The Wisconsin Epidemiologic Study of Diabetic Retinopathy

XVI. The Relationship of C-Peptide to the Incidence and Progression of Diabetic Retinopathy

Ronald Klein, Barbara E.K. Klein, and Scot E. Moss

The relationship between plasma C-peptide and the 6-year incidence and progression of diabetic retinopathy was examined in a population-based study in Wisconsin. Individuals with younger-onset (n = 548) and older-onset (n = 459) diabetes were included. C-peptide was measured by radioimmunoassay with Heding's M1230 antiserum. Retinopathy was determined from stereoscopic fundus photographs. Younger- and older-onset insulin-using individuals with undetectable or low plasma C-peptide (<0.3 nmol/l) at baseline had the highest incidence and rates of progression of retinopathy, whereas older-onset individuals with C-peptides >0.3 nmol/l had the lowest incidence and rates of progression of retinopathy. However, within each group (younger-onset using insulin, older-onset using insulin, and older-onset not using insulin), after we controlled for other characteristics associated with retinopathy, there was no relationship between higher levels of C-peptide at baseline and lower 6-year incidence or progression of retinopathy. These data suggest that glycemic control, and not C-peptide, is related to the incidence and progression of diabetic retinopathy. *Diabetes* 44:796–801, 1995

Diabetic retinopathy is a leading cause of blindness in the U.S. (1–3). Epidemiological data suggest a strong relationship between the level of glycemia and the incidence and progression of the retinopathy in individuals with both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) (4–9). However, the relationship of endogenous insulin secretion to diabetic retinopathy, independent of glycemic control, is not clear. Some studies suggest a protective effect, whereas others do not (10–23). This study examined the relationship of C-peptide, a measure of endogenous insulin secretion, and the incidence and progression of diabetic retinopathy in a large population-based study of people with IDDM and NIDDM.

From the Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, Wisconsin.

Address correspondence to Dr. Ronald Klein, Department of Ophthalmology and Visual Sciences, University of Wisconsin—Madison, 610 N. Walnut St., 460 WARF, Madison, WI 53705-2397.

Received for publication 11 November 1994 and accepted in revised form 23 February 1995.

CI, confidence interval; CSME, clinically significant macular edema; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; OR, odds ratio; PDR, proliferative diabetic retinopathy.

RESEARCH DESIGN AND METHODS

The study population was described in detail in previous reports (24–27). A population-based sample of 2,990 subjects was selected for examination. This sample was composed of two groups. The first group consisted of all patients in whom diabetes was diagnosed before 30 years of age who took insulin (younger onset, n = 1,210). The second group consisted of a probability sample of patients in whom diabetes were diagnosed at 30 years of age or older and who had their diagnosis confirmed by a random or postprandial serum glucose level of at least 11.1 mmol/l or a fasting serum glucose level of at least 7.8 mmol/l on at least two occasions (older onset, n = 1,780). The second group was sampled in strata defined by duration of disease (<5 years, n = 576; 5–14 years, n = 579; and ≥15 years, n = 625). Of the second group, 824 individuals were taking insulin and 956 individuals were not at the time that they were identified.

The 1980–1982, 1984–1986, and 1990–1992 examinations were performed in a mobile examination van in or near the cities where the subjects lived. All of the examinations followed a similar protocol, which was approved by the University of Wisconsin Human Subjects Committee. Informed consent was obtained from all subjects or their legal guardians. Pertinent parts of the ocular and physical examinations consisted of measuring the height, weight, and blood pressure (using a Hawksley random-zero sphygmomanometer after the Hypertension Detection and Follow-up Program protocol [28]); dilating the pupils; taking stereoscopic fundus photographs of seven standard fields for each eye (29); performing a urine analysis for the semiquantitative determination of protein levels with a reagent strip (Labstix, Ames, Elkhart, IN); and determining glycosylated hemoglobin levels (30).

A standard questionnaire was administered. A history of antihypertensive medication use and specific types was obtained from the participant. If there was any question concerning accuracy, the history was verified by contacting the participant's physician.

Plasma C-peptide was measured for the first time at the 1984–1986 examination. With a 5-ml vacutainer tube that contained 7.5 mg EDTA and 0.2 ml Trasylol (10^7 Kallikrein international units/l), 4 ml of blood was collected and spun immediately at 4°C. Plasma was frozen at −20°C and sent to the University of Chicago for determination of the C-peptide level. Plasma C-peptide was measured as described by Faber et al. (31) with Heding's M1230 antiserum. The lower limit of detection of C-peptide was 0.03 nmol/l, and the interassay coefficient of variation was 8%.

