Relationship of Glycemic Control, Exogenous Insulin, and C-Peptide Levels to Ischemic Heart Disease Mortality Over a 16-Year Period in People With Older-Onset Diabetes

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)

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OBJECTIVE — The purpose of this study was to examine the relationship of glycemic control and exogenous and endogenous insulin levels with all-cause and cause-specific mortality (ischemic heart disease and stroke) in an older-onset diabetic population.

RESEARCH DESIGN AND METHODS — The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is an ongoing, prospective, population-based cohort study of individuals with diabetes first examined in 1980–1982. A stratified sample of all individuals with diabetes diagnosed at 30 years of age or older was labeled "older-onset" (n = 1,370). Those participating in the 1984–1986 examination phase (n = 1,007) were included in the analysis. Endogenous insulin was determined by measurements of plasma C-peptide (in nanomoles per liter), and exogenous insulin was calculated in units per kilogram per day. Glycemic control was determined by levels of glycosylated hemoglobin (HbA_1).

RESULTS — After 16 years of follow-up, 824 individuals died (all-cause mortality); 358 deaths involved ischemic heart disease and 137 involved stroke. C-peptide and HbA_1 were significantly associated with all-cause and ischemic heart disease mortality in our study. The hazard ratio (95% CI) values for all-cause mortality were 1.12 (1.07–1.17) per 1% increase in HbA_1, 1.20 (0.85–1.69) per 1 unit · kg^{-1} · day^{-1} increase in exogenous insulin, and 1.15 (1.04–1.29) per 1 nmol/l increase in C-peptide and for ischemic heart disease mortality were 1.14 (1.06–1.22), 1.50 (0.92–2.46), and 1.19 (1.02–1.39) for HbA_1, exogenous insulin, and C-peptide, respectively, after adjusting for relevant confounders. C-peptide was associated with stroke mortality only among men (1.65 [1.07–2.53]).

CONCLUSIONS — Our results show that individuals with higher endogenous insulin levels are at higher risk of all-cause, ischemic heart disease, and stroke mortality.

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Abbreviations: CVD, cardiovascular disease; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

There has been an interest in investigating the association of high levels of endogenous and exogenous insulin with cardiovascular morbidity and mortality (1–9), particularly after the results of the Diabetes Control and Complications Trial (DCCT), which recommended tight glycemic control in order to decrease the risk of microvascular complications in diabetic individuals (10). The rationale has been based on results from clinical and experimental studies that demonstrated the influence of exogenous insulin on arterial wall changes that ultimately contributed to the development of atherosclerosis (11–13). However, increased levels of endogenous insulin and the use of exogenous insulin have been associated with increased cardiovascular morbidity and mortality in some studies (3,5–7,9) but not in others (2,14,15). The purpose of this study was to investigate the relationship of glycemic control and exogenous and endogenous insulin levels with all-cause and cause-specific mortality (ischemic heart disease and stroke) in an older-onset diabetic population.

RESEARCH DESIGN AND METHODS

— The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is an ongoing, prospective, population-based cohort study of individuals who were receiving care for diabetes in 11 counties in Wisconsin in 1978–1979. A stratified sample of all individuals with diabetes diagnosed at 30 years of age or older was included and was labeled "older-onset" (n = 1,370). The first examination phase was in 1980–1982, and follow-up examinations were performed every 4–6 years. Plasma C-peptide was first measured at the 1984–1986 follow-up visit, which, for the purposes of this report, was considered to be the baseline examination (n = 1,007).

Table 1—*Baseline characteristics of individuals with older-onset diabetes in the 1984–1986 WESDR*

	n	Mean ± SD or %
Age (years)	1,007	68.6 ± 11.0
Duration of diabetes (years)	1,007	15.3 ± 7.9
HbA_1 (%)	980	9.3 ± 1.9
C-peptide (nmol/l)	960	1.0 ± 0.9
Systolic blood pressure (mmHg)	979	143.1 ± 23.3
Diastolic blood pressure (mmHg)	978	75.4 ± 12.3
BMI (kg/m^2)	884	29.1 ± 5.9
Sex (percent male)	1,006	44.9
Insulin use (yes)	1,007	56.4
Cardiovascular disease (present)	990	34.1
Hypertension (present)	991	57.0
Smoking status (current)	1,001	12.9
Diabetic retinopathy (present)	992	66.0

Detailed protocols used in WESDR have been published elsewhere (16,17). Briefly, baseline and all follow-up examinations included detailed medical history with information about cardiovascular disease (CVD) and cigarette smoking and measurements of blood pressure, height, and weight. Nonfasting endogenous insulin was determined by measurement of plasma C-peptide (in nanomoles per liter), and exogenous insulin was calculated in units per kilogram per day. Glycemic control was determined by levels of glycosylated hemoglobin (HbA_1). Stereoscopic seven-field 30° color retinal photographs were taken, and diabetic retinopathy was classified according to a modified Airlie House Classification Scheme (18).

