Incidence of Remission in Adults With Type 2 Diabetes: The Diabetes & Aging Study

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OBJECTIVE

To estimate the incidence of remission in adults with type 2 diabetes not treated with bariatric surgery and to identify variables associated with remission.

RESEARCH DESIGN AND METHODS

We quantified the incidence of diabetes remission and examined its correlates among 122,781 adults with type 2 diabetes in an integrated healthcare delivery system. Remission required the absence of ongoing drug therapy and was defined as follows: *1*) partial: at least 1 year of subdiabetic hyperglycemia (hemoglobin A_{1c} [HbA_{1c}] level 5.7–6.4% [39–46 mmol/mol]); *2*) complete: at least 1 year of normoglycemia (HbA_{1c} level <5.7% [<39 mmol/mol]); and *3*) prolonged: complete remission for at least 5 years.

RESULTS

The incidence density (remissions per 1,000 person-years; 95% CI) of partial, complete, or prolonged remission was 2.8 (2.6–2.9), 0.24 (0.20–0.28), and 0.04 (0.01–0.06), respectively. The 7-year cumulative incidence of partial, complete, or prolonged remission was 1.47% (1.40–1.54%), 0.14% (0.12–0.16%), and 0.007% (0.003–0.020%), respectively. The 7-year cumulative incidence of achieving any remission was 1.60% in the whole cohort (1.53–1.68%) and 4.6% in the subgroup with new-onset diabetes (<2 years since diagnosis) (4.3–4.9%). After adjusting for demographic and clinical characteristics, correlates of remission included age >65 years, African American race, <2 years since diagnosis, baseline HbA_{1c} level <5.7% (<39 mmol/mol), and no diabetes medication at baseline.

CONCLUSIONS

In community settings, remission of type 2 diabetes does occur without bariatric surgery, but it is very rare.

It is widely believed that type 2 diabetes is a chronic progressive condition, which at best can be controlled, but never cured (1), and that once treatment with glucose-lowering medication is initiated, it is required indefinitely and is intensified over time (2,3). However, a growing body of evidence from clinical trials and case-control studies (4–6) has reported the remission of type 2 diabetes in certain populations, most notably individuals who received bariatric surgery. A post hoc analysis from the Action for Health in Diabetes (Look AHEAD) study, a randomized, controlled trial of an intensive lifestyle intervention among adults with type 2 diabetes, found evidence of remission in both the intensive lifestyle management, and the diabetes support and education groups, suggesting that metabolic/bariatric surgery is not the only pathway

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to remission and that remission may also be achieved through intensive lifestyle management (7). In addition to a return to normal or near-normal blood glucose levels in the absence of glucose-lowering treatment, these individuals have been found to have biologic evidence of remission, including normalization of β-cell function and hepatic insulin sensitivity (8,9).

Recently, the American Diabetes Association (ADA) convened an expert panel to define the term "cure of diabetes" (10). The ADA consensus statement borrowed from the cancer literature in defining the term "remission" as achieving glycemia below the diabetic range in the absence of active pharmacologic or surgical therapy. It defines the following three mutually exclusive states of remission: partial remission, which is subdiabetic hyperglycemia of at least 1 year (A1C level not diagnostic of diabetes [5.7–6.4%; 39–46 mmol/mol], fasting glucose level 100–125 mg/dL [5.6–6.9 mmol/L]); complete remission, which is normoglycemia of at least 1 year (A1C level in the normal range [<5.7%; <39 mmol/mol], fasting glucose <100 mg/dL [5.6 mmol/L]); and prolonged remission (or "cure"), complete remission of at least 5 years.

Despite the clinical relevance and importance of remission, little is known about the incidence of remission in community settings (11,12). Studies to date have focused largely on remission after gastric bypass or relied on data from clinical trials, which have limited generalizability. Therefore, we conducted a retrospective cohort study to describe the incidence rates and variables associated with remission among adults with type 2 diabetes who received usual care, excluding bariatric surgery, in a large, ethnically diverse population.

RESEARCH DESIGN AND METHODS

Study Cohort

Kaiser Permanente Northern California (KPNC) is an integrated healthcare delivery system that provides comprehensive medical services to >3 million members. KPNC membership closely approximates the general population ethnically and socioeconomically, except for the extremes of income distribution.