Definitions. The current age was defined as the age at the 1984–1986 examination. Age at diagnosis was defined as the age at the time the diagnosis of diabetes was first recorded by a physician on the patient's chart or a hospital record. Duration of diabetes was that time between age at diagnosis and age at the 1984–1986 examination. For this study, being overweight was defined as a body mass index of >27.8 kg/m^2 for men and >27.3 kg/m^2 for women (32). The mean systolic blood pressure was the average of the two systolic blood pressure determinations in the 1984–1986 examination; mean diastolic blood pressure was the average of the two diastolic blood pressures.

At each examination, all fundus photographs were graded using a

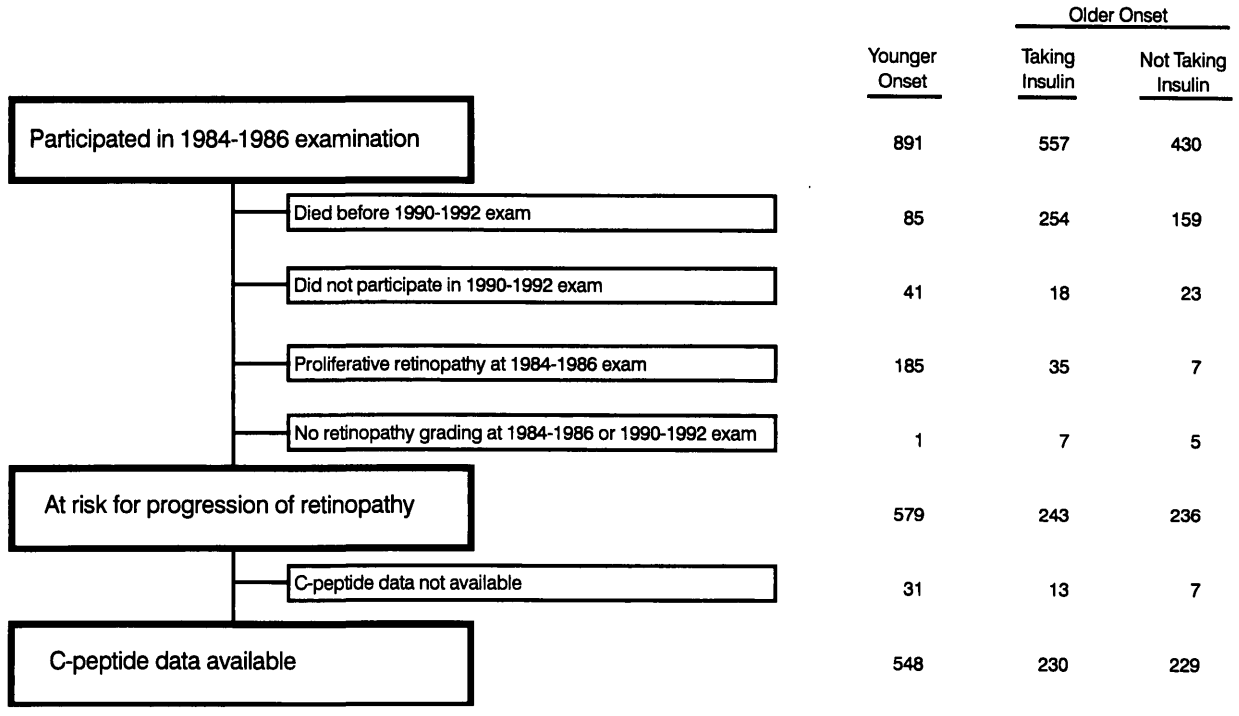

FIG. 1. Participation in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.

modification of the Early Treatment Diabetic Retinopathy Study classification scheme adapted for the Wisconsin Epidemiologic Study of Diabetic Retinopathy (27). Briefly, level 10 represents no retinopathy, levels 21, 31, 37, 43, 47, and 53 represent nonproliferative retinopathy of increasing severity, and levels 60 through 85 represent proliferative retinopathy of increasing severity. The retinopathy level for a person was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight. For example, the level for a person with level 31 in each eye is specified as 31/31, whereas the level for a person with level 31 in one eye and a lesser level in the other eye is denoted 31/<31. This scheme results in a 15-step scale (10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) when all levels of proliferative retinopathy are grouped as one level.

