

Effect of Youth-Onset Type 2 Diabetes Mellitus on Incidence of End-Stage Renal Disease and Mortality in Young and Middle-Aged Pima Indians

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THE CURRENT INCREASE IN obesity prevalence in children and adolescents in many parts of the world has led to an increasing prevalence of type 2 diabetes mellitus in these age groups. In the United States, the prevalence of type 2 diabetes mellitus in children is expected to exceed that of type 1 diabetes mellitus within the next 10 years.^{1,2} Many children with type 2 diabetes mellitus have a strong family history of type 2 diabetes mellitus and are the offspring of mothers with pregestational or gestational diabetes mellitus.³ Although only 3% of type 2 diabetes mellitus develops in persons younger than age 20 years,⁴ individuals who develop type 2 diabetes mellitus in childhood and adolescence are affected in early adulthood by the microvascular complications of diabetes mellitus.⁵ In Pima Indians, youth-onset type 2 diabetes mellitus is associated with a lower frequency of retinopathy for a given duration of diabetes mellitus than adult-onset type 2 diabetes mellitus, but with a similar frequency of overt nephropathy (protein to creatinine ratio ≥ 0.5 g/g), suggesting that youth does not offer the same protection from progressive diabetic kidney disease as it does

Context The long-term outcome of persons with youth-onset type 2 diabetes mellitus has not been well described.

Objective To compare incidence of diabetic end-stage renal disease (ESRD) and mortality in Pima Indians with youth- and older-onset type 2 diabetes mellitus.

Design, Setting, and Participants Longitudinal population-based study conducted between 1965 and 2002 in Pima Indians from the state of Arizona. Participants were divided into 2 groups: (1) youth-onset type 2 diabetes mellitus (onset < 20 years of age) and (2) older-onset type 2 diabetes mellitus (onset ≥ 20 - < 55 years of age). Events and person-years of follow-up were stratified in a time-dependent fashion by decades of age. End-stage renal disease was defined as dialysis attributed to diabetic nephropathy or death from diabetic nephropathy.

Main Outcome Measures Incidence rate of diabetic ESRD and mortality between 25 and 55 years of age, according to age at onset of type 2 diabetes mellitus.

Results Among the 1856 diabetic participants, 96 had youth-onset type 2 diabetes mellitus. The age-sex-adjusted incidence of diabetic ESRD was 25.0 cases per 1000 person-years (95% confidence interval [CI], 6.7-43.1) in youth-onset diabetes mellitus and 5.4 cases per 1000 person-years (95% CI, 4.4-6.4) in older-onset diabetes mellitus (incidence rate ratio, 4.6; 95% CI, 2.2-9.8). Age-specific incidence rates were higher in participants with youth-onset diabetes mellitus at all ages. Between 25 and 55 years of age, the age-sex-adjusted death rate from natural causes was 15.4 deaths per 1000 person-years (95% CI, 0.2-30.5) in participants with youth-onset diabetes mellitus and 7.3 deaths per 1000 person-years (95% CI, 5.9-8.7) in individuals with older-onset diabetes mellitus (death rate ratio, 2.1; 95% CI, 0.8-5.7). Compared with nondiabetic participants, the death rate was 3.0 times as high in individuals with youth-onset diabetes mellitus (95% CI, 1.1-8.0) and 1.4 times as high in individuals with older-onset diabetes mellitus (95% CI, 1.1-1.8). In a subset of 1386 participants with complete data for all covariates who were observed from the onset of diabetes mellitus, the age at onset of diabetes mellitus was not associated with the incidence of ESRD (hazard ratio, 1.0; 95% CI, 0.9-1.2) after adjusting for sex, mean arterial pressure, body mass index (calculated as weight in kilograms divided by height in meters squared), plasma glucose concentration, smoking, hypoglycemic medicines, and blood pressure medicines in a Cox proportional-hazards model.

Conclusions Early-onset type 2 diabetes mellitus is associated with substantially increased incidence of ESRD and mortality in middle age. The longer duration of diabetes mellitus by middle age in individuals diagnosed younger than age 20 years largely accounts for these outcomes.

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from diabetic retinopathy.⁵ This finding may have a significant economic and public health impact because individuals with youth-onset diabetes mellitus who develop diabetic kidney disease may have high morbidity during their peak productive years and may require increased and sustained health services.

