ORIGINAL ARTICLE

Specialist-led diabetes registries and predictors of poor glycemic control in type 2 diabetes: Insights into the functionally refractory patient from the LMC Diabetes Registry database

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Abstract

Background: The aim of the present study was to explore features associated with glycemic control in type 2 diabetes (T2D) patients undergoing care by specialist clinics.

Methods: Literature searches identified diabetes registries whose databases recorded outcomes of specialist care. The LMC Diabetes Registry database ($n = 58\,280$; LMC) was queried to identify patients with T2D who had been seen in a defined 14-month period. Logistic regression modeling was used to identify predictors of glycemic control in these patients. Poor glycemic control was defined as HbA1c ≥9.0% (75 mmol/mol) despite specialist care for ≥1 year.

Results: Few published registry-based studies have discussed glycemic control and outcomes of specialist care for T2D. Among 10 590 LMC patients with T2D, mean HbA1c was 7.6% (60 mmol/mol), with 38% of patients meeting the Canadian Diabetes Association target of ≤7.0% (53 mmol/mol). Overall, 15% showed poor glycemic control with persistent HbA1c ≥9.0% (75 mmol/mol); among insulin-treated patients ($n = 3856$), 28% met this criterion. Patient characteristics independently associated with poor glycemic control included early age of onset, the number of diabetes education program visits, the number of oral therapies, and insulin use.

Conclusions: Type 2 diabetes patients with poor glycemic control are found disproportionately in referral specialist care clinics. These functionally refractory patients demonstrate features that may assist in predicting their potential outcome, and may represent a group with specific barriers to care. Specialist patient registries, such as the LMC Diabetes Registry, may provide critical information regarding this cohort.

Keywords: database, diabetes, refractory, registry, specialist.

Significant findings of the study: A significant refractory type 2 diabetes patient group (15%) was found in specialist practice within the public health system. Predictors of poor control included early age of onset, number of education visits, number of oral therapies, and insulin use.
What this study adds: Recent trials have identified a patient subgroup that responds adversely to glycemic tightening. Little is known about the characteristics of this subgroup or its prevalence in specialist practice. The present study provides a cross-section of a specialist patient registry, describes high-risk patients, and presents a predictive model for recognizing them.

Introduction

Successful control of diabetes requires life-long adherence to multiple self-management behaviors, in close collaboration with healthcare providers (HCPs). The slow onset and progressive nature of type 2 diabetes (T2D) creates particular challenges in engaging patients in their own care and maintaining this engagement as they intensify their treatment regimens. It is therefore not entirely surprising that audits in Canada,[1–3] the US,[4] and other nations[5] have found poor control of T2D to be common, with only a minority of patients reaching accepted HbA1c targets.

The challenges associated with ongoing diabetes management are at least partly organizational, relating to the need to integrate the efforts of multiple HCPs to provide optimal care.[6,7] Building patient registries is an important step for organizations that manage patients with diabetes,[8] and a prerequisite for many other institutional quality improvement initiatives.[9] Such registries can measure the effectiveness of policy initiatives and are a critical component for the assessment of treatment delivery and outcome, as well as for guiding resource allocation.[6]

Although numerous primary care diabetes registries have been implemented in Canada[10] and internationally,[11,12] populations served by specialists may differ in important respects from those seen in primary care. Specialist practices have been shown to offer more frequent health surveillance testing and access to time-intensive interventions,[13] but may primarily see referred patients with longer treatment histories, more advanced diabetes, and more severe diabetic complications. Despite the advantages of specialist care, and the more frequent use of insulin in this setting, these patients may generally exhibit poorer glycemic control than may be expected in randomly selected patients managed in primary care.[14]