As C-peptide was first measured at the 1984–1986 follow-up examination, this examination was considered to be the baseline examination for this report. Development and progression of diabetic retinopathy over the 6-year period to 1990–1992 was examined. All retinopathy endpoints were defined for the individual. The incidence of any retinopathy was estimated from individuals who had no retinopathy in either eye at the 1984–1986 examination and had participated in the 1990–1992 examination. Any retinopathy was defined as a retinopathy severity of 21/<21 or worse at the 1990–1992 examination. For individuals with nonproliferative or no retinopathy, levels 10/10 through 53/53, in 1984–1986, progression was defined as an increase in severity of 2 steps or more on the 15-step scale, for example, 31/31 to 37/37. Progression to proliferative retinopathy was also estimated from subjects with nonproliferative or no retinopathy. Proliferative diabetic retinopathy (PDR) was defined as a retinopathy severity of 60+/<60+ or worse at the 1990–1992 examination.

Clinically significant macular edema (CSME) was based on the detailed gradings and was defined as the presence of any one of the following: thickening of the retina located ≤500 μm from the center of the macula, hard exudates with thickening of the adjacent retina ≤500 μm from the center of the macula, or a zone of retinal thickening one disc area or larger in size located one disc diameter or less from the center of the macula (33). Macular edema status for an individual was defined as being present if it was found on fundus photographs or there was a prior history of macular edema with prior photocoagulation treatment in at least one eye.

SAS was used for tabulating the data and calculating summary statistics (34). All analyses were limited to findings at the 1984–1986 and 1990–1992 examinations. Tests for linear trends in frequencies were done according to the method described by Mantel (35). Multivariate analyses for describing the severity as it related to C-peptide and other characteristics were performed by logistic regression (36).

TABLE 1
Characteristics of those with and without C-peptide measurements at the 1984–1986 examination in the younger-onset group

Characteristic	With C-peptide	Without C-peptide	*P*
Age at diagnosis (years)	548 (14.6 ± 7.5)	31 (12.4 ± 7.9)	0.12
Age at examination (years)	548 (29.4 ± 11.2)	31 (26.9 ± 10.7)	0.22
Duration of diabetes (years)	548 (14.8 ± 8.2)	31 (14.5 ± 9.7)	0.83
Glycosylated hemoglobin (%)	545 (9.9 ± 1.9)	13 (9.8 ± 1.3)	0.80
Systolic blood pressure (mmHg)	547 (119 ± 15)	17 (114 ± 15)	0.20
Diastolic blood pressure (mmHg)	547 (76 ± 10)	17 (73 ± 11)	0.30
Body mass index (kg/m^2)	544 (24.5 ± 4.0)	23 (22.5 ± 3.0)	<0.05
Male	548 (49.5)	31 (35.5)	0.14
Proteinuria	542 (13.1)	19 (21.1)	0.30
Retinopathy			
None	93 (17.0)	10 (32.3)	
Mild	337 (61.5)	18 (58.1)	0.05
Moderate	118 (21.5)	3 (9.7)	

Data are *n* (mean ± SD) or *n* (%).

TABLE 2
Spearman correlations among C-peptide, glycosylated hemoglobin, and exogenous insulin

	Younger-onset group		Older-onset group			
			Taking insulin		Not taking insulin	
	r	*P*	*r*	*P*	*r*	*P*
C-peptide with glycosylated hemoglobin	−0.01	0.88	−0.16	<0.05	0.07	0.27
C-peptide with exogenous insulin	−0.18	<0.0001	−0.20	<0.005	—	—
Glycosylated hemoglobin with exogenous insulin	−0.01	0.84	0.14	<0.05	—	—

For *P*, test of $r = 0$.

RESULTS

C-peptide data, at the 1984–1986 examination, were available for 94.6% (n = 548 of 579) of younger-onset individuals and 95.8% (n = 459 of 479) of older-onset individuals of the original selected samples who had participated in both the 1984–1986 and 1990–1992 examinations and who were at risk for progression of retinopathy (Fig. 1). Among younger-onset subjects who participated in both examinations, there were few differences in those with and without measured C-peptide levels at the 1984–1986 examination (Table 1); among the older-onset groups there were no statistically significant differences (data not shown).

The relationships among C-peptide, glycosylated hemoglobin, and exogenous insulin at the 1984–1986 examination are presented in Table 2. C-peptide was significantly and inversely correlated with glycosylated hemoglobin only in the older-onset group taking insulin. C-peptide was inversely correlated with exogenous insulin use in the two insulin-taking groups.