The source population was identified from the KPNC Diabetes Registry (13,14). Established in 1993, the registry is updated annually by identifying all health plan members with diabetes from four automated databases using a validated algorithm (15), as follows: primary hospital discharge diagnosis of diabetes; ≥2 outpatient visit diagnoses of diabetes; any prescription for a diabetes-specific medication; or two abnormal outpatient laboratory results (fasting glucose level ≥126 mg/dL; random or postchallenge [75 g] glucose level ≥200 mg/dL; hemoglobin A_{1c} [HbA_{1c}] level ≥6.5% [≥48 mmol/mol]) from tests performed on separate days, within a 3-year period, after excluding those identified due to gestational diabetes (based on ICD-9 code 648.8) or cases identified based on medications only where there were competing indications (e.g., HIV lipodystrophy, polycystic ovary syndrome). Starting with a sampling frame that included the 197,699 plan members in the KPNC Diabetes Registry as of 1 January 2005, we excluded subjects based on the following criteria: *1*) if they lacked continuous KPNC membership with pharmacy benefits since 1 January 2004 (no gap of ≥3 months) (*n* = 12,507); *2*) if they were <19 years of age as of 1 January 2005 (*n* = 1,401); *3*) if they had type 1 diabetes (based on self-report or had diabetes onset at <30 years of age, treated with insulin only and was never treated with oral agents) (*n* = 6,625); *4*) if they had less than two HbA_{1c} measurement results during follow-up (*n* = 23,310); *5*) if they had no diabetes medication dispensed in the year prior to baseline and had either no HbA_{1c} measurements or all HbA_{1c} measurements of <6.5% (<48 mmol/mol) (e.g., did not have recent evidence of clinical diabetes such as pharmacologic treatment or a recent HbA_{1c} level in the diabetic range) (*n* = 27,271); *6*) if they had a history of bariatric surgery, including gastric bypass, sleeve gastrectomy, or lap banding, or had undergone any of these procedures during the study period (see Supplementary Table 1 for complete listing) (*n* = 1,564); or *7*) if they had been a long-term user (>60 days) of oral steroids in the year prior to baseline (*n* = 2,240). The remaining 122,781 eligible subjects were the focus of our analysis.

Follow-up of this analytic cohort members was initiated on 1 January 2005, and individuals were censored at the first occurrence of one of the following events: *1*) if any of the remission case definitions were met; *2*) if there had been a gap of ≥3 months in either membership or prescription benefits; *3*) if death had occurred from any cause; or *4*) the end of the study (31 December 2011). We collected data on demographic characteristics (age, sex, race), and laboratory data related to glycemic control, pharmacy data, outpatient diagnoses, and inpatient hospitalizations, including diagnoses and procedures. All HbA_{1c} tests were analyzed at a single regional laboratory. This high-volume Kaiser laboratory is licensed by the California Department of Health Services, and is inspected and accredited by the College of American Pathologists. Since 2002, the regional laboratory has used the Diabetes Control and Complications Trial standardization of HbA_{1c} implemented by the National Glycohemoglobin Standardization Group. In 2011, KPNC updated its assay for measuring HbA_{1c}. This change resulted in a slight increase in test values compared with the period of 2005–2011 and biased our study toward more conservative estimates of remission. Survival status and dates of death were captured from KPNC records and the Death Data Files from the California Department of Public Health.

Case Definition

Our definitions of remission were based on the 2009 ADA consensus statement (10). "Partial remission" of diabetes was defined as having two or more consecutive subdiabetic HbA_{1c} measurements, all of which were in the range of 5.7–6.4% [39–46 mmol/mol] over a period of at least 12 months. "Complete remission" was defined as having two or more consecutive normoglycemic HbA_{1c} measurements, all of which were <5.7% [<39 mmol/mol] over a period of at least 12 months. "Prolonged remission" was defined as having two or more consecutive normoglycemic HbA_{1c} measurements, all of which were <5.7% [<39 mmol/mol] over a period of at least 60 months. Each definition of remission requires the absence of pharmacologic treatment during the defined observation period. Periods of no pharmacologic therapy were defined as beginning on the last date that a diabetes medication prescription was filled plus two times the daily supply last dispensed, and ending when and if a new diabetes medication prescription was filled (patients who have had no

medication dispensed automatically meet the criteria of having no pharmacologic therapy). By definition, patients who met the criteria for complete remission also met the definition for partial remission. However, the categories were mutually exclusive and, similar to the oncologic literature (16), periods of remission were categorized by the most advanced category observed even though they also qualified for a less advanced stage (i.e., prolonged remission is more advanced than complete remission, and complete remission is more advanced than partial remission). Thus, patients who met the criteria for partial remission for at least 1 year who, after longer follow-up, eventually met the criteria for complete remission were classified as having complete remission. A fourth, summary, definition, "Any remission," was applied to patients who met any of the above remission category definitions.