Deaths were ascertained by contacting family members and physicians, review of newspaper obituaries, and use of vital status records. For cause-specific analyses, any mention on the death certificate was considered an event. Causes of death were defined according to the ICD 9th and 10th revisions. Ischemic heart disease mortality was defined according to codes 410.0–414.9 (ICD-9) and I20.0–I25.9 (ICD-10), and stroke mortality was defined according to codes 430.0–438.9 (ICD-9) and I60.0–I69.9 (ICD-10). The survival interval considered in the current analysis was a 16-year period from baseline until death or the date of last contact by 31 December 2002. Of the 1,007 examined, 824 had died, 151 were living as of 31 December 2002, and 32 had their last living contact date before 31 December 2002. The survival interval for the latter group was the period between the baseline examination and the last contact date.

Diabetic retinopathy was defined as the presence of mild (i.e., microaneurysms only, hard or soft exudates, or hemorrhages with or without microaneurysms) or worse retinopathy. A positive history of CVD was defined as having history of angina, heart attack, or stroke. A person was considered hypertensive if systolic or diastolic blood pressure was ≥140 or 90 mmHg, respectively, or using antihypertensive medication. Current smokers were those who had smoked more than 100 cigarettes and continued to smoke until the day of the examination.

Statistical analysis

Age- and sex-adjusted and multivariable analyses were performed. The use of exogenous insulin was analyzed as a binary variable (yes/no) and as a continuous variable (units · kg^{-1} · day^{-1}), and plasma C-peptide (nmol/l) and HbA_1 (%) were analyzed as continuous variables in the whole population. To analyze the influence of the use of exogenous insulin on mortality, we calculated a propensity score that was a conditional probability of receiving insulin given some individual covariates (age, duration of diabetes, levels of HbA_1, BMI, history of CVD, and presence of diabetic retinopathy) in order to decrease the chances of bias by indication (i.e., physicians tend to prescribe insulin to those with poorer glycemic control and therefore at higher risk for developing comorbidities and for death). Propensity score was then added to our regression models, and multivariable analyses were performed with the Cox proportional hazards model. Hazard ratios (HRs) and 95% CIs were estimated, and P values <0.05 were considered significant.

In addition, HbA_1, plasma C-peptide, and exogenous insulin were categorized into tertiles or quartiles. Dummy variables were created and added into multivariable models. It was observed that the magnitude of HRs remained constant for each category increment in all these variables. For example, C-peptide was categorized into tertiles, and changes from one tertile to another showed similar HR values (~1.05); thus, those variables were kept as a continuous variable in our analyses. Analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

The institutional review board approved the study, and consent forms were obtained from all participants. This research was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS — After 16 years of follow-up, 824 individuals died (all-cause mortality); 358 deaths involved ischemic heart disease, and 137 involved stroke. Table 1 shows the characteristics of individuals with older-onset diabetes at baseline. The mean age was 68.6 ± 11.0 years, and 44.9% of the individuals were male.

Age- and sex-adjusted HR showed that HbA_1 was significantly associated with increased all-cause (HR 1.13 [95% CI 1.09–1.17], per 1% increase) and ischemic heart disease mortality (1.14 [1.08–1.21], per 1% increase) (Table 2). Use of exogenous insulin was also associated with increased age- and sex-adjusted all-cause mortality (1.62 [1.41–1.87] comparing those using vs. not using exogenous insulin and 1.70 [1.23–2.34] per 1 unit · kg^{-1} · day^{-1} increase) and ischemic heart disease mortality (1.74 [1.40–2.16] comparing those using vs. not using exogenous insulin and 2.10 [1.32–3.36] per 1 per 1 unit · kg^{-1} · day^{-1} increase). Plasma C-peptide was not significantly associated with all-cause mortality (0.95 [0.87–1.03] per 1 nmol/l increase) and ischemic heart disease mortality (0.96 [0.85–1.09] per 1 nmol/l increase) in the age- and sex-adjusted models.

In multivariable analyses, HbA_1 and C-peptide were significantly associated with all-cause and ischemic heart disease mortality after controlling for potential confounders (age, sex, BMI, duration of diabetes, systolic blood pressure, history

of CVD, diabetic retinopathy status, and smoking) (Table 2). We also assessed the association of HbA_1, plasma C-peptide, and amount of insulin used with mortality stratified by sex in our multivariable analysis. HbA_1 was associated with increased all-cause mortality among both men (HR 1.16 [95% CI 1.08–1.25]) and women (1.09 [1.03–1.15] per 1% increase), with ischemic heart disease mortality among both men (1.24 [1.11–1.38]) and women (1.09 [1.00–1.19]), and with stroke mortality among men only (1.26 [1.10–1.53]). Higher levels of plasma C-peptide were also associated with increased all-cause mortality among women (1.18 [1.03–1.36] per 1 nmol/l increase) and ischemic heart disease mortality (1.43 [1.13–1.83]) and stroke mortality (1.65 [1.07–2.53]) among men (Table 3).