Participants were grouped by C-peptide levels. Younger-onset individuals were divided into three groups: those with undetectable C-peptide (n = 472), those with low C-peptide (≥0.03-<0.3 nmol/l, n = 63), and those with higher C-peptide (≥0.3 nmol/l, n = 13). These classifications were based on previous observations that the lower limit of detection of plasma C-peptide by our assay is 0.03 nmol/l (32) and that 98% of a nondiabetic comparison group, measured in a similar fashion, had C-peptide ≥0.3 nmol/l (R.K., unpublished observations). Older-onset individuals using insulin were also divided into three groups: those with no C-peptide (n = 48), those with low C-peptide (≥0.03-<0.3 nmol/l, n = 57), and those with higher C-peptide (≥0.3 nmol/l, n = 125). Older-onset individuals not using insulin were divided into two groups: those with low C-peptide (<0.3 nmol/l, n = 4) and those with higher C-peptide (≥ 0.3 nmol/l, n = 225). In the latter group, the mean C-peptide (1.49 nmol/l) was significantly ($P < 0.0005$) higher than in a nondiabetic comparison group of similar age (1.18 nmol/l).

Comparisons among the groups for various characteristics measured at the 1984–1986 examination have been presented elsewhere (20). The 6-year incidence and/or progression of diabetic retinopathy and macular edema for each group are presented in Tables 3–5.

There were no statistically significant differences in the incidence or rates of progression of diabetic retinopathy or the incidence of macular edema or of CSME between the younger-onset group with undetectable C-peptide and the group with detectable but very low C-peptide (Table 3).

For the older-onset group taking insulin, those with undetectable C-peptide had a relative risk of progression to PDR of 1.9 (95% confidence interval [CI] 1.0–3.5) compared with the subgroup with the C-peptide ≥0.3 nmol/l (Table 4). However, the older-onset group using insulin with the highest C-peptide had the highest incidence of macular edema or CSME. Crude incidence of any retinopathy, two-step progression, or progression to proliferative retinopathy was comparable for older- and younger-onset groups with undetectable C-peptide ($P > 0.40$) (Tables 3 and 4). In addition, younger- and older-onset subjects taking insulin with no or low C-peptide (<0.30 nmol/l) had significantly higher ($P < 0.0001$) incidence of retinopathy, progression of retinopathy, and progression to PDR than older-onset subjects not taking insulin with high C-peptide (≥ 0.30 nmol/l [Table 6]).

Because body mass index may be an important influence on utilizable insulin, the older-onset group not using insulin with C-peptide ≥0.3 nmol/l was further subdivided into an overweight group and a group that was not overweight. Body mass data were not available for 11 subjects. The overweight group had higher progression of any retinopathy and progression to PDR than those not overweight (Tables 5 and 6).

To evaluate the association of C-peptide and several other

TABLE 3
Relationship of 6-year incidence and progression of diabetic retinopathy, progression to PDR, incidence of macular edema, and incidence of CSME in the younger-onset group defined by C-peptide level

Endpoint	C-peptide			*P*
	Undetectable	<0.3 nmol/l	≥0.3 nmol/l	
Incidence of retinopathy	76 (76.3)	14 (78.6)	3 (33.3)	0.31
Two-step progression	472 (57.6)	63 (63.5)	13 (61.5)	0.42
Progression to PDR	472 (22.0)	63 (20.6)	13 (30.8)	0.75
Incidence of macular edema	450 (11.1)	65 (18.5)	13 (15.4)	0.13
Incidence of CSME	450 (8.2)	65 (12.3)	13 (15.4)	0.17

Data are number at risk of developing the complication (%). *P* value is based on the Mantel-Haenszel test for trend.

TABLE 4
Relationship of 6-year incidence and progression of diabetic retinopathy, progression to PDR, incidence of macular edema, and incidence of CSME in the older-onset diabetic group using insulin, defined by C-peptide level

Endpoint	C-peptide			*P* value
	Undetectable	<0.3 nmol/l	≥0.3 nmol/l	
Incidence of retinopathy	10 (80.0)	12 (58.3)	29 (55.2)	0.20
Two-step progression	48 (60.4)	57 (50.9)	125 (49.6)	0.24
Progression to PDR	48 (27.1)	57 (14.0)	125 (14.4)	0.08
Incidence of macular edema	41 (12.2)	46 (8.7)	97 (20.6)	0.12
Incidence of CSME	41 (2.4)	46 (8.7)	97 (15.5)	0.02

Data are number at risk of developing the complication (%). *P* value is based on the Mantel-Haenszel test for trend.

characteristics with the incidence and progression of diabetic retinopathy or macular edema, we developed a series of models based on a stepwise logistic regression. These models are used to test the significance of variables in predicting an outcome (incidence of retinopathy, progression of retinopathy, progression to PDR, or incidence of macular edema) when the effects of other variables are also being evaluated. The effects of characteristics, including glycosylated hemoglobin, sex, age, duration of diabetes, and baseline retinopathy level that we previously found to be potentially related to incidence and progression of diabetic retinopathy for the younger-onset group, the older-onset group using insulin, and the older-onset group not using insulin were included in the models. In addition, we included time since the last meal was eaten.