Patients who do not reach adequate glycemic control despite intensified therapy under specialist care represent an important but poorly studied group that has recently been shown to bear a higher mortality risk than diabetic patients as a whole.[15] Such patients may be considered "functionally refractory", a term that emphasizes that, despite the theoretical ability of available oral and injectable therapies to control hyperglycemia, these patients have not achieved glycemic control despite ongoing, comprehensive, evidence-based care. The particular natural history of diabetes and the specific barriers to effective glycemic control in these functionally refractory patients have not been well characterized. To address this, we undertook a systematic review of published diabetes patient databases and extracted any relevant information regarding specialist care. We also undertook a cross-sectional analysis of a large ($n = 58\,280$) Canadian registry database from the LMC national group of diabetes specialty clinics. We hypothesized that diabetes databases from specialist care clinics would include a significant proportion of functionally refractory individuals, and so undertook an exploratory analysis of the LMC database to define the patient characteristics that may predict poor glycemic control.

Methods

The study protocol and registry were reviewed and approved by the Research Ethics Board, IRB Toronto, Canada Services.

Diabetes registries

To identify published reports of diabetes databases, Ovid Medline, ProQuest, Web of Science, and PubMed were searched in November 2013, and the PubMed search was repeated in February 2014 using the MeSH terms "uncontrolled", "refractory", "diabetes", "registry", "database", and "outcomes". English-language publications were screened to identify reports of national, regional, and institutional diabetes registries and diabetes databases from multicenter research consortia. Inclusion criteria for these searches were reports that provided the proportion of patients under specialist care and either the mean HbA1c or a measure of the prevalence of poor control in the specialist care population. Exclusion criteria included databases that were restricted based on therapy, complication, ethnicity, or age group.

The LMC database

The nine LMC Diabetes and Endocrinology (LMC) clinics provide multidisciplinary diabetes care for patients referred by their primary care provider (PCP); this care is funded entirely within Canada's public healthcare system. All LMC HCPs have well-defined medical directives and work as a team with individual accountability. All use a common electronic medical record system, integrated with the provincial laboratory information system, and follow care paths defined by the Clinical Practice Guidelines of the Canadian Diabetes Association (CDA),[16] supplemented by defined patient flow protocols at each clinic. The LMC Patient Registry represents all patients cared for at LMC sites and holds all their medical information, including past medical history, medications, and laboratory investigations. All patients are offered the opportunity to be part of the research database and nearly all (>99%) provide their informed consent and are included in the Patient

Registry. All subsequent analyses are undertaken on a de-identified copy of the database.

The LMC database was queried in May 2013 to identify patients with T2D who had been seen in one of the LMC centers between January 2011 and March 2013 and were receiving continuing specialist care. Patients were excluded from the analysis if they had type 1 diabetes or had been receiving care at LMC for less than 1 year. Where multiple serial measurements were available, the most recent assessment was used. "Functional refractory" status was defined as HbA1c ≥9.0% (75 mmol/mol) at the most recent measurement.

Statistical analysis

Descriptive statistics were calculated for all variables. Continuous and categorical variables are reported as mean (± SE) values and percentages, respectively.

To develop a model for predicting patients' refractory status, we used the cross-validation method where data were randomly allocated into a training or validation group ($n = 5295$ in each). The model was built using the training data and then tested on the validation data. Chi-squared tests and t-tests were then used to assess differences in refractory status and demographic variables between the training and validation groups. The built model becomes generalizable to the target population if no meaningful differences are found in the prediction between training and validation data.

To build the model, we started by investigating baseline patient factors, including demographics (age, sex, weight, body mass index (BMI), waist circumference, blood pressure, age at diagnosis, prereferral diabetes duration, duration of diabetes, ethnicity, household income), medication use, and medical history, for their ability to predict poor glycemic control (HbA1c >9.0%) in our population. Using the training data, each factor was analyzed separately in a univariate logistic regression model, and factors found to be significant were then included in a multivariate logistic regression model. Multicolinearity was checked for each factor by means of the variance inflation factor (VIF),[17] and any highly colinear variables (VIF >5) were excluded. To examine the robustness of the fitted model, a sensitivity analysis was conducted by replacing missing data using multiple imputation (assuming that missing values were randomly distributed); 10 replicates were generated by the Markov Chain Monte Carlo (MCMC) algorithm in the multiple imputation procedure. Odds ratios (ORs) with the corresponding 95% confidence intervals (CI) and P-values were reported for regression analyses. A receiver operating characteristic (ROC) analysis was then used to assess the predictive ability of the final model, and the area under the ROC curve (AUC) was reported as a measure of model predictability.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Specialist care registries and outcomes