Pima Indians have a very high prevalence and incidence of type 2 diabetes mellitus, and the prevalence of type 2 diabetes mellitus in youth has doubled between 1967 and 1998.⁶ Kidney disease is a major complication of diabetes mellitus in this population, with 93% of end-stage renal disease (ESRD) attributable to diabetes mellitus.⁷ In this study we examined the impact of age at onset of type 2 diabetes mellitus on the incidence of ESRD and on natural causes of death in young and middle-aged Pima Indians.

METHODS

Research Design

Members of the Gila River Indian Community participated in a longitudinal study of diabetes mellitus and its complications. This study was approved by the review board of the National Institute of Diabetes and Digestive and Kidney Diseases and by the Tribal Council of the Gila River Indian Community. Each participant gave informed consent.

Since 1965, each person older than 5 years of age was invited to participate in a research examination approximately every 2 years, regardless of health status. These examinations included measurements of venous plasma glucose concentration obtained 2 hours after a 75-g oral glucose load, measurement of height and weight, and assessment for the complications of diabetes mellitus. All participants, including the 1 child who weighed less than 42 kg at the research examination, received the 75-g oral glucose load. Diabetes mellitus was diagnosed by the 1985 World Health Organization criteria.⁸ Date of diagnosis and age of onset were determined from these research examinations or from review of clinical records if diabetes mellitus was diagnosed in the course of routine medi-

cal care. Mean arterial pressure was calculated as equal to two thirds of the diastolic arterial pressure plus one-third the systolic arterial pressure. Usage of medication and smoking habits were assessed by interviewer-administered questionnaires. Current smoking was defined as cigarette smoking in any amount during the past year. Previous smokers, who reported no smoking during the past year, were included in the nonsmoking category.

Study Population

The study population included Pima Indians and the closely related Tohono O'odham (Papago) Indians who resided in the community during follow-up and attended 1 or more research examinations when they were between the ages of 25 and 55 years. We limited the analysis of ESRD and mortality to young- and middle-aged Pima Indians, as there were insufficient data to compute adjusted incidence rates in the youth-onset group older than age 55 years and in the older-onset group younger than age 25 years. The underlying causes of death were determined by review of clinical records, autopsy reports, and death certificates.

Five participants diagnosed with diabetes in the course of routine medical care were not included in the analysis of ESRD incidence because they had no research examination between the date of diabetes diagnosis and the onset of dialysis. Three of these participants developed ESRD due to diabetic nephropathy and 2 to causes other than diabetic nephropathy. The causes of ESRD were determined by review of clinical records.

Terminology and codes of the *International Classification of Diseases, Ninth Revision (ICD-9)* were used for recording causes of death. Deaths were considered natural if they were due to disease (ICD-9 codes 001.0-799.9) and external if they were due to injury or poisoning (ICD-9 codes 800.0-999.9).

Statistical Analysis

The incidence rates of diabetic ESRD and death were computed as the number of new cases per 1000 person-

years at risk. The date of ESRD was defined as the date of initiation of dialysis or the date of death from diabetic nephropathy if dialysis was refused or not available. The period of risk began at age 25 years in participants with a previous diabetic examination or the first diabetic examination after this age in individuals with no previous research examinations. The period of risk for the mortality analysis ended with death, the 55th birthday, or December 31, 2002, whichever came earliest. For the ESRD analysis, follow-up ended at the date of ESRD, the 55th birthday, date of death, or December 31, 2002, whichever came first. For 8 participants who developed ESRD due to causes other than diabetes mellitus, follow-up ended when dialysis began, but they were not counted as cases. Incidence rates of ESRD and death were stratified in a time-dependent fashion, according to decades of age, as follows: (1) youth-onset diabetes mellitus, ie, participants diagnosed with diabetes when younger than aged 20 years; (2) older-onset diabetes, ie, participants diagnosed with diabetes mellitus between the ages of 20 and 55 years.

Nondiabetic participants aged 25 to 55 years were included in the analysis of death rates for comparison with the 2 diabetes mellitus groups. The nondiabetic period of risk began at age 25 years or the first research examination after this age and ended with death, the 55th birthday, the development of diabetes, or December 31, 2002, whichever came earliest.