For the younger- and older-onset groups taking insulin, a total of eight models was developed (Table 7). Two models were developed for each endpoint (incidence of retinopathy, progression of retinopathy, progression to proliferative retinopathy, and incidence of macular edema), one in which C-peptide was entered as undetectable or detectable and the other, which only included individuals with detectable C-peptide at baseline, in which C-peptide was entered as a continuous variable. Similarly, another eight models were developed for the whole population using the same endpoints (Table 8). Four of these models included all individuals in which C-peptide was entered as undetectable or detectable; in the other four, which included only individuals with detectable C-peptide, C-peptide was entered as a continuous variable. The odds ratio (OR) represents the change in the risk of developing the endpoint for a specified change in the independent variables. In the case of glycosylated hemoglobin, this is a 1% increase. For C-peptide, it is either having a detectable compared with an undetectable level (for all subjects) or a 1 nmol/l increase (for subjects with detectable levels). ORs >1 represent an increase in risk; those <1 represent a decrease. In all the models, glycosylated hemoglobin was significantly related to the incidence or progression of retinopathy (Tables 7 and 8). After we controlled for glycosylated hemoglobin, C-peptide was not significantly related to the incidence or progression of retinopathy or the incidence of proliferative retinopathy in any of the models. Neither was exogenous insulin. However, subjects with detectable C-peptide had a higher odds of developing macular edema than those in whom C-peptide was not detectable (Tables 7 and 8). Higher amounts of exogenous insulin were associated with increased risk of developing macular edema (Table 7).

TABLE 5
Relationship of 6-year incidence and progression of diabetic retinopathy, progression to PDR, incidence of macular edema, and incidence of CSME in the older-onset diabetic group not using insulin, defined by weight status

Endpoint	Not overweight	Overweight	*P*
Incidence of retinopathy	35 (42.9)	84 (47.6)	0.69
Two-step progression	56 (27.8)	158 (48.1)	<0.01
Progression to PDR	56 (0)	158 (10.8)	<0.01
Incidence of macular edema	54 (7.4)	142 (12.7)	0.45
Incidence of CSME	54 (3.7)	141 (7.8)	0.52

Data are number at risk of developing the complication (%). *P* value based on the Mantel-Haenszel test for trend.

DISCUSSION

These data suggest that regardless of age at diagnosis, diabetic individuals who use insulin and have undetectable or very low plasma C-peptide (<0.3 nmol/l) have a higher 6-year incidence and rate of progression of diabetic retinopathy than older-onset individuals who have higher levels of C-peptide (≥ 0.3 nmol/l). These results are consistent with previous observations of a more severe course in people with IDDM compared with people who do not have IDDM (27,37). However, these data suggest that it is glycemic control, as measured by glycosylated hemoglobin, and not C-peptide secretion that is associated with increased risk of development and progression of diabetic retinopathy. These data are consistent with previous findings that the specific level of glycemic control, and not the type of diabetes, is the most important predictor of diabetic complications (13,15, 20,22). It is possible that the effect of undetectable or low levels of insulin secretion is indirectly associated with the development of diabetic complications because of increased difficulty in achieving glycemic control.

TABLE 6
6-year incidence and progression of diabetic retinopathy, progression to PDR, and incidence of CSME in younger- and older-onset individuals taking insulin with undetectable or low (<0.3 nmol/l) C-peptide levels compared with older-onset individuals not taking insulin with high (≥0.3 nmol/l) C-peptide levels

Endpoint	Younger- and older-onset taking insulin	Older-onset not taking insulin	*P*
Incidence of retinopathy	112 (75.0)	128 (46.9)	<0.0001
Two-step progression	640 (57.8)	225 (41.8)	<0.0001
Progression to PDR	640 (21.6)	225 (7.6)	<0.0001
Incidence of CSME	602 (8.3)	203 (6.4)	0.45

Data are number at risk of developing the complication (%). *P* value based on the Mantel-Haenszel test for trend.

