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Type 1 Diabetes Population Surveillance Through the BETTER Patient-Engagement Registry: Development and Baseline Characteristics

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Abstract

Objective: The BETTER registry is a type 1 diabetes population surveillance system co-developed with patient-partners to address the burden of hypoglycemia and assess impact of new therapies and technologies. The aim of the present report was to describe the baseline characteristics of the BETTER registry cohort.

Methods: Cross-sectional baseline evaluation of a Canadian clinical cohort established by online questionnaire. Participants were recruited through clinics, public foundations advertising and social media. As of February 2021, 1430 persons living with type 1 diabetes or latent-autoimmune diabetes (LADA) aged 14 years or older were enrolled. The trial was registered on clinicaltrials.gov: NCT03720197.

Results: Participants were (mean ± SD) 41.2 ± 15.7 years old with a diabetes duration of 22.0 ± 14.7 years, 62.0% females, 92.1% Caucasians, 7.8% self-reporting as LADA, 40.9% using a continuous subcutaneous insulin infusion system (CSII), and 78.0% a continuous glucose monitoring system (CGMs). Most recent A1C ≤ 7% was reported by 29.7% of participants. At least one episode of hypoglycemia < 3.0 mmol/L (level-2-H) in the last month was reported by 78.4% of participants, median 5 episodes [3.0-10.0]. The occurrence of severe hypoglycemia (level-3-H) in the last 12 months was reported by 13.3% of participants. Among those, the median number of episodes was 2.0 [1.0-3.0].

Conclusions: We established the first surveillance registry for people living with type 1 diabetes in Canada relying on patient-reported outcomes and experiences. Hypoglycemia is a highly prevalent burden despite a relatively wide adoption of CSII and CGM use.

Key messages:

- Hypoglycemia is the most frequent acute complication of type 1 diabetes and is the main barrier to achieving A1C goals.
- The BETTER registry is the first registry in Canada to collect patient-reported outcomes to address the burden of hypoglycemia.
- Our data show a persistently high hypoglycemia risk and a low percentage of participants reaching A1C targets.

Introduction

Hypoglycemia is the most frequent acute complication of type 1 diabetes (T1D) and is the main barrier to achieving A1C goals [1]. Hypoglycemia is burdensome for PWT1D as symptoms are highly unpleasant (e.g. sudden weakness, blurry vision) and it has physical (e.g. fall and accidents) [2], societal (e.g. driving limitations) [3] and economic (e.g. work-time loss) [4] consequences as well as negative impacts on mental health and quality of life (e.g. fear of hypoglycemia) [5]. Hypoglycemia is also associated with increased mortality and neurocognitive dysfunction [3].

Hypoglycemia is divided into 3 categories: 1) Level-1-H (≤ 3.9 mmol/L; alert blood glucose); 2) Level-2-H (< 3.0 mmol/L; high risk of complications) and 3) Level-3-H (no defined glucose; severe hypoglycemia requiring a third-party assistance) [6]. Level-1-H and level-2-H, referred to as non-severe hypoglycemia, are usually resolved with prompt ingestion of simple carbohydrates. Conversely, level-3-H can lead to coma and death; it requires rapid external intervention which can include glucagon or intravenous glucose. In real life settings, hypoglycemia frequency is variable between countries but is usually higher than that reported in clinical trials [7]. In Canada, Aronson et al. [7] reported, among 183 people with type 1 diabetes (PWT1D), an annualised incidence rate of hypoglycemia ≤ 3.1 mmol/L of 128 events/adult/year. We also previously reported in a cohort of 121 PWT1D a mean number of 2.2 episodes over a 2-day period. These episodes included both preventive snacking for imminent hypoglycemia and self-treated hypoglycemia (glycemia < 4.0 mmol/L and 4.0 to 5.0 mmol/L with symptoms) [8]. Actual rates could be higher because of the high frequency asymptomatic nocturnal hypoglycemia [9]. The frequency of level-3-H episodes, for which third party assistance is required, varies between 0.3-3.0 events per patient-year [10]. Back in 2013, before CGM was largely available, 11.8% of participants included in T1D exchange registry reported having had a seizure or loss of

consciousness due to hypoglycemia in the prior 12 months [11]. Hypoglycemia frequency vary widely between studies depending on definition used, data collection methodology (e.g. prospective vs. retrospective, questionnaires vs, database) and population risk [12].

