Published in final edited form as:
Diabetes Care. 2008 March ; 31(3): 493–497. doi:10.2337/dc07-1161.

The Relationship of Glycemic Control, Exogenous Insulin, and C-peptide Levels to Ischemic Heart Disease Mortality Over a 16-year period in Persons with Older-Onset Diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Abstract

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 is an ongoing prospective population-based cohort study of individuals with diabetes first examined in 1980–82. A stratified sample of all individuals with diabetes diagnosed at 30 years of age or older were labeled “older-onset” (n=1370). Those participating in the 1984–86 examination phase (n=1007) were included in the analysis. Endogenous insulin was determined by measurements of plasma c-peptide (nmol/l) and exogenous insulin was calculated in units/kg/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. Hazard ratios (95% CI) 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/day increase in exogenous insulin, and 1.15 (1.04–1.29) per 1 nmol/l increase in c-peptide. For ischemic heart disease mortality: 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.

Keywords

insulin; c-peptide; type 2 diabetes mellitus; epidemiology; survival

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

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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 have 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 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

Study Population

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is an ongoing prospective population-based cohort study of individuals who were receiving care for their diabetes in 11 counties in Wisconsin in 1978–79. A stratified sample of all individuals with diabetes diagnosed at 30 years of age or older was included and was labeled “older-onset” (n=1370). The first examination phase was in 1980–82 and follow-up examinations were performed every 4–6 years. Plasma c-peptide was first measured at the 1984–86 follow-up visit which, for the purposes of this report, was considered to be the baseline examination (n=1007).

Procedures

Detailed protocols used in WESDR were published elsewhere (16,17). Briefly, baseline and all follow-up examinations included detailed medical history with information about cardiovascular disease and cigarette smoking, and measurements of blood pressure, height, and weight. Nonfasting endogenous insulin was determined by measurement of plasma c-peptide (nmol/l) and exogenous insulin was calculated in units/kg/day. Glycemic control was determined by levels of glycosylated hemoglobin (HbA_1). Stereoscopic 7-field 30° color retinal photographs were taken, and diabetic retinopathy (DR) 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 International Classification of Diseases (ICD) 9^{th} and 10^{th} 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 December 31, 2002. Of the 1007 examined, 824 had died, 151 were living as of December 31, 2002, and 32 had their last living contact date before December 31, 2002. The survival interval for the latter group was the period between the baseline examination and the last contact date.

Definitions

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 cardiovascular disease was defined as having history of angina, heart attack,

or stroke. A person was considered hypertensive if systolic or diastolic blood pressure was above or equal 140 or 90 mmHg, respectively, or using anti-hypertensive 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-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/day); plasma c-peptide (nmol/l) and HbA_1 (%) were analyzed as a continuous variable in the whole population. To analyze the influence of the use of exogenous insulin in mortality, we calculated a propensity score which was a conditional probability of receiving insulin given some individual's covariates (age, duration of diabetes, levels of glycosylated hemoglobin, body-mass index, history of cardiovascular disease, 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 of developing comorbidities and of death). Propensity score was then added to our regression models and multivariable analyses were performed with the Cox Proportional Hazards Model. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated and p values less than 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 hazard ratios 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 hazard ratio values (approximately 1.05); thus, those variables were kept as a continuous variable in our analyses. Analyses were performed in SAS v.9 (SAS Institute, Cary, NC, USA).

The Institutional Review Board approved the study and consent forms were obtained from all participants. This research was conducted in accordance to 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 hazard ratios (HR) showed that HbA_1 was significantly associated with increased all-cause (HR and 95% CI, 1.13 (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 (1.62 (1.41–1.87), comparing those using vs not using exogenous insulin; 1.70(1.23–2.34), per 1 units/kg/day increase) and ischemic heart disease mortality (1.74 (1.40–2.16), comparing those using vs not using exogenous insulin; 2.10 (1.32–3.36), per 1 unit/kg/day increase). Plasma c-peptide was not significantly associated with all-cause (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, body-mass index, duration of diabetes, systolic blood pressure, history of cardiovascular disease,

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 gender in our multivariable analysis. HbA_1 was associated with increased all-cause mortality among men (1.16 (1.08–1.25)) and women 1.09 (1.03–1.15), per 1% increase), with ischemic heart disease mortality among men (1.24 (1.11–1.38)) and women (1.09 (1.00–1.19)) and with stroke mortality among men (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 sub-sample (n=369) showed that the inclusion of serum lipids in our multivariable models did not change the positive association of endogenous (HR and 95% CI, 1.12 (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).