TABLE 7
The relationship of C-peptide level to incidence, progression of retinopathy, progression to PDR, or incidence of macular edema in the younger- and older-onset diabetic groups using insulin after controlling for other factors

	All individuals			Individuals with detectable C-peptide		
		OR	95% CI		OR	95% CI
Incidence of retinopathy						
n	138	—	—	54	—	—
Glycosylated hemoglobin (per 1%)	—	1.40	1.05, 1.86	—	—	—
C-peptide	—	0.58	0.23, 1.49	—	—	—
Insulin (per $U \cdot kg^{-1} \cdot day^{-1}$)	—	2.20	0.43, 11.26	—	—	—
Progression of retinopathy						
n	758	—	—	248	—	—
Glycosylated hemoglobin (per 1%)	—	1.63	1.46, 1.82	—	1.47	1.22, 1.77
C-peptide	—	0.91	0.64, 1.29	—	0.63	0.39, 1.03
Insulin (per $U \cdot kg^{-1} \cdot day^{-1}$)	—	1.38	0.76, 2.50	—	1.23	0.47, 3.22
Progression to PDR						
n	758	—	—	248	—	—
Glycosylated hemoglobin (per 1%)	—	1.62	1.42, 1.84	—	1.49	1.15, 1.93
C-peptide	—	0.88	0.48, 1.60	—	0.79	0.35, 1.80
Insulin (per $U \cdot kg^{-1} \cdot day^{-1}$)	—	0.79	0.34, 1.81	—	1.06	0.32, 3.59
Incidence of macular edema						
n	693	—	—	211	—	—
Glycosylated hemoglobin (per 1%)	—	1.49	1.31, 1.69	—	1.72	1.34, 2.20
C-peptide	—	2.12	1.29, 3.50	—	1.14	0.58, 2.25
Insulin (per $U \cdot kg^{-1} \cdot day^{-1}$)	—	1.52	0.72, 3.22	—	3.12	1.01, 9.60

n = number at risk of developing the complication. For all individuals, C-peptide was detectable or undetectable. For individuals with detectable C-peptide, C-peptide was continuous (per 1 nmol/l).

Over the 6-year period of the study, overweight people not using insulin with normal or high levels of C-peptide at baseline were more likely to develop macular edema and proliferative retinopathy than those who were not overweight. This is inconsistent with previous observations (20,37,38). Turkington and Weindling (38) reported that individuals with hyperglycemia but sufficient or excessive endogenous insulin secretion (60 μU/ml) in response to a 100-g glucose load (equivalent to C-peptide of ≥0.3 nmol/l) never developed retinopathy. Our data suggest that these patients are at increased risk of developing both proliferative retinopathy and macular edema. It is not clear why those who were overweight at the 1984–1986 examination were at a higher risk of developing severe retinopathy than those whose weight was normal. We have previously shown that older-onset people with proliferative retinopathy are at higher risk of death (39). The higher proportion of people in the older-onset normal weight group who died (47.2%) compared with the overweight group (24.6%, $P < 0.0001$) might, in part, explain our finding (R.K., unpublished data).

Exogenous insulin itself has been suggested to be a possible cause of atherosclerotic vascular disease and diabetic retinopathy (16,40). In our study, in groups using insulin, we found no association of the amount of exogenous insulin used with the incidence and progression of retinopathy. These findings suggest that the amount of exogenous insulin itself is not causally related to the incidence or progression of diabetic retinopathy. Higher amounts of ex-

TABLE 8
Relationship of C-peptide level to incidence, progression of retinopathy, progression to PDR, or incidence of macular edema in the whole population after controlling for other factors

	All individuals			Individuals with detectable C-peptide		
		OR	95% CI		OR	95% CI
Incidence of retinopathy						
n	270	—	—	186	—	—
Glycosylated hemoglobin (per 1%)	—	1.71	1.40, 2.09	—	1.94	1.50, 2.50
C-peptide	—	0.74	0.27, 2.01	—	0.85	0.54, 1.34
Progression of retinopathy						
n	999	—	—	482	—	—
Glycosylated hemoglobin (per 1%)	—	1.63	1.49, 1.79	—	1.60	1.41, 1.82
C-peptide	—	1.12	0.71, 1.75	—	0.84	0.62, 1.13
Progression to PDR						
n	999	—	—	482	—	—
Glycosylated hemoglobin (per 1%)	—	1.66	1.48, 1.88	—	1.56	1.28, 1.89
C-peptide	—	0.83	0.45, 1.53	—	0.88	0.46, 1.67
Incidence of macular edema						
n	912	—	—	424	—	—
Glycosylated hemoglobin (per 1%)	—	1.52	1.36, 1.70	—	1.63	1.38, 1.93
C-peptide	—	1.86	1.03, 3.34	—	1.09	0.69, 1.71

n = number at risk of developing the complication. For all individuals, C-peptide was detectable or undetectable. For individuals with detectable C-peptide, C-peptide was continuous (per 1 nmol/l).

ogenous insulin were related to increased incidence of macular edema. The reason for this relationship is not understood.