In total, 175 reports were identified, of which 46 met the inclusion criteria. Seven papers described specialist care populations and provided their mean HbA1c or prevalence of poor control; a further six reports provided the same information for both specialist care and primary care populations (Table 1). Of the rejected reports, 22 described mixed care registries in which the specialist component was not sufficiently characterized, five described primary care populations only, and the balance of primary versus specialist care was not defined in six. The size of the databases included ranged from approximately 200 to more than 220 000.

Mean HbA1c levels in the primary care registry populations ranged from 6.8% to 7.1% (51–54 mmol/mol). In specialist care registries, the mean HbA1c generally included a higher range, from 7.7% to 8.6% (61–71 mmol/mol). Success in achieving glycemic control varied across studies and was usually based on local guideline-identified HbA1c targets (HbA1c ≤7.0% [53 mmol/mol]). Most registries that reported on poor control used a threshold of HbA1c ≥8.0% (64 mmol/mol); one[26] (B.H. Heng, pers. comm, 2013) used a threshold of ≥9.0% (75 mmol/mol). In all registries specialist-led practices demonstrated higher mean HbA1c levels and/or a higher proportion of patients.

The factors most commonly associated with poor control were specialist care, number of oral antidiabetic drug (OAD) therapies and treatment with both insulin and OADs. In addition, both duration of diabetes and presence of microvascular complications were frequently correlated with higher HbA1c levels.

Although these registries provided analyses of overall patient outcomes, trends, and associations in their respective settings, none was reported as being actively used to provide ongoing feedback on outcomes to the HCPs.

Patient characteristics in the LMC diabetes database

Table 2 provides cross-sectional data from the LMC Diabetes Registry, including 10 590 individuals who met the inclusion criteria and had received care for T2D during a 14-month period, as well as a subgroup of 1681

Table 1 Glycemic control under specialist care in published diabetes databases

Registry location and description (reference)	n	Mean HbA1c	Definition of suboptimal control	Proportion with suboptimal control	Suboptimal glycemic control associated with:
Specialist care					
Diabcare-Asia[18]	22 177	8.6% (70 mmol/mol)	HbA1c ≥8.0% (64 mmol/mol)	55%	Microvascular complications, poor access to local HbA1c
Hong Kong, single center[19]	7549	7.7% (61 mmol/mol)	HbA1c ≥8.0% (64 mmol/mol)	36%	Diabetes duration, no. OADs, treatment complexity, poor compliance
Thailand, 11 tertiary care institutions[20]	8913	n/a	HbA1c >7.0% (53 mmol/mol)	73.7%	Insulin-containing treatment regimens
Bangkok, single center[21]	243	Median 8.0% (64 mmol/mol)	HbA1c >8.0% (64 mmol/mol)	50.2%	Poor adherence (diet, exercise, and medications)
Korea, single center[22]	4994	n/a	HbA1c >8.0% (64 mmol/mol)	29.6%	
Tsukuba (Japan), single center[23]	1713	7.1% (54 mmol/mol)		n/a	Microalbuminuria
Chennai (India), specialty clinics[24]	>220 000	8.6% (70 mmol/mol)		n/a	Microvascular complications
Combined primary and specialist care					
Belgium, primary care and specialist clinics[11]	Primary 2182 Specialist 313	7.1% (54 mmol/mol) 7.8% (62 mmol/mol)	HbA1c ≥8.0% (64 mmol/mol)	Primary 16% Specialist 38%	Specialist care, insulin therapy
Japan, primary care and specialist clinics[25]	Primary 14 556 Specialist 1095	6.8% (51 mmol/mol) 7.0% (53 mmol/mol)	HbA1c ≥8.0% (64 mmol/mol)	Primary 14.8% Specialist 17.5%	Specialist care, insulin therapy
Singapore, primary care and specialist clinics[26,27]	170 513	7.0% (53 mmol/mol) 8.1% (65 mmol/mol)	HbA1c ≥9.0% (75 mmol/mol)	Primary 11.8% Specialist 22.3%	Specialist care, insulin use, younger age, high LDL, hypertension, vascular comorbidities
Jiangsu Province (China)[28]	Primary 2670 Specialist 296	7.2% (55 mmol/mol)	HbA1c >7.5% (58 mmol/mol)	Primary 32.2% Specialist 31%	Age, BMI, diabetes duration, less adherence, less education, less self-monitoring, lower income
Italy, primary care and specialist clinics[29]	Primary 790 Specialist 2646	7.2% (55 mmol/mol)	HbA1c ≥8.0% (64 mmol/mol)	Primary 25.6% Specialist 26.7%	
Bradford (UK)[30]*	Primary 1015 Specialist 474	8.5% (69 mmol/mol) 7.8% (62 mmol/mol)		n/a	Younger age, ethnicity