Analysis of a subsample (n = 369) showed that the inclusion of serum lipids in our multivariable models did not change the positive association of endogenous insulin (HR 1.12 [95% CI 0.96–1.32] for all-cause and 1.09 [0.87–1.38] for ischemic heart disease) or exogenous insulin (1.17 [0.87–1.57] for all-cause and 1.18 [0.75–1.84] for ischemic heart disease mortality).

Table 2—*Association of glycemic control, C-peptide, and exogenous insulin with all-cause and cause-specific mortality*

	All-cause mortality		Ischemic heart disease mortality		Stroke	
	Age-sex adjusted	Multivariable	Age-sex adjusted	Multivariable	Age-sex adjusted	Multivariable
HbA_1 (per 1%)	1.13 (1.09–1.17)	1.12 (1.07–1.17)	1.14 (1.08–1.21)	1.14 (1.06–1.22)	1.08(0.98–1.18)	1.11 (0.99–1.23)
C-peptide (per 1 nmol/l)	0.95 (0.87–1.03)	1.15 (1.04–1.29)	0.96 (0.85–1.09)	1.19 (1.02–1.39)	0.96(0.79–1.16)	1.09 (0.85–1.40)
Exogenous insulin (yes/no)	1.62 (1.41–1.87)	1.12 (0.93–1.35)	1.74 (1.40–2.16)	1.06 (0.80–1.42)	1.61(1.13–2.28)	1.28 (0.81–2.02)
Exogenous insulin (per 1 unit · kg^{-1} · day^{-1})	1.70 (1.23–2.34)	1.20 (0.85–1.69)	2.10 (1.32–3.36)	1.50 (0.92–2.46)	0.90(0.37–2.14)	0.73 (0.29–1.79)

Data are HR (95% CI). Multivariable models included *1)* for HbA_1: age, sex, BMI, diabetes duration, systolic blood pressure, history of CVD, presence of diabetic retinopathy, cigarette smoking, plasma C-peptide, and exogenous insulin use; *2)* for exogenous insulin: sex, systolic blood pressure, smoking status, plasma C-peptide, and propensity score; *3)* For plasma C-peptide: age, sex, BMI, diabetes duration, systolic blood pressure, history of CVD, presence of diabetic retinopathy, cigarette smoking, time since last meal, exogenous insulin use, and HbA_1.

CONCLUSIONS — The WESDR provides a unique opportunity to investigate long-term longitudinal associations of risk factors due to its population-based design and length of follow-up. Our results showed that higher levels of endogenous insulin, measured by plasma levels of C-peptide at baseline, and HbA_1 were associated with increased risk of all-cause and CVD mortality among individuals with older-onset diabetes.

In our study, exogenous insulin was associated with all-cause and ischemic heart disease mortality independently of HbA_1 level. Our results are consistent with data from previous population-based studies investigating the association of endogenous insulin and mortality (6,7,19). However, most of these studies were done in the general population. In a population-based study in Finland, hyperinsulinemia had a modest association with increased cardiovascular mortality in middle-aged men (7). In a meta-analysis, Hu et al. (6) evaluated 11 European studies and concluded that plasma fasting insulin levels were associated with a 1.5-times increased chance of CVD mortality in men and ~2.7 in women after controlling for potential confounders.

In the Atherosclerosis Risk in Communities (ARIC) study, higher levels of endogenous insulin were significantly associated with increased thickness of the carotid artery wall in both men and women (20). It is believed that insulin stimulates smooth muscle cell proliferation in arterial walls and increases lipid synthesis and, as a consequence, leads to the formation of lipid lesions in arterial tissues (12). Insulin is also associated with the activation of plasminogen activator inhibitor-1, which is involved in the development of thrombosis (21).

In our study, higher levels of plasma C-peptide were also associated with increased risk of death involving stroke among men. In the ARIC study (22), elevated fasting insulin concentrations were also associated with up to a 19% increase in ischemic stroke incidence.