To operationalize the ADA case definitions of remission (10), we made several conservative modifications of the definitions. We used an HbA_{1c} level of $<5.7\%$ [<39 mmol/mol] to define complete and prolonged remission rather than 6.0% [42 mmol/mol], as some studies have (17). This approach follows from reference ranges used by the KPNC centralized laboratory, which defines normoglycemia as an HbA_{1c} level of $<5.7\%$ [<39 mmol/mol] and prediabetes as an HbA_{1c} level of 5.7–6.4% [39–46 mmol/mol], and is consistent with national and international guidelines for the diagnosis of prediabetes and diabetes (18,19). We also required at least two HbA_{1c} measurements at least 12 or 60 months apart for partial/complete and prolonged remission, respectively (5,7,20,21). Finally, our definitions specified a minimum time interval between measurements rather than a time interval from the first measurement. We chose only HbA_{1c} levels because fasting blood glucose levels are rarely used at KPNC after the diagnosis of diabetes.

Covariates

Using previously published methods (15), the date that a patient first received a diagnosis of diabetes was calculated preferentially from self-report or else from the date of inclusion in the diabetes registry if this occurred at least 6 months after joining KPNC as a member; in the absence of these conditions, the variable was set to "missing," which occurred in 14.2% of individuals. Other covariates included comorbid conditions, defined using standard outpatient and inpatient Diagnosis-Related Group and ICD-9 codes as well as laboratory findings in the 12 months prior to baseline (see Supplementary Table 1 for details). BMI was obtained from the most recent measurement available, but because electronic data capture of BMI was not fully implemented across all KPNC medical centers until 2006, these data are missing in 29.7% of participants. Diabetes medications in the year prior to baseline and since 2002 were obtained from outpatient pharmacy dispensing. Finally, we used a validated, standardized deprivation index as an indicator of neighborhood-level socioeconomic status (22,23).

Statistical Analyses

We estimated the incidence density (number of remissions per 1,000 person-years at risk) for partial, complete, and prolonged remission separately, as well as the incidence density of any remission. In addition, we calculated the 7-year cumulative incidence of any remission (reported as the percentage of subjects who experienced remission during a 7-year follow-up) using the Kaplan-Meier method of estimating the cumulative probability of an event (24). Seven years was chosen as the period for analysis because complete remission requires at least 5 years of data. Results were stratified by years since diagnosis and baseline diabetes therapy.

Cox proportional hazards models were specified to identify significant variables associated with the time to any remission (partial, complete, or prolonged remission) (24). We also performed a subgroup analysis of patients with new-onset diabetes ($\leq$2 years since diagnosis at baseline). We examined unadjusted and adjusted models based on a complete case–only analysis. The adjusted model included demographic factors (age at cohort entry, sex, race, deprivation index), baseline risk factors (BMI, estimated glomerular filtration rate [eGFR], HbA_{1c} level), comorbidities (cardiovascular disease, hypertension, dyslipidemia, diabetic retinopathy, diabetic neuropathy, congestive heart failure), and diabetes factors (oral or insulin use, years since diabetes diagnosis).

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). All statistical testing was two sided; the level of significance was <0.05. The study was approved by the Institutional Review Boards of Kaiser Permanente and The University of Chicago.

RESULTS

As of 1 January 2005, 122,781 individuals met our study criteria, yielding 709,005 person-years of total follow-up time. The median duration of follow up in the overall cohort was 7 years (25th percentile 4.7; 75th percentile 7.0), and in the new-onset cohort it was 7 years (25th percentile 4.5; 75th percentile 7.0). A total of 11,510 subjects were censored because of having a gap of $\geq$3 months in either membership or prescription benefits within the first 2 years of follow-up. The average age of participants was 62 years, 47.1% were female, and 51.6% were nonwhite (Table 1). The mean (SD) interval between HbA_{1c} tests in the remission group was 256 days (139 days). The mean interval (SD) between HbA_{1c} tests among patients not in the remission group was 212 days (118 days). The median time since the diagnosis of diabetes in our cohort was 5.9 years, and the average baseline HbA_{1c} level was 7.4% [57 mmol/mol]. The 18,684 individuals (15.2%) in the subset with new-onset diabetes, defined as $\leq$2 years since diagnosis, were younger, were more likely to have their diabetes controlled by diet, and had fewer comorbidities (Table 2).