Age-sex-adjusted incidence rates and incidence rate ratios were standardized to the 1985 Pima Indian population that was aged 25 to 55 years. Tests for general association were computed by the Mantel-Haenszel test⁹ and for linear association by the Mantel extension test¹⁰ modified for person-years denominators.¹¹

Unadjusted cumulative incidence of ESRD and mortality were estimated by the Kaplan-Meier method in a subset of 1684 participants in whom follow-up were available from the diagnosis of diabetes mellitus to an event or December

2002. Differences in the Kaplan-Meier curves were assessed by the log-rank test. The effect of age at onset of diabetes mellitus as a continuous variable was then examined in 1386 of these participants who had complete data for all covariates by using a Cox proportional hazards analysis adjusted for sex and baseline values of mean arterial pressure, body mass index (calculated as weight in kilograms divided by height in meters squared), 2-hour postload plasma glucose concentration, antihypertensive medication, hypoglycemic medication, and smoking. The final model for ESRD was stratified by hypoglycemic medication and the final model for natural mortality was stratified by tertiles of mean arterial pressure, as these covariates violated the proportionality assumption. Statistical analyses were performed using SAS System for Windows, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

Among 1856 participants with type 2 diabetes mellitus (767 men and 1089 women), 96 had youth-onset diabetes mellitus and 1760 had older-onset diabetes mellitus. Youth-onset diabetes mellitus was diagnosed in children as young as 3.5 years (median, 16.8 years). During follow-up, 148 progressed to ESRD: 15 (16%) of those with youth-onset diabetes mellitus and 133 (8%) with older-onset diabetes mellitus. The sex-adjusted incidence rate of ESRD in youth-onset diabetes mellitus was 8.4 times as high (95% confidence interval [CI], 1.5-46.0) as in older-onset diabetes mellitus for ages 25 to 34 years, 5.0 times as high (95% CI, 2.2-11.3) for ages 35 to 44 years, and 4.0 times as high (95% CI, 1.2-13.6) for ages 45 to 54 years (FIGURE 1). The age-sex-adjusted ESRD incidence in youth-onset diabetes mellitus was 25.0 cases per 1000 person-years (95% CI, 6.7-43.1) and in older-onset diabetes mellitus was 5.4 cases per 1000 person-years (95% CI, 4.4-6.4; incidence rate ratio, 4.6; 95% CI, 2.2-9.8).

To further explore differences in outcomes between the youth- and older-

onset groups, death rates were computed and compared with those in 4189 nondiabetic participants. TABLE 1 shows baseline characteristics of participants. Of 594 deaths, 337 were from natural causes: 167 in participants without diabetes mellitus, 8 in participants with youth-onset diabetes mellitus, and 162 in individuals with older-onset diabetes mellitus. In the nondiabetic participants, the most prevalent underlying cause of death was alcoholic liver disease. By contrast, more than half of the diabetic participants died from diabetic nephropathy, cardiovascular disease, or infections, regardless of the age at onset of diabetes mellitus (TABLE 2). FIGURE 2 presents age-specific death rates in the 3 groups. As expected, nondiabetic participants had the lowest death rates. The age-sex-adjusted death rate in participants with youth-onset diabetes mellitus was 3.0 times as high (95% CI, 1.1-8.0) as in nondiabetic participants and 2.1 times as high (95% CI, 0.8-5.7) as in individuals with older-onset diabetes mellitus. The death rate in individuals with older-onset diabetes mellitus was 1.4 times as high (95% CI, 1.1-1.8) as in the nondiabetic participants.

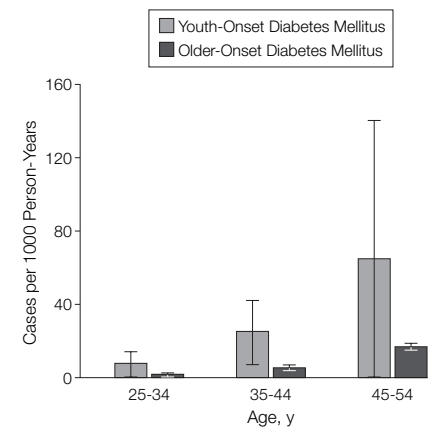
FIGURE 3 compares the unadjusted cumulative incidence of diabetic ESRD and mortality by duration of diabetes according to age at onset. In this subset of 1684 participants (87 with youth-onset and 1597 with older-onset diabetes mellitus), 227 participants developed ESRD (n=9 with youth-onset diabetes mellitus), and 305 died from natural causes (n=4 with youth-onset diabetes mellitus). The cumulative incidence of both these outcomes

increased with duration of diabetes, but for the same duration of diabetes, participants in the youth-onset group had a significantly lower risk of ESRD ($P=.007$) and death ($P<.001$) than those in the older-onset group. After adjustment for baseline covariates in a Cox proportional hazards model, there was no association between age at onset of diabetes mellitus and ESRD (hazard ratio, 1.0; 95% CI, 0.9-1.2). By contrast, natural mortality was 1.7 times as high with each 10-year increase in the age at onset of diabetes mellitus (hazard ratio, 1.7; 95% CI, 1.5-2.0).