OAD, oral antidiabetic drug; LDL, low-density lipoprotein; BMI, body mass index; n/a, not available. *Data drawn from Visit 3 of six sequential visits provided.

Table 2 Characteristics of type 2 diabetes patients in the LMC Diabetes Registry (National Health and Nutrition Examination Survey [NHANES] patient data[4] are shown for reference only)

Characteristic	LMC Registry (n = 10 590)*	LMC Registry, HbA1c ≥9% (75 mmol/mol; n = 1681)*	NHANES (2007–10; n = 1444)
Patient age (%)			
18–44 years	9.2 ± 0.3	12.4 ± 0.8	13.0 ± 1.1
45–64 years	58.8 ± 0.5	65.41.2	46.2 ± ± 1.5
≥65 years	32.0 ± 0.5	22.2 ± 1.0	40.8 ± 1.5
Female gender (%)	47.2 ± 0.5	40.8 ± 1.7	50.8 ± 2.1
Race or ethnic group (%)			
Caucasian	47.9 ± 0.7	40.8 ± 1.7	61.4 ± 3.7
African	6.7 ± 0.4	9.7 ± 1.0	18.0 ± 2.1
Hispanic	2.5 ± 0.2	3.8 ± 0.7	8.4 ± 1.5
Asian	33.0 ± 0.7	33.0 ± 1.7	–
Caribbean	7.1 ± 0.4	9.9 ± 1.1	–
Other	2.1 ± 0.2	2.9 ± 0.6	12.2 ± 1.4
Income (%)			
Below poverty level[†]	14.8 ± 0.3	17.0 ± 0.9	25.9 ± 2.3
>C$30 000 annual income	15.3 ± 0.3	15.3 ± 0.9	–
Refused to report	69.9 ± 0.4	67.6 ± 1.1	–
Time since diagnosis (%)			
0 to <5 years	20.0 ± 0.4	8.3 ± 0.7	34.1 ± 1.6
5 to <15 years	49.8 ± 0.5	54.6 ± 1.3	39.4 ± 1.3
≥15 years	30.3 ± 0.5	37.2 ± 1.3	26.5 ± 1.4
Body mass index (%)			
kgm^2	13.7 ± 0.3	11.8 ± 0.8	13.0 ± 0.9
25.0–29.9 kg/m^2	32.5 ± 0.5	30.6 ± 1.1	24.0 ± 1.5
≥30.0 kg/m^2	53.8 ± 0.5	57.6 ± 1.2	63.0 ± 1.9
Medication use (%)			
Insulin use	36.4 ± 0.5	67.4 ± 1.1	30.3 ± 1.8
Basal insulin + OADs	14.8 ± 0.3	24.0 ± 1.0	–
Basal-bolus insulin + OADs	21.6 ± 0.4	43.4 ± 1.2	–
Any diabetes medication	92.7 ± 0.3	98.2 ± 0.3	89.0 ± 1.3
HbA1c (%)			
<7.0% (53 mmol/mol)	37.7 ± 0.5	0.0	52.2
≥9.0% (75 mmol/mol)[‡]	16.1 ± 0.4	100.0	12.6
Controlled LDL-C (%)[§]	59.0 ± 0.5	49.0 ± 1.3	56.8
No microalbuminuria (%)**	47.0 ± 0.6	32.1 ± 1.4	69.8%
Blood pressure <130/80 mmHg (%)	40.7 ± 0.5	33.5 ± 1.2	51.3
Medical history			
Neuropathy	7.2 ± 0.3	9.7 ± 0.7	–
Retinopathy	6.6 ± 0.2	10.4 ± 0.7	–
Nephropathy	19.7 ± 0.4	24.3 ± 1.0	–