We found positive relationships between exogenous insulin use and mortality in our age- and sex-adjusted models. However, the use of exogenous insulin could have been targeted more to those at higher risk of developing complications and possibly with higher risk of death. Thus, the significant associations observed in the age- and sex-adjusted models were no longer statistically significant after the adjustment for several confounders and the propensity score. Although some studies showed positive associations between the use of exogenous insulin and the development of CVD, findings from randomized controlled clinical trials showed that the benefits of tight glycemic control in reducing the risk of long-term complications of diabetes (i.e., retinopathy, nephropathy, and neuropathy) outweigh the possible harmful effects of exogenous insulin treatment (13,23). The University Group Diabetes Program showed no evidence that insulin treatment influenced the risk of CVD or mortality (24) in individuals with type 2 diabetes. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term follow-up of the DCCT, reported a slower rate of progression of arterial wall thickness (25) and a 42% reduced risk of cardiovascular events (26) in the intensive therapy group compared with the group under conventional treatment among type 1 diabetic patients. In the UK Prospective Diabetes Study (UKPDS), there was no increase in rates of myocardial infarction among participants assigned to receive either insulin therapy or sulfonylurea compared with those under conventional therapy (diet)

Table 3—*Association of glycemic control, C-peptide, and exogenous insulin with all-cause and cause-specific mortality stratified by sex*

	All-cause mortality		Ischemic heart disease mortality		Stroke	
	Men	Women	Men	Women	Men	Women
HbA_1 (per 1%)	1.16 (1.08–1.25)	1.09 (1.03–1.15)	1.24 (1.11–1.38)	1.09 (1.00–1.19)	1.26 (1.04–1.53)	1.02 (0.89–1.18)
C-peptide (per 1 nmol/l)	1.19 (0.99–1.41)	1.18 (1.03–1.36)	1.43 (1.13–1.83)	1.09 (0.88–1.36)	1.65 (1.07–2.53)	0.99 (0.71–1.39)
Exogenous insulin (yes/no)	0.92 (0.70–1.21)	1.35 (1.04–1.75)	0.94 (0.62–1.43)	1.23 (0.83–1.84)	0.95 (0.44–2.02)	1.52 (0.85–2.73)
Exogenous insulin (per 1 unit $\cdot$ $kg^{-1} \cdot day^{-1}$)	1.05 (0.53–2.09)	1.25 (0.84–1.85)	1.21 (0.45–3.23)	1.62 (0.92–2.86)	0.10 (0.01–1.01)	1.05 (0.42–2.63)

Data are HR (95% CI). Multivariable models included *1*) for HbA_1: age, sex, BMI, diabetes duration, systolic blood pressure, history of CVD, presence of diabetic retinopathy, cigarette smoking, plasma C-peptide, and exogenous insulin use; 2) for exogenous insulin: sex, systolic blood pressure, smoking status, plasma C-peptide, and propensity score; 3) for plasma C-peptide: age, sex, BMI, diabetes duration, systolic blood pressure, history of CVD, presence of diabetic retinopathy, cigarette smoking, time since last meal, exogenous insulin use, and HbA_1.

(27). However, hyperglycemia was associated with increased risk of myocardial infarction in that study (28), providing further evidence of the benefits of tight glycemic control.

One of the major concerns regarding the role of endogenous or exogenous insulin as a predictor of CVD has been their close association with other important risk factors for CVD such as obesity, dyslipidemia, and hypertension (29). Després et al. (19) reported that hyperinsulinemia was an independent risk factor for incident ischemic heart disease in the Quebec Cardiovascular Study, after controlling for these variables. In our study, adjustments for potential confounders, as well as the role of glycemic control, were addressed in our multivariable analysis. However, residual confounding is always a concern. We did not adjust for levels of serum lipids in our analysis because serum levels of cholesterol and HDL were only measured in a subsample of this cohort ($n = 369$) during this second examination phase. Analysis of this subsample showed that the inclusion of lipid profile in our multivariable models did not change the positive association between endogenous or exogenous with all-cause and ischemic heart disease mortality. These associations were not statistically significant possibly due to the smaller sample size. In addition, the need to have insulin therapy and the higher levels of endogenous insulin might reflect underlying insulin resistance, which is also known to be associated with some CVD risk factors such as atherosclerosis, dyslipidemia, and hypertension (8,30).

Another possible limitation might be due to loss to follow-up in the 4-year interval between the between the first and second examination phases. Because we used the second follow-up visit as baseline, if death (our main cause of loss to follow-up) was associated with insulin levels or use of exogenous insulin, we might have underestimated the strength of the association reported. In addition, women had a lower number of events (i.e., deaths) than men, and therefore low power might have also influenced our ability to detect associations among female participants.

Future reports from clinical trials such as the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial (31), with longer follow-up, may lead to a better understanding of the influence of insulin in cardiovascular morbidity and mortality. Our results support the idea that individuals with higher endogenous insulin levels should be closely followed due to their higher risk of all-cause and ischemic heart disease mortality.

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