COMMENT

Diabetes in Pima Indian children and adolescents is entirely type 2 diabetes mellitus and it is characterized by the lack

Figure 1. Sex-Adjusted Incidence and 95% Confidence Intervals of Diabetic End-Stage Renal Disease by Onset of Diabetes and Age Group



Person-years at risk were counted from the first diabetic examination or the 25th birthday, whichever occurred later.

Table 1. Characteristics of Participants by Diabetes Mellitus Category

Characteristic	No Diabetes Mellitus*	Youth-Onset Diabetes Mellitus	Older-Onset Diabetes Mellitus
Participants, No.	4189	96	1760
Men	2001	36	767
Women	2188	60	1089
Baseline age, median (range), y	25.0 (25.0-54.9)	25.0 (25.0-48.7)	36.9 (25.0-54.9)
Baseline diabetes mellitus duration, median (range), y	NA	8.3 (5.0-33.2)	1.3 (0-23.2)

Abbreviation: NA, not applicable.

*Of these participants, 1060 were also included in the older-onset diabetes mellitus group after they developed diabetes mellitus.

Table 2. No. of Deaths And Death Rates for Underlying Causes in Pima Indians Aged 25 to 55 Years

Underlying Cause of Death (ICD-9 Codes)	Nondiabetic (n = 4189)		Youth-Onset Diabetes Mellitus (n = 96)		Older-Onset Diabetes Mellitus (n = 1760)	
	Deaths, No.	Death Rate (95% Confidence Interval)*	Deaths, No.	Death Rate (95% Confidence Interval)*	Deaths, No.	Death Rate (95% Confidence Interval)*
Cardiovascular disease (410.0-414.9, 431.0-437.9)	5	0.2 (0-0.4)	1	5.3 (0-15.6)	32	1.1 (0.7-1.5)
Diabetic nephropathy (250.4)	2†	0.1 (0-0.2)	4	3.1 (0.4-6.2)	36	1.4 (0.9-1.8)
Infections‡	15	0.5 (0.2-0.7)	3	6.9 (0-17.5)	21	0.9 (0.4-1.3)
Malignancy (140.0-208.9)	18	0.6 (0.3-0.9)	0	0	12	0.5 (0.2-0.9)
Alcoholic liver disease (571.0-571.3)	67	2.0 (1.5-2.6)	0	0	26	1.4 (0.7-2.0)
Other natural§	60	1.8 (1.3-2.3)	0	0	35	2.2 (1.2-3.1)
All natural	167	5.2 (4.4-6.0)	8	15.4 (0.2-30.5)	162	7.3 (5.9-8.8)
All external (800.0-999.9)	194	4.8 (4.1-5.5)	3	3.2 (0-7.1)	60	5.4 (3.7-7.1)
Suicide (950.0-959.9)	26	0.6 (0.3-0.8)	0	0	5	0.6 (0-1.2)
All causes	361	10.0 (8.9-11.1)	11	18.6 (3.0-34.2)	222	12.7 (10.5-14.9)

Abbreviation: NA, not applicable; ICD-9, International Classification of Diseases, Ninth Revision.

*Age-sex-adjusted, presented as deaths per 1000 person-years.

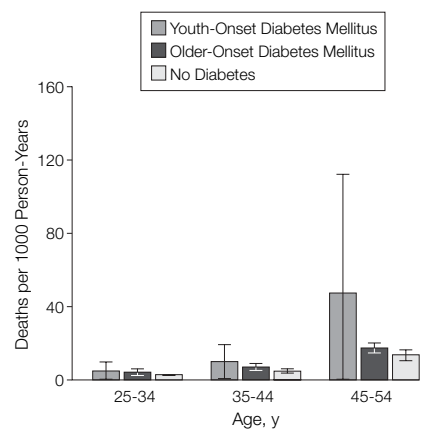
†The 2 participants who died from diabetic nephropathy and were classified as nondiabetic developed diabetes after their last research examination. For consistency with our definition of diabetes, which is based on data from research examinations, these participants remained in the nondiabetic group.