The incidence densities of partial, complete, and prolonged remission in the full cohort were 2.8 (95% CI 2.6–2.9), 0.24 (95% CI 0.20–0.28), and 0.04 (95% CI 0.01–0.06) cases per 1,000 person-years, respectively (Table 3). The 7-year cumulative incidences of partial, complete, and prolonged remission were 1.5% (95% CI 1.4–1.5%), 0.14% (95% CI 0.12–0.16%), and 0.01% (95% CI 0.003–0.02%), respectively. The 7-year cumulative incidence of any remission decreased with longer time since diagnosis from a high of 4.6% (95% CI 4.3–4.9%) for individuals diagnosed with diabetes in the past 2 years to a low of 0.4% (95% CI 0.3–0.5%) in those diagnosed $>$10 years ago. The 7-year cumulative incidence of any remission

Table 1—Baseline demographics and diabetes characteristics

Characteristic	Full cohort* (*N* = 122,781)	New-onset cohort† (*N* = 18,684)
Age, mean (SD), years	61.8 (12.6)	56.5 (13.1)
Female sex	57,779 (47.1)	8,723 (46.7)
Race/ethnicity		
African American	13,169 (11.3)	1,751 (10.5)
Asian	11,505 (9.9)	1,810 (10.8)
Filipino	8,793 (7.5)	1,469 (8.8)
Latino	17,391 (14.9)	2,798 (16.7)
White	56,493 (48.4)	7,825 (46.8)
Mixed	7,592 (6.5)	828 (5.0)
Other	1,894 (1.6)	249 (1.5)
Socioeconomic status: neighborhood deprivation index		
1st quartile (least deprived)	22,370 (19.8)	3,301 (19.5)
2nd quartile	34,142 (30.2)	5,092 (30.0)
3rd quartile	33,122 (29.3)	5,138 (30.3)
4th quartile (most deprived)	23,363 (20.7)	3,434 (20.2)
HbA_{1c}		
<5.7% [<39 mmol/mol]	4,807 (3.9)	1,288 (7.1)
5.7–6.4% [39–46 mmol/mol]	27,232 (22.3)	5,213 (28.6)
6.5–7.9% [47–63 mmol/mol]	59,286 (48.6)	8,225 (45.1)
8.0% + [≥64 mmol/mol]	30,775 (25.2)	3,495 (19.2)
BMI, mean (SD), kg/m^2	31.1 (5.4)	31.5 (5.4)
eGFR, mean (SD), mL/min/1.73 m^2	77.5 (23.8)	85.2 (21.5)
Diabetes medication		
None	13,639 (11.1)	5,133 (27.5)
Oral agents only	86,064 (70.1)	12,632 (67.6)
Any insulin	23,078 (18.8)	919 (4.9)
Diabetes duration, median (IQR), years	5.9 (2.9–11.2)	0.9 (0.6–1.4)

Data are expressed as *n* (%), unless otherwise indicated. IQR, interquartile range. *Missing data in full cohort: race (*N* = 5,944), socioeconomic status (*N* = 9,784), HbA_{1c} level (*N* = 681), diabetes duration (*N* = 19,229), BMI (*N* = 36,513), eGFR (*N* = 7,300). †New-onset diabetes defined as <2 years since diagnosis. Missing data in new-onset cohort: race (*N* = 1,954), socioeconomic status (*N* = 1,719), HbA_{1c} level (*N* = 463), BMI (*N* = 4,946), eGFR (*N* = 1,054).

was much lower for individuals using insulin (0.05%; 95% CI 0.03–0.1%) or oral agents (0.3%; 95% CI 0.2–0.3%) at baseline compared with diabetes patients not using medication at baseline (12%; 95% CI 12–13%).

In bivariate and multivariable analyses, in the full cohort, any remission was associated with older age, less time since diagnosis, lower baseline HbA_{1c} level, and not taking diabetes medications ($P < 0.0001$) (Table 4). Higher socioeconomic status, moderate renal impairment, and no dyslipidemia were also associated with remission in bivariate analyses ($P < 0.0001$), but these associations attenuated in multivariable analyses ($P < 0.05$). In addition, African American race was associated with remission in the multivariable analysis only (hazard ratio 1.4; 95% CI 1.15–1.75; $P = 0.001$).

In the new-onset cohort, any remission was also associated with lower baseline HbA_{1c} level, and not taking diabetes medications in both bivariate and multivariable analyses ($P < 0.0001$) (Supplementary Table 2). In addition, older age, higher socioeconomic status, and moderate renal impairment were associated with remission in bivariate analyses ($P < 0.0001$), but were attenuated after adjustment ($P < 0.05$). In addition, African American race and no dyslipidemia were associated with remission only after adjustment.