Care must be exercised in the interpretation of our data. We measured C-peptide in a casual specimen, not fasting or at a prescribed time as is often done after a standard meal or glucagon, Sustacal, tolbutamide, or glucose stimulation. To minimize the variability in C-peptide, we controlled for the time elapsed since the last meal was eaten to the time blood for the C-peptide sample was drawn.

In summary, these population-based data suggest that glycemic control and not C-peptide or exogenous insulin secretion is related to the incidence and progression of diabetic retinopathy. These data, along with data from the Diabetes Control and Complications Trial, suggest a benefit of glycemic control, regardless of C-peptide level, in terms of prevention of vision-threatening complications in people with IDDM and possibly NIDDM.

ACKNOWLEDGMENTS

This research was supported by National Institutes of Health Grant EYO-3083 (to R.K. and B.E.K.K.) from the National Eye Institute and, in part, by the Research to Prevent Blindness (R.K., Senior Scientific Investigator Award). Determinations of glycosylated hemoglobin levels were performed in the Core Laboratory of the Clinical Nutrition Center with support from U.S. Public Health Service, National Institutes of Health Grant P-30-AM-AG-26659 (to Earl Shrago, MD). Determination of C-peptide was done in the Core Laboratory of the Diabetes Research and Training Center at the University of Chicago (DK-20595). Partial support for the assay was also derived from Grant DK-13941 (Arthur Rubenstein, MD).

We are also grateful to the 452 Wisconsin physicians and their staffs who participated in and supported this study; to Karen J. Cruickshanks, PhD, Polly Newcomb, PhD, and Matthew Davis, MD, who provided consultation and criticism at different stages of the project; to Paul Rue who provided technical help; and to Colleen Comeau and Karen Klosterman for secretarial assistance.