Data are given as the mean ± SE.

*Except as indicated: the number of available records for LMC patients may differ across outcomes, reflecting missing responses on specific items. No data imputation was used.

[†]Defined as household income <C$30 000 (Canadian dollars) in LMC patients and <US$20 000 in the NHANES report.

[‡]Percentage of HbA1c >9% instead of ≥9% was reported in NHANES.

[§]Defined as low-density lipoprotein cholesterol (LDL-C) < 2.0 mmol/L in LMC patients and <140 mg/dL in NHANES.

**Defined as urinary albumin creatinine ratio (uACR) < 2.0 μg/mL in LMC patients and uACR <30 mg/g in NHANES.

OAD, oral antidiabetic drug.

refractory patients defined by HbA1c >9.0% (75 mmol/mol). In the overall Registry population, approximately half the patients were female and the mean (± SE) age was 58.7 ± 0.1 years. Mean HbA1c was 7.6 ± 1.5% (60 ± 7 mmol/mol).

In the overall Registry population, 92.7% of patients were receiving some antidiabetic therapy, with 36.4% using insulin. Within the refractory subgroup, 98.2% were receiving some form of therapy, and the proportion using insulin was nearly double that in the overall population (67.4%). Nevertheless, only 37.7% of patients had reached the CDA target of HbA1c ≤7.0% (53 mmol/mol) at their most recent assessment, and 16.1% had HbA1c ≥9.0% (75 mmol/mol). Among insulin users, substantially fewer patients (~16%) reached the CDA HbA1c target, and the proportion with HbA1c ≥9% (75 mmol/mol) was higher than in the entire cohort (28%).

Mean (± SD) total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides in the complete Registry population were 3.9 ± 1.0, 2.0 ± 0.8, and 1.7 ± 1.3 mmol/L, respectively. These values were significantly higher in the refractory subpopulation (4.2 ± 1.2, 2.2 ± 0.9, and 2.0 ± 1.7 mmol/L, respectively) compared with patients with controlled HbA1c. Microvascular complications, such as retinopathy or neuropathy, were all more common in the refractory population than in the overall registry population (Table 2).

The recently published patient set from the US National Health and Nutrition Examination Survey (NHANES) has been included in Table 2 for comparison, although it describes a general patient population that included both primary and specialist care populations. The LMC patient population was similar to the NHANES group with regard to sex ratio and use of insulin or other antihyperglycemic medications. Younger patients (18–44 years) were considerably more common in the LMC group, and disease duration was longer. Obesity (BMI ≥30 kg/m^2) was less common in the LMC Registry compared with the NHANES group. Nevertheless, good glycemic control (HbA1c ≤7.0% [53 mmol/mol]) was less likely in the LMC group than in the NHANES population (37.7% vs 52.2%, respectively). Rates of microalbuminuria were lower and blood pressure was controlled to a target (130/80 mmHg) in a higher proportion of patients in the NHANES population than in the LMC Registry patients.