Table 2—Baseline comorbidities

Characteristic	Full cohort (*N* = 122,781)	New-onset cohort* (*N* = 18,684)
Hypertension	103,171 (84.0)	13,800 (73.9)
Hyperlipidemia	96,938 (79.0)	13,469 (72.1)
Cardiovascular disease	25,115 (20.5)	2,161 (11.6)
Diabetic retinopathy	20,305 (16.5)	724 (3.9)
Diabetic neuropathy	23,806 (19.4)	1,877 (10.1)
Congestive heart failure	8,289 (6.8)	724 (3.9)

Data are expressed as *n* (%). *New-onset diabetes defined as <2 years since diagnosis.

CONCLUSIONS

In this large cohort of insured adults with type 2 diabetes not treated with bariatric surgery, we found that 1.5% of individuals with recent evidence of clinical diabetes achieved at least partial remission over a 7-year period. If these results were generalized to the 25.6 million U.S. adults living with type 2 diabetes in 2010 (25), they would suggest that 384,000 adults could experience remission over the next 7 years. However, the rate of prolonged remission was extremely rare (0.007%), translating into only 1,800 adults in the U.S. experiencing remission lasting at least 5 years. To provide context, 1.7% of the cohort died, while only 0.8% experienced any level of remission, during the calendar year 2006. Thus, the chances of dying were higher than the chances of any remission.

Remission is common among patients with diabetes who have undergone bariatric surgery (~70% experienced remission within 5 years after surgery) (5). To the best of our knowledge, this is the first report of remission in a usual care setting among the broad population of adults with type 2 diabetes (e.g., not those who underwent bariatric surgery). Although remission of type 2 diabetes is uncommon, it does occur in patients who have not undergone surgical interventions. Moreover, we found evidence of remission, albeit rare, even in individuals previously requiring oral antiglycemic medication or insulin therapy. It is important to consider that these findings were based on a conservative sampling frame that excluded patients without recent evidence of clinical diabetes at baseline and using a more stringent definition of remission than typically used in the literature. These findings challenge widespread assumptions that type 2 diabetes is uniformly irreversible and progressive.

Table 3—Incidence rates of remission for the full cohort and stratified by time since diagnosis

	Total person-years at risk*	Incident events (*n*)	7-Year cumulative incidence (95% CI)†	Incidence rate per 1,000 person-years (95% CI)
Any remission				
All	586,725	1,761	1.60% (1.53–1.68)	3.00 (2.86–3.14)
Time since diagnosis <2 years (*n* = 18,451)	88,473	776	4.55% (4.25–4.88)	8.77 (8.15–9.39)
Time since diagnosis 2–3 years (*n* = 18,127)	89,526	424	2.54% (2.31–2.79)	4.74 (4.29–5.19)
Time since diagnosis 4–5 years (*n* = 15,122)	75,304	228	1.67% (1.46–1.89)	3.03 (2.63–3.42)
Time since diagnosis 6–9 years (*n* = 20,270)	102,270	152	0.82% (0.70–0.96)	1.49 (1.25–1.72)
Time since diagnosis ≥10 years (*n* = 30,326)	147,333	98	0.37% (0.30–0.45)	0.67 (0.53–0.80)
Baseline diabetes therapy, no medication (*n* = 13,502)	62,009	1,538	12.33% (11.76–12.93)	24.80 (23.56–26.04)
Baseline diabetes therapy, OHA only (*n* = 84,968)	419,376	212	0.28% (0.24–0.32)	0.51 (0.44–0.57)
Baseline diabetes therapy, insulin (*n* = 22,625)	105,340	11	0.05% (0.03–0.10)	0.10 (0.04–0.17)
Partial remission	587,341	1,615	1.47% (1.40–1.54)	2.75 (2.62–2.88)
Complete remission	593,216	140	0.14% (0.12–0.16)	0.24 (0.20–0.28)
Prolonged remission	170,356	6	0.007% (0.003–0.02)	0.035 (0.007–0.063)

OHA, oral hypoglycemic agent. *Defined as the total number of person-years 12 months after cohort inception for partial and complete remission, and after 60 months for prolonged remission. †Defined as 100% minus the cumulative survival probability calculated using the Kaplan-Meier method.

Our study should be considered in light of the Look AHEAD study (7). Investigators reported the incidence of any remission (partial or complete) at 1 year was 11.5% in the intensive management arm, and 2.0% in the diabetes support and education arm, compared with a 1.6% incidence over 7 years in our study. Several important differences between the study populations and study design should be noted. The Look AHEAD study presumably enrolled patients who were willing or motivated to make extensive lifestyle changes, while our study population is representative of a general adult diabetes population. Patients in our study also had a longer duration of diabetes and a higher burden of comorbidity than those enrolled in the Look AHEAD study. In addition, the two studies use different operational definitions of remission. Future studies should seek to validate and extend our findings in other populations, including children and adolescents.