‡ICD-9 codes 001.0-139.8; 320.0-326.9; 460.0-466.1; 480.0-487.8; 540.0-543.9; 572.0; 599.0-590.9; 599.0; 680.0-686.9; 729.4.

§Includes deaths from cardiovascular diseases other than ischemic heart disease and stroke, from other diabetic causes, and from other natural causes.

||Deaths due to injury or poisoning.

Figure 2. Sex-Adjusted Death Rates and 95% Confidence Intervals From Natural Causes by Age Group in the 3 Groups



Person-years at risk were counted from the first diabetic examination or the 25th birthday, whichever occurred later.

of insulin dependence,¹² absent or low levels of islet cell¹³ and glutamic acid decarboxylase antibodies,¹⁴ and absence of strong linkage or association with maturity-onset diabetes of youth loci.¹⁵⁻¹⁷ Onset of type 2 diabetes mellitus in participants younger than age 20 years was associated with a nearly 5-fold increase in the incidence of ESRD in Pima Indians between 25 and 54 years of age, compared with a later onset of diabetes melli-

tus. The incidence of ESRD and mortality increased with age and with duration of diabetes mellitus, but duration of diabetes mellitus was the stronger of these 2 determinants of ESRD incidence. Hence, serious long-term complications of diabetes mellitus in midlife are due to the longer duration of diabetes mellitus for a given age in the youth-onset group. Indeed, an equivalent duration of type 2 diabetes mellitus in a young person is as damaging to the kidneys as it is in an older person. These findings are compatible with the previous observation of similar duration-specific incidence rates of proteinuria in Pima Indians with youth- and adult-onset diabetes mellitus.⁵ Although the number of events in the participants with youth-onset diabetes mellitus is small, these participants were observed for up to 30 years and represent the longest and most complete follow-up of youth-onset diabetes mellitus reported to date. Although susceptibility to diabetic kidney disease differs by ethnicity,¹⁸ the rise in childhood type 2 diabetes mellitus in many different ethnic groups is likely to increase the frequency of kidney disease in these populations.

Information on long-term outcomes of persons with childhood onset type 2 diabetes mellitus in other

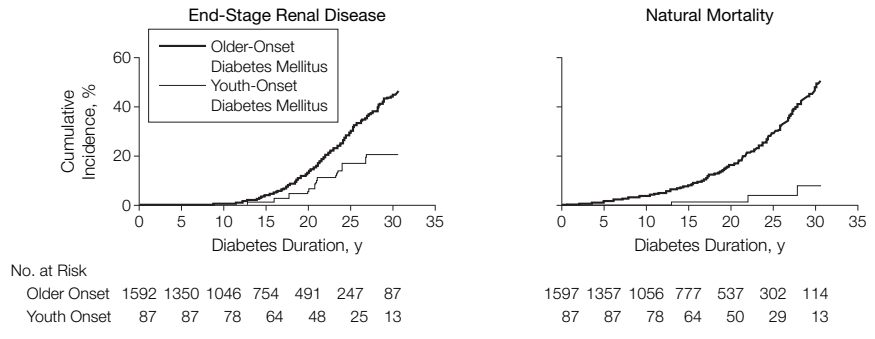
populations is very limited because of the small number of cases and the absence of long-term follow-up of young adults in whom type 2 diabetes mellitus is clearly differentiated from type 1 diabetes mellitus.⁴ The Multinational Study of Vascular Disease in Diabetes¹⁹ reported that American Indians (including Pimas) from Arizona and Oklahoma who were diagnosed with type 2 diabetes mellitus at an age younger than 30 years had a higher age-adjusted incidence rate of albuminuria, proteinuria, and kidney failure during a mean follow-up of 9.5 years than the Asian and European diabetic populations²⁰ with onset of type 2 diabetes mellitus at the same age. The different rates may reflect genetic, environmental, and risk factor differences among ethnic groups or countries. In a study of long-term micro- and macrovascular complications in Japanese participants with onset of type 2 diabetes mellitus aged younger than 30 years,^{21,22} 5% of the participants had ESRD after 20 years duration of diabetes and 23% of individuals who had proliferative retinopathy progressed to dialysis by age 35 years (mean). Atherosclerotic vascular disease, including cerebrovascular, cardiac, and peripheral artery disease, was the leading cause of death in

this Japanese population and was largely related to poor glycemic control and progression to ESRD.