Back in 2017, we convened a group of PWT1D, healthcare providers and scientists to discuss the current key issues for PWT1D. This meeting was based on four key principles for patient-oriented research: (1) embracing inclusive research processes; (2) collaborating respectfully with stakeholder populations; (3) recognizing the value of patients' lived experiences and; (4) conducting research that focuses on patient-identified priorities [13]. The main conclusion was that hypoglycemia remains PWT1D' highest preoccupation affecting all of their daily activities and constituting the main barrier to achieve recommended glycemic targets and should thus be a research priority. There was also a great hope that new therapies and technologies could reduce hypoglycemia burden.

The BETTER (**BE**haviors, **T**herapies, **TE**chnologies and hypoglycemic **R**isk in Type 1 diabetes) registry, a population surveillance system [14], was co-developed with a group of patient-partners. Patient-partners were PWT1D or a parent of a child living with T1D. Careful attention was given to diversity in terms of gender, age, living area and diabetes treatment modality. Patient-partners guided the research team in determining the research objectives of the BETTER registry, were involved in the development and revision of questionnaires and in establishing recruitment strategies. Patient-partners participated in the analysis of results and in data dissemination. The BETTER registry was launched in 2019 and is the first registry to prospectively collect patient-reported outcomes in the province of Quebec to address the burden of hypoglycemia and to assess the impact of new therapies and technologies on this burden. The objective of this paper is to describe the BETTER registry and provide an overview of the baseline characteristics of the 1430 participants aged ≥ 14 years enrolled as of February 2021. As

age is strongly associated with mean A1c and severe hypoglycemic risk [15], we investigated the impact of age on key parameters collected in the BETTER registry

Methods

The BETTER registry is coordinated by the Montreal Clinical Research Institute, a non-profit research center. This registry is approved by the research ethics board of the Centre hospitalier de l'Université de Montréal (18.232 – MP-02-2019-7992). The list of participating centers is available in Appendix A and the list of members of the BETTER study group is presented in Appendix B. As of February 2021, recruitment of participants is active in 16 out of 17 administrative areas of the province of Quebec (Supplementary Table 1). Participants self-register and provide online informed consent: from participants aged ≥ 14 years and, according to Quebec legislation, from parents/guardians of participants < 14 years old (https://type1better.com/en/home).

To enroll in the BETTER registry, individuals must self-report a clinical diagnosis of T1D or LADA (latent autoimmune diabetes in adults), provide a valid address in the province of Quebec (Canada) and be able to read French or English.

Participants are recruited through various means. In partner hospital centers or medical clinics, 1) potential participants may be approached by a research assistant during their follow-up appointment and/or 2) flyers available in waiting rooms, and/or 3) letters or emails that are sent as invitations to enroll in the registry. Recruitment also relies on social media, 4) by collaborating with different associations such as Diabète Québec, Diabetes Canada, Juvenile Diabetes Research Foundation and Diabetic Children's Foundation to promote enrollment or 5) directly on Facebook groups for PWT1D. Other means used include, 6) networks of healthcare professionals; 7) presentation of the project during conferences/seminars for healthcare professionals to incite them to invite their patients to participate; 8) promotion during events for patients (e.g. JDRF Walk to

Cure Diabetes); 9) study website (https://type1better.com/en/home/); 10) Connect1d platform (connect1d.ca) and 11) patient-partners advocacy within the community.