Conclusions

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 cardiovascular disease (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 levels. 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 eleven European studies and concluded that plasma fasting insulin levels were associated with 1.5 times increased chance of CVD mortality in men and about 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. Also 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 persons 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 event (26) in the intensive therapy group compared to the group under conventional treatment among type 1 diabetic patients. In the United Kingdom Prospective Diabetes Study (UKPDS), there was no increase in rates of myocardial infarction among participants assigned to receive either insulin therapy or sulphonylurea compared to those under conventional therapy (diet) (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 measured only in a sub-sample of this cohort (n=369) during this second examination phase. Analysis of this sub-sample 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.

Acknowledgments

We are indebted to the WESDR cohort participants and physicians and their staff for their continued support and participation since 1980.

This work was partially presented at the American Diabetes Association's 66th Scientific Sessions, Washington DC, June 9–13, 2006.

Funding/Support: This work was supported, in part, by research grants EY016379 (Klein R, Klein BEK) from the National Institutes of Health, Bethesda, MD, and by the Mentor-Based Postdoctoral Fellowship Award to Dr. Klein from the American Diabetes Association, Alexandria, VA.

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Table 1

Baseline Characteristics of Individuals with Older-Onset Diabetes Taking Exogenous Insulin.

Characteristic	N	Mean (SD) or %
Age, years	1007	68.6 ± 11.0
Duration of diabetes, years	1007	15.3 ± 7.9
Glycosylated hemoglobin, %	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
Body-mass index, kg/m^2	884	29.1 ± 5.9
Sex, male	1006	44.9
Insulin use, yes	1007	56.4
Cardiovascular disease, present	990	34.1
Hypertension, present	991	57.0
Smoking status, current	1001	12.9
Diabetic retinopathy, present	992	66.0

SD=standard deviation

Table 2

Hazard Ratios and 95% Confidence Interval of the Association of Glycemic Control, C-Peptide, and Exogenous Insulin with All-Cause and Cause-Specific Mortality.

	All-cause		Ischemic Heart Disease		Stroke	
	Age-sex adjusted HR and 95% CI	Multivariable HR and 95% CI	Age-sex adjusted HR and 95% CI	Multivariable HR and 95% CI	Age-sex adjusted HR and 95% CI	Multivariable HR and 95% CI
Glycosylated hemoglobin, 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/day	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)

HR=hazard ratio; CI=confidence interval

Multivariable models included:

1. For glycosylated hemoglobin: age, sex, BMI, diabetes duration, systolic blood pressure, history of cardiovascular disease, 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 cardiovascular disease, presence of diabetic retinopathy, cigarette smoking, time since last meal, exogenous insulin use, and glycosylated hemoglobin.

Table 3

Multivariable-Adjusted Hazard Ratios and 95% Confidence Interval of the Association of Glycemic Control, C-Peptide, and Exogenous Insulin with All-Cause and Cause-Specific Mortality Stratified by Gender.

	All-cause		Ischemic Heart Disease		Stroke	
	Men	Women	Men	Women	Men	Women
	HR and 95% CI	HR and 95% CI	HR and 95% CI	HR and 95% CI	HR and 95% CI	HR and 95% CI
Glycosylated hemoglobin, 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/kg/day	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)

HR=hazard ratio; CI=confidence interval

Multivariable models included:

1. For glycosylated hemoglobin: age, sex, BMI, diabetes duration, systolic blood pressure, history of cardiovascular disease, 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 cardiovascular disease, presence of diabetic retinopathy, cigarette smoking, time since last meal, exogenous insulin use, and glycosylated hemoglobin.