Consistent with prior literature, we observed that the incidence of remission was not uniform across individuals. Variables associated with remission were similar to those identified in the Look AHEAD study (7); they included no glucose-lowering medication and lower baseline HbA_{1c} level. We also observed an association of remission with fewer years since diagnosis, although the size of the effect weakened after controlling for demographic, diabetes, and health status covariates—a finding that may reflect differences between the actual physiologic onset of diabetes versus the point of clinical recognition (i.e., diagnosis) (26), as well as the multitude of factors that influence the natural history of β-cell function and mass (8,27,28). These findings, combined with our observation that remission was more common in adults with lower baseline HbA_{1c} levels who had not been previously treated with insulin or oral hypoglycemic medications, provide indirect evidence of the potential benefits of screening, diagnosis, and initiating intensive lifestyle management before the onset or early in the natural history of the disease (18). Although lower BMI was associated with remission in the unadjusted analysis, these associations did not persist after controlling for covariates. Baseline BMI was similarly not associated with remission in the Look AHEAD study, which found that only a change in BMI predicted remission. These findings may have important implications when considering treatment options (lifestyle vs. surgical therapy) for overweight and obese individuals with diabetes.

We also identified a number of variables associated with higher rates of remission that have not been previously described, as follows: older age, African American race, higher socioeconomic status, renal impairment, and absence of dyslipidemia. Higher rates of remission in adults over age 65 years are consistent with evidence from the Diabetes Prevention Program demonstrating that older adults experienced the greatest risk reduction in diabetes from lifestyle modification (29,30), findings that have particular salience given that the prevalence of type 2 diabetes is highest among the elderly (25). Although the unadjusted analysis suggested no association between remission and African American race, after controlling for covariates including neighborhood-level socioeconomic status we found that African American race was positively associated with remission. Despite a higher incidence of diabetes in African Americans (15), this finding complements earlier reports (14,31) in our study population of lower rates of certain diabetes complications including heart disease among African Americans. Higher socioeconomic status was associated with remission in both unadjusted and adjusted analyses, although the effect size was modest. The rates of remission increased with renal impairment; however, we did not see marked differences across stages of chronic kidney disease. Because insulin is normally metabolized by the kidney (32), worsening renal function can lead to improved glycemic control (33); however, this typically occurs at later stages of renal impairment and cannot fully explain our findings. Finally, higher rates of remission among individuals without dyslipidemia may reflect common biologic pathways in the metabolic syndrome among dyslipidemia, obesity, and impaired glucose tolerance (34), and should be investigated in future studies, given the high rates of comorbid dyslipidemia in patients with type 2 diabetes.

More research is needed on how and whether to refine the case definitions for diabetes remission. Considerable

Table 4—Full cohort: unadjusted and adjusted Cox proportional hazard ratios for any remission