The higher rates of ESRD in young- and middle-aged adults with youth-onset diabetes mellitus may contribute to a rise in cardiovascular complications in these age groups.^{23,24} Indeed, the effect of youth-onset diabetes mellitus on cerebral and coronary artery diseases may be quite profound. In a large predominantly white population, adults with onset of diabetes between 18 and 44 years of age had 8 times the incidence rate of cardiovascular complications than nondiabetic age- and sex-matched control participants, whereas, individuals with onset of diabetes at an age older than 45 years had 4 times the rate.²⁵ Cardiovascular disease mortality is lower in diabetic Pima Indians than in the white population²⁶ and occurs most frequently in association with kidney failure.²⁴ In this study the only cardiovascular disease death in the youth-onset diabetes group occurred in a patient receiving dialysis. Among participants with older-onset diabetes mellitus, 48% of the cardiovascular disease deaths occurred in individuals receiving dialysis and another 32% in individuals with earlier stages of kidney disease, confirming that among Pima Indians fatal cardiovascular disease occurs predominantly in individuals with kidney disease regardless of age at onset of diabetes mellitus.

Follow-up began at 25 years of age, so survival bias among individuals with youth-onset diabetes mellitus could influence our findings if those with more severe youth-onset diabetes mellitus died before reaching 25 years of age. However, all 7 deaths occurring before 25 years of age in individuals with youth-onset diabetes mellitus were due to external causes, particularly injuries, suggesting that survival bias was not a factor. With the exception of age at menarche in girls, no specific measures of puberty are collected in Pima Indians in the longitudinal study, so we were unable to assess the effect of puberty on progression of kidney disease. Nevertheless, only 2.6% of the follow-up to 25 years of age in the youth-onset group oc-

Figure 3. Cumulative Incidence of Diabetic End-Stage Renal Disease and Cumulative Natural Mortality



For any duration category, participants with youth-onset type 2 diabetes have a lower risk of diabetic end-stage renal disease ($P = .007$) and natural mortality ($P < .001$) than those with older-onset diabetes mellitus. Participants were observed from onset of diabetes mellitus to outcome or December 2002. Natural mortality panel has 5 more participants than the end-stage renal disease panel because 5 participants diagnosed with diabetes mellitus in the course of routine medical care were excluded because they had no research examination between date of diagnosis and onset of dialysis.

curred before 12 years of age, the average age of menarche in Pima girls, so the extent of prepubertal exposure to diabetes is likely to be quite small.

In summary, the age-sex-adjusted incidence of ESRD in young- and middle-aged Pima Indians with youth-onset type 2 diabetes mellitus was nearly 5 times as high as in those of the same age with older-onset diabetes mellitus. The longer duration of diabetes by middle age in those diagnosed at younger than 20 years is largely responsible for the higher incidence of ESRD. The age-sex-adjusted death rate from natural causes in participants with youth-onset type 2 diabetes mellitus was 3 times as high as in individuals without diabetes and was slightly but not significantly higher than in participants with older-onset diabetes mellitus. Fatal cardiovascular disease was associated with ESRD regardless of the age at onset of diabetes. Because youth-onset diabetes mellitus leads to substantially increased complication rates and mortality in middle age, efforts should focus on preventing or delaying the onset of diabetes, delaying the onset of diabetic nephropathy, or both.

Author Contributions: Dr Pavkov had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pavkov, Bennett, Knowler, Nelson.

Acquisition of data: Pavkov, Knowler, Krakoff, Sievers, Nelson.

Analysis and interpretation of data: Pavkov, Knowler, Krakoff, Sievers, Nelson.

Drafting of the manuscript: Pavkov.

Critical revision of the manuscript for important intellectual content: Bennett, Knowler, Sievers, Nelson.

Statistical analysis: Pavkov, Knowler, Nelson.

Obtained funding: Knowler.

Administrative, technical, or material support: Knowler, Krakoff, Sievers, Nelson.

Study supervision: Bennett, Knowler, Nelson.

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