An online questionnaire is answered at enrollment for all participants, with the possibility, for participants 14 years or older, to participate to additional data collections (two additional questionnaires, food intake, physical activity) and to prospective annual follow-ups. Questionnaire data is collected using REDCap (https://www.project-redcap.org/). Food intake is collected using an online 24-hour food recall as previously described [16], and physical activity, using a pedometer provided by the research team [17]. The data collected in each questionnaire are presented in Supplementary Table 2. The 1st questionnaire includes sociodemographic data, diabetes duration, current treatment modalities, reported A1C, diabetes complications, commonly used medications (e.g. cardio-renal or antidepressant drugs) and history of non-severe and severe hypoglycemia as well as impaired awareness of hypoglycemia (IAH) based on the Gold score [18] (score ≥ 4) and glucagon usage. The 2nd questionnaire includes questions on management and consequences of hypoglycemia, diabetes treatment, fear of hypoglycemia, diabetes distress, IAH (Clarke score) and some lifestyle habits (smoking status and alcohol/drugs consumption). The 3rd questionnaire provides additional information on diabetes and hypoglycemia treatment, management of hyperglycemia, sleep habits, stigmatization, barriers to physical activity and depression. Each questionnaire completed gave participants a one-entry in a lottery (one gift card [$CAD500]) per 500 entries).

A research coordinator is responsible of verifying that the same individuals did not participate more than once by using the first name, last name, date of birth and email address of participants. Lower and higher thresholds for variables with numerical values were determined to allow data verification.

The BETTER registry database is managed using the suite of open source software (Opal and Mica) developed by the Maelstrom team at the Research Institute of the McGill University Health Centre. The detailed list of collected variables is available at: https://www.maelstrom-research.org/mica/individual-study/better.

Demographic and clinical characteristics were tabulated according to age groups (14 to 25, 26 to 49, 50 to 64, and 65 years and over) as previously proposed [1]. Continuous variables were described with mean ± standard deviation or median (interquartile range), while categorical variables were reported as percentages. A one-way analysis of variance (ANOVA) with Games-Howell post hoc (or its nonparametric alternative Kruskal-Wallis H test with multiple pairwise comparisons using Dunn's procedure) were used to compare reported frequency of level-2 and level-3 hypoglycemia, number of capillary blood glucose per day, as well as diabetes duration as continuous variables between the four age groups. Games-Howell test was chosen as it does not need to fulfill equal variance or sample sizes between groups' assumptions. For categorical variables, Chi-squared ($\chi 2$) test of homogeneity was used to determine the differences in participant characteristics (socioeconomic data, T1D related characteristics, complications, and use of medication) compared across the age groups, followed by a post hoc pairwise comparison using a z-test of two proportions with a Bonferroni correction to correct for multiple comparisons. Socioeconomic data (income, highest level of education, employment status) was included for adult participants only (≥ 18 years). A value of $P < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics 27 (SPSS, Inc., Chicago, IL).

Results

The data presented in this paper was collected between February 2019 and February 2021. During that period, 1430 participants ≥ 14 years old registered. Among those participants, 859 answered the second questionnaire and from those, 596 participants answered the third questionnaire. This publication presents the data of the first questionnaire.

Sociodemographic characteristics of the 1430 participants are presented in Table 1. The mean age of the participants was 41.2 ± 15.7 years, with 19.0% being aged between 14 and 25 years and 7.8% aged 65 and over; 62.0% were female, 92.1% were Caucasian, and 43.6% had a university degree. A little more than one quarter (28.6%) of participants had an annual household income above 100,000CAN$; 56.8% of participants worked full time, and 67.3% had private insurance while remaining participants where covered by the public system (universal coverage).

A significant percentage of participants self-reported having LADA (7.8%). Mean diabetes duration was 22.0 ± 14.7 years, with 29.2% of participants having diabetes for more than 30 years and 4.2% for more than 50 years (Table 2 and Figure 1). Continuous subcutaneous insulin infusion (CSII) was used by 40.9% of participants; with a significantly more frequent use in participants 14-25 years old (52.8%) as compared to other age groups ($p < 0.001$). Use of real time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM) in the last year was reported by 78.0% of participants. The proportion of participants using a rtCGM or isCGM was the highest in the 26-49 age group (82.2%) and this was significantly different from the 14-25 (72.3%) and ≥ 65 (70.5%) age groups ($p = 0.018$). Among participants not using a CGM, the average number of capillary blood glucose tests was 4.8 per day, with 44.4% testing 5 or more times a day (6% testing 10 times or more). Between 85.8% and 89.3% of participants had seen an endocrinologist in the last year for a diabetes

follow-up appointment with no significant difference between age groups. Most recent A1C ≤ 7% was reported by about a third (29.7%) of participants. Participants aged 26-49 years had a A1C ≤ 7% in a greater proportion (34.5%) compared to other age groups ($p < 0.001$) (Table 2 and Supplementary Figure 1).