		Any remission (n = 1,761)			
		Hazard ratio (95% CI)			
Characteristic	n (%)	Unadjusted	P value	Fully adjusted*	P value
Sex					
Men	820 (1.3)	1.0 (Ref)		1.0 (Ref)	
Women	941 (1.7)	1.29 (1.17–1.41)	<0.0001	1.04 (0.91–1.19)	0.5532
Age, years					
<45	81 (0.7)	1.0 (Ref)		1.0 (Ref)	
45–65	551 (0.9)	1.28 (1.01–1.61)	0.0403	1.55 (1.04–2.31)	0.0323
≥65	1,129 (2.2)	3.02 (2.41–3.78)	<0.0001	2.54 (1.67–3.86)	<0.0001
Race/ethnicity					
White	780 (1.4)	1.0 (Ref)		1.0 (Ref)	
African American	189 (1.5)	1.02 (0.87–1.2)	0.7931	1.42 (1.15–1.75)	0.001
Asian	162 (1.4)	0.99 (0.84–1.18)	0.9315	0.91 (0.72–1.14)	0.407
Filipino	80 (0.9)	0.64 (0.51–0.8)	0.0001	0.75 (0.56–1.01)	0.0551
Latino	160 (0.9)	0.66 (0.56–0.78)	<0.0001	1.05 (0.84–1.31)	0.6587
Mixed race	83 (1.1)	0.78 (0.62–0.98)	0.0318	0.97 (0.73–1.3)	0.8497
Other	17 (0.9)	0.66 (0.41–1.06)	0.0844	1.09 (0.56–2.11)	0.8083
Socioeconomic status: neighborhood deprivation index					
1st quartile (least deprived)	398 (1.8)	1.55 (1.33–1.81)	<0.0001	1.28 (1.03–1.61)	0.0288
2nd quartile	522 (1.5)	1.34 (1.15–1.55)	0.0001	1.08 (0.87–1.35)	0.4599
3rd quartile	463 (1.4)	1.24 (1.06–1.44)	0.0056	1.14 (0.91–1.41)	0.2485
4th quartile (most deprived)	259 (1.1)	1.0 (Ref)		1.0 (Ref)	
Time since diagnosis					
<2 years	776 (4.2)	13.2 (10.7–16.29)	<0.0001	2.19 (1.63–2.95)	<0.0001
2–3 years	424 (2.3)	7.21 (5.79–8.98)	<0.0001	1.68 (1.24–2.28)	0.0008
3–10 years	380 (1.1)	3.28 (2.62–4.09)	<0.0001	1.6 (1.19–2.15)	0.0017
≥10 years	98 (0.3)	1.0 (Ref)		1.0 (Ref)	
Baseline HbA_{1c} level					
<5.7% (<39 mmol/mol)	131 (2.8)	24.46 (16.84–35.51)	<0.0001	19.2 (11.79–31.27)	<0.0001
5.7–6.4% (39–46 mmol/mol)	628 (2.3)	20.46 (14.55–28.75)	<0.0001	6.61 (4.23–10.32)	<0.0001
6.5–7.9% (47–63 mmol/mol)	963 (1.6)	14.24 (10.16–19.95)	<0.0001	2.7 (1.74–4.2)	<0.0001
≥8% (≥64 mmol/mol)	35 (0.1)	1.0 (Ref)		1.0 (Ref)	
Diabetes medication in the past 1 year					
None	1,538 (11.4)	239.75 (132.5–433.81)	<0.0001	132.51 (61.62–284.97)	<0.0001
Oral agents only	212 (0.2)	4.99 (2.72–9.15)	<0.0001	3.71 (1.71–8.03)	0.0009
Any insulin	11 (0)	1.0 (Ref)		1.0 (Ref)	
Diabetes medication since 2002					
None	1,447 (12.3)	128.07 (85.56–191.7)	<0.0001		
Oral agents only	290 (0.3)	3.37 (2.22–5.11)	<0.0001		
Any insulin	24 (0.1)	1.0 (Ref)			
BMI, kg/m^2					
<25	219 (1.9)	1.53 (1.29–1.82)	<0.0001	1 (0.79–1.25)	0.973
≥25 to <30	435 (1.7)	1.33 (1.15–1.54)	0.0001	0.83 (0.69–1)	0.0504
≥30 to <35	290 (1.3)	1.02 (0.87–1.2)	0.7886	0.8 (0.66–0.96)	0.0184
≥35	308 (1.3)	1.0 (Ref)		1.0 (Ref)	
CKD stage†					
0 + 1	349 (0.9)	1.0 (Ref)		1.0 (Ref)	
2	808 (1.6)	1.8 (1.59–2.04)	<0.0001	1.1 (0.91–1.33)	0.3475
3	467 (2)	2.25 (1.95–2.58)	<0.0001	1.33 (1.06–1.67)	0.0143
4	48 (2)	2.45 (1.81–3.31)	<0.0001	2.11 (1.37–3.26)	0.0008
5	12 (1.6)	1.9 (1.07–3.39)	0.0283	2.51 (1.14–5.51)	0.0221
No hypertension	262 (1.4)	0.91 (0.79–1.03)	0.1373	0.97 (0.79–1.19)	0.7791
Hypertension	1,499 (1.5)	1.0 (Ref)		1.0 (Ref)	
No dyslipidemia	445 (1.7)	1.28 (1.15–1.42)	<0.0001	1.21 (1.03–1.43)	0.0216
Dyslipidemia	1,316 (1.4)	1.0 (Ref)		1.0 (Ref)	
No cardiovascular disease	1,392 (1.4)	0.91 (0.81–1.02)	0.1174	0.91 (0.76–1.08)	0.2781
Cardiovascular disease	369 (1.5)	1.0 (Ref)		1.0 (Ref)	
No diabetic retinopathy	1,677 (1.7)	3.86 (3.1–4.81)	<0.0001	1.11 (0.81–1.52)	0.5129
Diabetic retinopathy	84 (0.4)	1.0 (Ref)		1.0 (Ref)	

Continued on p. 3194

Table 4—Continued

		Any remission (n = 1,761)			
		Hazard ratio (95% CI)			
Characteristic	n (%)	Unadjusted	P value	Fully adjusted*	P value
No diabetic neuropathy	1,498 (1.5)	1.32 (1.16–1.51)	<0.0001	0.84 (0.7–1.01)	0.0689
Diabetic neuropathy	263 (1.1)	1.0 (Ref)		1.0 (Ref)	
No congestive heart failure	1,630 (1.4)	0.78 (0.65–0.93)	0.0068	0.88 (0.68–1.14)	0.3312
Congestive heart failure	131 (1.6)	1.0 (Ref)		1.0 (Ref)	