Refractory status in the LMC diabetes database

Univariate logistic analyses identified a number of patient characteristics that were significantly associated with functional refractory status, including BMI, duration of diabetes, use of insulin, levels of TC, LDL-C, and triglycerides, and existing diagnoses of neuropathy, retinopathy, or nephropathy. The number of OADs was also significantly correlated with refractory status in the population of non-insulin users. Age at diagnosis was negatively correlated with refractory status in the overall group. The duration of specialist care at LMC was not correlated with refractory status, but refractory patients showed the highest frequency of visits with our Diabetes Education Program (DEP) staff. Blood pressure control was not correlated with glycemic control. Data on ethnicity and household income were not sufficiently complete to permit their inclusion in the univariate analysis.

A multivariate logistic regression model to predict refractory status then included the significant variables identified in the univariate analyses (Fig. 1; except for TC, which was highly collinear with triglycerides). Body mass index, duration of diabetes, and existing diagnoses of neuropathy, retinopathy, or nephropathy were found to not be individually correlated with refractory status when the other characteristics were taken into account. Insulin therapy was most closely associated with refractory status: insulin-treated patients were 3.2-fold more likely
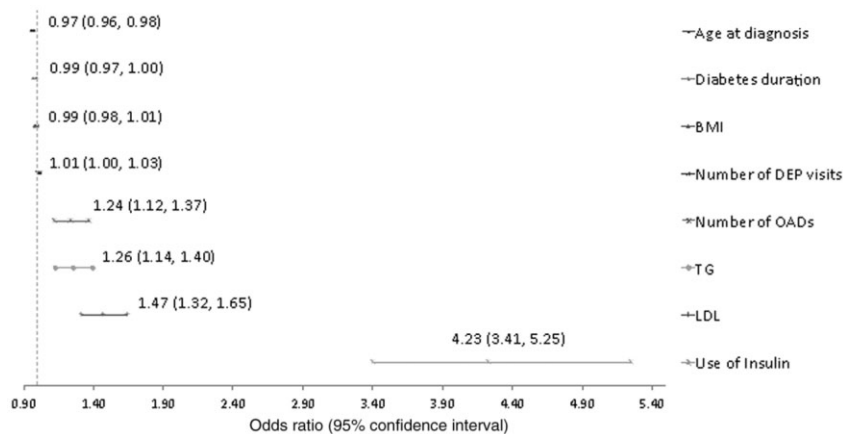

Figure 1 Multivariate logistic regression model on training data. BMI, body mass index; DEP, Diabetes Education Program; OAD, oral antidiabetic drug; TG, triglycerides; LDL, low-density lipoprotein.

to be refractory than those who were not receiving insulin. Low-density lipoprotein cholesterol was positively associated with refractory status, such that with each 1 mmol/L increase in LDL-C a patient's likelihood of being refractory increased by 47%. A smaller association was seen with age at diagnosis: for each incremental year, the risk of being refractory declined by 3%.

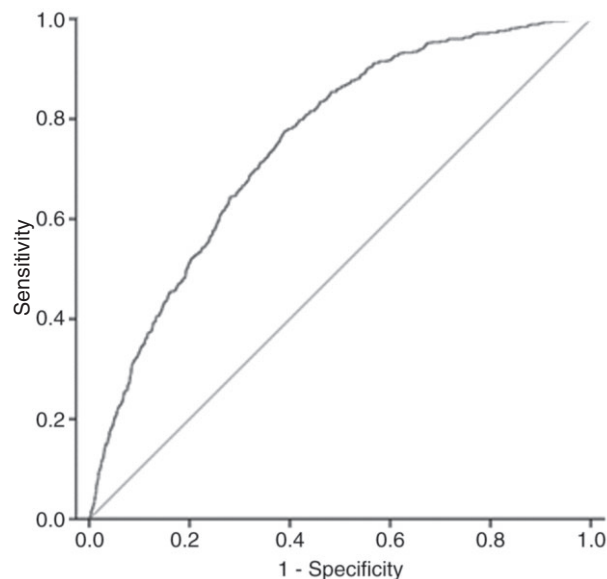Using the final model, a patient's probability (p) of being functionally refractory could be expressed as:

$$p = \frac{\text{Odds}}{1+\text{Odds}}$$

where:

$$
\begin{aligned}
\text{Odds} \approx \exp(&-2.220 - 0.031 \times \text{diagnosis age} - 0.006 \times \text{BMI} \\
&- 0.012 \times \text{diabetes duration} + 0.014 \times \text{no. DEP} \\
&\text{visits} + 0.215 \times \text{no. OADs} + 1.443 \times \text{insulin use} \\
&+ 0.388 \times \text{LDL} + 0.232 \times \text{TG} - 0.094 \times \text{Neuropathy} \\
&+ 0.318 \times \text{Retinopathy} + 0.002 \times \text{Nephropathy})
\end{aligned}
$$

and exp is the mathematical exponential function.

The final model was fitted on the validation data and showed highly consistent results. Finally, an ROC analysis was performed to examine the ability of the model to accurately discriminate between patients with and without functional refractory status. The AUC of the model for the training and validation groups was 0.75 (95% CI 0.73–0.77) and 0.76 (95% CI 0.74–0.78), respectively, indicating modest to good discriminatory ability (Fig. 2).

Discussion

Among people diagnosed with T2D in Canada[3] and the US,[4] only approximately half meet targets for glycemic control and 10%–12% do not achieve even minimal control, defined here as HbA1c <9.0% (75 mmol/mol). Our analysis of various diabetes registry databases suggests that specialist care clinics include a disproportionately high number of patients with poor glycemic control, of whom a significant proportion appear to be functionally refractory, with persistently poor glycemic control.

Within these registry populations, refractory status appears to share elements common to the peak of the traditional accumulative approach to diabetes care: the longest duration of diabetes, the greatest complexity of treatment, and the most existing complications. Interestingly, insulin use alone was not commonly linked to poor glycemic outcome, whereas combination therapy that included OAD or non-insulin therapy based on complex OAD therapies were predictive of poor glycemic outcome. Newer initiatives that include earlier and more intensive insulin therapy may prevent the therapy accumulation snowball and may be optimally aligned with improved glycemic control.

In the LMC diabetes database, 38% of patients had good glycemic control (HbA1c ≤7%; 53mmol/mol), whereas 16.1% showed poor control (HbA1c ≥9.0%; 75 mmol/mol). These latter patients had had access to LMC HCPs and publicly funded resources within the same clinic settings, delivered by a common guideline-based care pathway, for at least 1 year, which suggests that they are refractory to usual care measures. Because specialist-supervised care, along with intensified glucose management including insulin therapy, can arguably achieve improved glycemic control in nearly all patients, the refractory nature of these patients must represent functional refractoriness, rather than classic therapeutic unresponsiveness. The proportion of such patients in the LMC Registry is similar to the rates reported in an earlier analysis of specialist care populations in a Canadian province[13] and at a diabetes care consortium in Singapore (B.H. Heng, pers. comm., 2013),[26] but higher than that seen in a selective survey of Canadian T2D populations in primary care.[3]

Understanding the functionally refractory patient is an important step towards developing new therapeutic strategies to improve their glycemic status. These

	AUC	95% CI	*P*-value
Training data	0.75	0.73–0.77	<0.01
Validation data	0.76	0.74–0.78	<0.01

Figure 2 Receiver operating characteristic (ROC) curve for predicting refractory status in the LMC type 2 diabetes dataset. AUC, area under the curve; CI, confidence interval.

patients are at high risk of cardiovascular mortality, stroke, and microvascular disease such as retinopathy, neuropathy, and nephropathy.[31,32] Furthermore, retrospective analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial have suggested that persistent non-responders to intensive treatment, who resemble our cohort of functionally refractory patients, show an increased risk of death.[15] Partially based on this finding, current guidelines[7] recognize the increased vulnerability of this cohort to poorer outcomes. Better understanding of this functionally refractory cohort may lead to more effective strategies to safely improve glycemic control. Early identification of such patients is a key first step, so that barriers to glycemic control can be identified and strategies devised to help deliver care more effectively.