REFERENCES

1. National Society to Prevent Blindness: *Vision Problems in the U.S.: Data Analysis: Definitions, Data Sources, Detailed Data Tables, Analysis, Interpretation.* New York, National Society to Prevent Blindness, 1980
2. Moss SE, Klein R, Klein BEK: The incidence of vision loss in a diabetic population. *Ophthalmology* 95:1340–1348, 1988
3. Prevent Blindness America: *Vision Problems in the U.S.: A Report on Blindness and Vision Impairment in Adults Age 40 and Older.* Schaumburg, IL, Prevent Blindness America, 1994
4. Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR: Risk of proliferative diabetic retinopathy in juvenile-onset type I diabetes: a 40-year follow-up study. *Diabetes Care* 9:443–452, 1986
5. Teuscher A, Schnell H, Wilson PWF: Incidence of diabetic retinopathy and relationship to baseline plasma glucose and blood pressure. *Diabetes Care* 11:246–251, 1988
6. Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D: Glucose control and the renal and retinal complications of insulin-dependent diabetes. *JAMA* 261:1155–1160, 1989
7. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 260:2864–2871, 1988
8. Klein R, Klein BEK, Moss SE, Cruickshanks KJ: The relationship of hyperglycemia to long-term incidence and progression of diabetic retinopathy. *Arch Intern Med* 154:2169–2178, 1994
9. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes. *N Engl J Med* 329:977–986, 1993
10. Faber O, Deckert T: Persistent insulin secretion, assessed by plasma C-peptide estimation. *Diabetologia* 15:169–172, 1978
11. Smith RBW, Pyke DA, Watkins PJ, Binder C, Faber OK: C-peptide response to glucagon in diabetics with and without complications. *NZ Med J* 89:304–306, 1979
12. Sjoberg S, Gunnarsson R, Gjotterberg M, Lefvert AK, Persson A, Ostman J: Residual insulin production, glycaemic control and prevalence of microvascular lesions and polyneuropathy in long-term type I (insulin dependent) diabetes mellitus. *Diabetologia* 30:208–213, 1987
13. Sjoberg S, Gjotterberg M, Lefvert AK, Gunnarsson R, Ostman J: Significance of residual insulin production in long-term type I diabetes mellitus. *Transplant Proc* 18:1498–1499, 1986
14. Suzuki K, Watanabe K, Motegi T, Kajinuma H: High prevalence of proliferative retinopathy in diabetic patients with low pancreatic B-cell capacity. *Diabetes Res Clin Pract* 6:45–52, 1989
15. Mosier MA: Circulating C-peptide and diabetic retinopathy. *Diabetes Res* 1:151–154, 1984
16. Serghieri G, Bartolomei G, Pettenello C, Mammini P, DeGiorgio LA: Raised retinopathy prevalence rate in insulin-treated patients: a feature of obese type II diabetes. *Transplant Proc* 18:1576–1577, 1986
17. Sberna P, Valentini U, Cimino A, Sabatti C, Rotondi A, Crisetig M, Spandrio S: Residual B-cell function in insulin-dependent (type I) diabetes with and without retinopathy. *Acta Diabetol Lat* 23:339–344, 1986
18. Madsbad S, Lauritzen E, Faber OK, Binder C: The effect of residual beta-cell function on the development of diabetic retinopathy. *Diabetic Med* 3:42–45, 1986
19. Snehalatha C, Mohan R, Mohan V, Ramachandran A, Viswanathan M: Pancreatic B-cell function in relation to diabetic retinopathy in Asian Indian NIDDM patients. *Acta Diabetol Lat* 95–100, 1988
20. Klein R, Moss SE, Klein BEK, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XII. The relationship of C-peptide and diabetic retinopathy. *Diabetes* 39:1445–1450, 1990
21. Kernell, Ludvigsson J, Finnstrom K: Vitreous fluorophotometry in juvenile diabetics with and without retinopathy in relation to metabolic control: insulin antibodies and c-peptide levels. *Acta Ophthalmol* 68:415–420, 1990
22. Winocour PH, Jeacock J, Kalsi P, Gordon C, Anderson DC: The relevance of persistent C-peptide secretion in type I (insulin-dependent) diabetes mellitus to glycaemic control and diabetic complications. *Diabetes Res Clin Pract* 9:23–35, 1990
23. Sjoberg S, Gjotterberg M, Berglund L, Moller E, Ostman J: Residual C-peptide excretion is associated with a better long-term glycemic control and slower progress of retinopathy in type I (insulin-dependent) diabetes mellitus. *J Diabetic Complications* 5:18–22, 1991
24. Klein R, Klein BEK, Moss SE, DeMets DL, Kaufman I, Voss PL: Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol* 119:54–61, 1984
25. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is <30 years. *Arch Ophthalmol* 107:237–243, 1989
26. Klein BEK, Klein R, Moss SE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years of age or older. *Arch Ophthalmol* 107:244–249, 1989
27. Klein R, Klein BEK, Moss SE, Cruickshanks KJ: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol* 112:1217–1228, 1994
28. Hypertension Detection and Follow-up Program Cooperative Group: The hypertension detection and follow-up program. *Prev Med* 5:207–215, 1976
29. Early Treatment Diabetic Retinopathy Study: *Manual of Operations.* Baltimore, ETDRS Coordinating Center, Dept. of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, 1985, Chapter 13, p. 5–7; Chapter 18, p. 1–53
30. *Quick-Step, Fast Hemoglobin Test System.* Akron, OH, Isolab, 1981
31. Faber OK, Binder C, Markussen J, Heding LG, Naithani VK, Kuzuya H, Blix P, Horwitz DL, Rubenstein AH: Characterization of seven C-peptide antisera. *Diabetes* 27 (Suppl. 1):170–177, 1978
32. Itallie TBV: Health implications of overweight and obesity in the United States. *Ann Intern Med* 103:983–988, 1985
33. Early Treatment Diabetic Retinopathy Study Research Group: Report no. 1: photocoagulation for diabetic macular edema. *Arch Ophthalmol* 103: 1796–1806, 1985
34. SAS/STAT User's Guide: *Statistics. Version 6.* Vol. 1, 4th ed. Cary, NC, SAS Inst., 1989, p. 851–889
35. Mantel N: Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc* 58:690–700, 1963
36. SAS/STAT User's Guide: *Statistics. Version 6.* Vol. 2, 4th ed. Cary, NC, SAS Inst., 1989, p. 1071–1126
37. West KM: *Epidemiology of Diabetes and Its Vascular Lesions.* New York, Elsevier, 1978, p. 403–407
38. Turkington RW, Weindling HK: Insulin secretion in the diagnosis of adult-onset diabetes mellitus. *JAMA* 240:833–836, 1978
39. Klein R, Klein BEK, Moss SE, DeMets DL: Relation of ocular and systemic factors to survival in diabetes. *Arch Intern Med* 149:266–272, 1989
40. Stout RW: The relationship of insulin to the development of atherosclerosis. In *Diabetes and Atherosclerosis Connection. Juvenile Diabetes Foundation Medical Series,* Moskowitz J, Ed. New York, Juvenile Diabetes Foundation, 1982, p. 241–245