of FPG with retinopathy.

Retinopathy is the only diabetic complication believed to show a strong threshold effect with FPG, and this threshold underlies the current diagnostic criteria for diabetes. We now show in three contemporary populations that the relation between FPG and both prevalent and incident retinopathy, ascertained accurately from multiple field retinal photographs, may be continuous with no clear evidence of a consistent threshold. We found poor performance of current FPG cutoffs in separating individuals with and without retinopathy. These findings suggest that both macrovascular and microvascular complications do not seem to respect a glycemic threshold and help unify understanding of the risk of complications from diabetes. Our findings question the validity of the current WHO and ADA approach of using retinopathy to derive FPG thresholds for diagnosing diabetes and point to the need to revisit current diagnostic criteria for diabetes. ■

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1. Sicree R, Shaw J, Zimmet P. The Global Burden. Diabetes and impaired glucose tolerance: prevalence and projections In: Gan D, ed. Diabetes atlas. Brussels: International Diabetes Federation, 2006:16-103.
2. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. 2007. Accessed April 23, 2007.
3. American Diabetes Association. All about diabetes. Accessed April 23, 2007.
4. Arky RA. "Doctor, is my sugar normal?" *N Engl J Med*. 2005;353:1511-1513.
5. Gerstein HC, Yusuf S. Dysglycaemia and risk of cardiovascular disease. *Lancet*. 1996;347:949-950.
6. Balkau B, Bertrais S, Ducimetiere P, Eschwege E. Is there a glycemic threshold for mortality risk? *Diabetes Care*. 1999;22:696-699.
7. Wei M, Gibbons LW, Mitchell T, Kampert JB, Stern MP, Blair SN. Low fasting plasma glucose level as a predictor of cardiovascular disease and all-cause mortality. *Circulation*. 2000;101:2047-2052.
8. Shaw JE, Zimmet PZ, Hodge AM, et al. Impaired fasting glucose: how low should it go? *Diabetes Care*. 2000;23:34-39.
9. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233-240.
10. Diabetes Control and Complications Trial Research Group. The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes*. 1996;45:1289-1298.
11. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated hemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ*. 1994;308:1323-1328.
12. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. *Diabetes Care*. 1997;20:785-791.
13. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183-1197.
14. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26:S5-S20.
15. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. *Ophthalmology*. 1995;102:647-661.
16. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
17. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med*. 2007;24:137-144.
18. Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. *Arch Ophthalmol*. 1998;116:83-89.
19. Mitchell P, Smith W, Wang JJ, Attebo K. Prevalence of diabetic retinopathy in an older community. The Blue Mountains Eye Study. *Ophthalmology*. 1998;105:406-411.
20. Dunstan DW, Zimmet PZ, Welborn TA, et al. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab)—methods and response rates. *Diabetes Res Clin Pract*. 2002;57:119-129.
21. Tapp RJ, Zimmet PZ, Harper CA, et al. Diagnostic thresholds for diabetes: the association of retinopathy and albuminuria with glycaemia. *Diabetes Res Clin Pract*. 2006;73:315-321.
22. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol*. 2006;141:446-455.
23. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871-881.
24. Diabetes Control and Complications Trial Research Group. The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes*. 1996;45:1289-1298.
25. van Leiden HA, Dekker JM, Moll AC, et al. Risk factors for incident retinopathy in a diabetic and non-diabetic population: the Hoorn study. *Arch Ophthalmol*. 2003;121:245-251.
26. Ito C, Maeda R, Ishida S, Harada H, Inoue N, Sasaki H. Importance of OGTT for diagnosing diabetes mellitus based on prevalence and incidence of retinopathy. *Diabetes Res Clin Pract*. 2000;49:181-186.
27. Klein R, Klein BE, Moss SE, Wang Q. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. *Arch Ophthalmol*. 1994;112:92-98.
28. Kawasaki R, Wang JJ, Rochtchina E, et al. Cardiovascular risk factors and retinal microvascular signs in an adult Japanese population: the Funagata Study. *Ophthalmology*. 2006;113:1378-1384.
29. Wong TY, Mohamed Q, Klein R, Couper DJ. Do retinopathy signs in non-diabetic individuals predict the subsequent risk of diabetes? *Br J Ophthalmol*. 2006;90:301-303.
30. Klein R, Klein BE, Moss S, Wong TY. The relationship of retinopathy in persons without diabetes to the fifteen year incidence of diabetes and hypertension: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 2006;104:98-107.
31. Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycaemia and implications for the classification of diabetes. *Arch Intern Med*. 2007;167:1545-1551.
32. Wong TY, Liew G, Tapp RJ, et al. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. *Lancet*. 2008;371:736-743.