Prior registry reports that have included a specialist care patient cohort have frequently identified predictors of poor glycemic control. Other than specialist care itself (when compared with primary care alone), important predictors have included the number of OAD therapies, insulin treatment, longer duration of diabetes, and younger age. Given this combination, one may hypothesize that younger age at diagnosis would be similarly predictive of poor glycemic control; in our analysis, younger age at diagnosis was indeed correlated with later refractory status. The presence of microvascular complications also correlates with poor glycemic control. Although this association may be related to glycemia itself, it nevertheless serves as a useful predictor for the clinician wishing to individualize their approach to these patients. Surprisingly, factors such as BMI, waist circumference, ethnicity, and socioeconomic factors have not been consistently related to poor glycemia in these registries. Toh et al.[33] applied a logistic regression analysis within a Singaporean diabetes database and found that elevated LDL-C, younger patient age, and higher BMI were significantly predictive of poor glycemic control, defined in that study as HbA1c >8.0% (64 mmol/mol). In our analysis, BMI was negatively correlated with refractory status but was not statistically significant when other factors were taken into account.

Neither the duration of care in LMC clinics nor the prereferral diabetes duration were correlated with HbA1c outcome. Indeed, we have previously shown that despite extended durations of poor control prior to referral, patients generally do respond well to specialist-led team care following referral, achieving a mean HbA1c reduction of 1.1%.[34] Other potential variables of interest, such as incidence of hypoglycemia, therapy non-adherence, and clinic non-attendance, could not be assessed due to limitations in our data collection, but will be assessed separately in an ongoing initiative to address persistent barriers to care within the functionally refractory cohort.

The strengths of this study include the size of the LMC database (~52 800), which is among the largest of any specialist care diabetes registry, and the inclusion of patients with T2D from across Canada, with broad ranges of age, ethnicity, and socioeconomic status. Uniform clinical data collection procedures at LMC centers may have contributed to data consistency and reduced the incidence of missing data. Similarly, consistent diabetes care practices and diabetes education, and a common electronic medical record system, all contribute to the homogeneity of the outcome data. The publicly funded nature of the Canadian healthcare system has potentially eliminated socioeconomic status as a factor that may limit access to care in some settings. Despite the diverse ethnicities within the patient population, physician care, diabetes education, or both were provided with support in 18 languages. Finally, the threshold selected for poor glycemic control was conservative.

Potential limitations should be acknowledged. Because the data were strictly cross-sectional, it was not possible to consider prior glycemic control as a potential predictor of outcomes under specialist care. In addition, in common with other published analyses of predictors of glycemic control, patients' experience of hypoglycemia could not be reliably included in the models. Similarly, data on family income and ethnicity were not complete enough to allow their inclusion in the regression model. Finally, because the models were not applied prospectively, the present model of refractory outcomes should be regarded as hypothesis generating. Nevertheless, these models were robust in several respects: multivariate logistic regression was used to address potential confounding, and the conclusions were quantitatively and qualitatively similar and independent of different approaches to analysis. Indeed, similar conclusions (not shown) were reached using multiple linear regression to model patient HbA1c as a continuous variable rather than a dichotomized outcome as described here.

Although the number of publicly shared population registries of diabetes patients has grown in recent years, there remain very few reports of specialist care-level patient registries. Given the historical challenges of achieving glycemic targets for our patients, the feedback on outcomes achieved should be helpful for the organization of specialist care, and continuing effort should be devoted to developing such registries, with the primary aim of providing this feedback to caregivers. Furthermore, once this valuable information has accumulated, it should be shared publicly to support analyses of optimal methods of healthcare delivery, real-life evidence collection, and hypothesis generating. Analysis of the large,

multispecialist LMC group diabetes patient registry has confirmed and defined the disproportionately greater representation of persistently poorly controlled T2D patients within specialty care clinics that receive their patients only by referral from primary care. These patients represent a group that is effectively functionally refractory to usual care, an ongoing challenge at specialist clinics, and are likely to carry a higher risk of mortality. Studies are now under way to better identify barriers to effective treatments and education, and to implement changes in care to address these barriers.

Acknowledgments

Disclosure

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