CKD, chronic kidney disease; Ref, reference value. *Fully adjusted model includes all variables listed in the table. †Stage 0 + 1, eGFR ≥90 mL/min/1.73 m^2; stage 2, eGFR 60–89 mL/min/1.73 m^2; stage 3, eGFR 30–59 mL/min/1.73 m^2; stage 4, eGFR 15–29 mL/min/1.73 m^2; stage 5, eGFR <15 mL/min/1.73 m^2.

uncertainty lies in the appropriate glycemic thresholds for partial and complete remission, the choice of glycemic measure (fasting blood glucose vs. HbA_{1c} level), and the number and timing of measurements. Studies of different definitions of remission in bariatric surgery suggest that the choice of thresholds can have a significant impact on estimates of remission rates (20,35), although the frequency of measurement remains unexplored. Given the growing importance of this area of research, operational definitions of remission for different study designs are needed, and, once established, should be considered in future diabetes clinical trials and epidemiologic studies as a clinical outcome measure.

Our study also has important implications for clinical decision making. Without an empiric trial of withdrawal of glucose-lowering medication in a type 2 diabetes patient with subdiabetic glucose levels or normoglycemia, it is impossible to ascertain whether their medication regimen is still needed. Clinical inertia, although primarily used to refer to the failure of clinicians to initiate or intensify therapy (36), may also be applied to underdiagnosis of remission if doctors do not test a patient's ability to maintain metabolic control without medications. Such an empiric trial, if successful, may reduce the potential adverse effects of diabetes medications and reduce healthcare costs, while improving patient outcomes, a hypothesis that should be tested in future clinical trials.

Several limitations need to be acknowledged. First, these data were collected from routine clinical practice rather than from a prescribed study protocol with regular collection intervals. As a result, the frequency of HbA_{1c} testing varied widely, particularly in our population of interest, which consisted of individuals with subdiabetic HbA_{1c} levels. This limitation is a direct result of ambiguity in clinical guidelines about the intensity of diabetes management required for these individuals. Second, the criteria by which diabetes was first identified differed for subjects who experienced remission versus those who did not. The patients who eventually went into remission had similar likelihoods of having two or more outpatient diagnoses of diabetes as their basis for being identified as having diabetes when compared with subjects not going into remission (96% vs. 97%, respectively). However, patients who experienced remission were less likely than patients who did not experience remission to be first identified due to a diabetes-related medication (29% vs. 93%, respectively), abnormal laboratory test results (68% vs. 93%, respectively), or hospital discharge (4% vs. 9%, respectively). This suggests that patients who eventually experienced remission had less advanced diabetes at the onset and more often received diagnoses from their provider without laboratory evidence. Third, although the consensus definition of remission includes both fasting glucose and HbA_{1c} measures, this study used only HbA_{1c} measures because fasting glucose measures are not routinely collected after an established diabetes diagnosis by physicians at KPNC. Fourth, during the period of follow-up in 2011, KPNC updated its assay for measuring HbA_{1c}. This change increased test values compared with the period of 2005–2011, which would tend to bias our study toward more conservative estimates of remission. Fifth, because electronic capture of BMI occurred gradually over the baseline period, BMI was missing in 30% of participants. However, the proportion of patients with missing BMI data was relatively constant across states of remission, as follows: nonremission (30%), partial remission (29%), complete remission (31%), and prolonged remission (33%). While not eliminating the potential for bias, this greatly reduces the concern. Sixth, our results are partially dependent on methodological decisions about operationalizing definitions of remission. In general, we favored a conservative approach. As discussed above, the appropriate definitions of diabetes remission remain an area of considerable debate (10), which this study seeks to partially inform.

Despite these limitations, to our knowledge, this is the first study of the epidemiology of remission in type 2 diabetes in adults not treated with bariatric surgery. Our analysis shows that remission is rare and variable. The likelihood of remission is more common among individuals with early-onset diabetes and those not treated with glucose-lowering medications at the point of diabetes diagnosis. Although rare, remission can also occur in individuals with more severe diabetes and those previously treated with insulin. This information will help providers discuss the prognosis of diabetes in their newly diagnosed patients. The large differences in remission rates from our community setting, compared with those from lifestyle intervention trials like Look AHEAD, should inform a wider debate about the appropriate strategies for managing diabetes.

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