As shown in Table 2, 31.3% of participants aged ≥ 65 years had a cardiovascular disease, which is significantly greater compared to the younger age groups ($p < 0.001$). In all participants, the prevalence of nephropathy, retinopathy and neuropathy was respectively 10.7%, 20.1% and 16.9%. In addition, in all participants, 21.2% of participants reported one microvascular complication, 7.7% reported two microvascular complications and 3.7% reported three microvascular complications (data not shown). The proportion of participants taking medication for hypertension or cardio-renal protection increased with age, going from 4.1% in 14-25 years old to over 60% among participants aged 50 and over. Similar results were observed for medication taken for the prevention or treatment of dyslipidemia (1.8% in 14-25 years old to over 70% in 50 years old and over). Medication taken for depression was also reported in 20.6% of participants, with the highest prevalence in the 26-49 age group (24.1%).

The frequency of level-2 and level-3 hypoglycemia is presented in Table 3. The proportion of participants with a level-2-H (< 3.0 mmol/L) in the last month was 78.4% with no significant difference between age groups ($p = 0.077$). Among participants reporting a level-2-H in the last month, the median number of level-2-H episodes in the last month was 5.0 [3.0-10.0] in all age groups except in the ≥ 65 age group in which the median number of episodes was 4.0 [2.0-7.7] ($p = 0.098$). For level-3-H (low blood glucose level requiring help from another person, or use of glucagon, or leading to hospitalization or resulting in loss of consciousness), 13.3% reported experiencing at least one episode in the last year. A higher proportion of participants in the 26-49 (14.1%) and 50-64 (15.3%) age groups reported a level-3-H in the last 12 months compared to the

14-25 age group (7.4%) ($p < 0.001$). However, when comparing the number of level-3-H episodes in the last 12 months, there was no statistically significant difference across different age groups; with an overall median number of 2.0 [1.0-3.0] episodes in participants reporting at least one episode. IAH was assessed using the threshold ≥ 4 with the Gold score. We observed that more participants in the 50-64 (24.3%) and ≥ 65 (28.6%) age groups had IAH compared to participants aged 14-25 years old (13.7%) and 26-49 years old (18.3%) ($p < 0.05$). In line with this, a significantly higher proportion of participants aged 50-64 (4.3%) or ≥ 65 (5.4%) had no feeling of symptoms of hypoglycemia compared to participants aged 26-49 (1.0%) ($p < 0.001$).

Discussion

The BETTER registry focus on the burden of hypoglycemia as well as the role played by new therapies and technologies to possibly mitigate this burden. This first description of this population surveillance system, showed that hypoglycemia remains a significant burden with 78% of them reporting a median of 5 level-2-H episodes in the last month and 45% of participants having experienced a level-3-H episode since T1D diagnosis out of which 13.3% reported experiencing at least one episode in the last year. Accordingly, a fifth of participants had IAH (19%) and only a fourth perceived symptoms of hypoglycemia above 3.8 mmol/L (27%). Close to a third of participants (30%) reached the main therapeutic goal for an A1C ≤ 7%; the percentage of participants affected by chronic complications remained high (7% for macrovascular and 21% for microvascular complications).

Over the years, many diabetes registries have been created. The BETTER registry differs from other available registries for PWT1D [19-25]. The BETTER registry was co-developed with patient-partners, is mainly based on patient-reported outcomes and experiences and participants are recruited through various means. Other registries are mainly using data collected by healthcare teams of through databases. The T1D Exchange Clinic Registry consists of a network of adult and pediatric diabetes clinics that prospectively collects clinical data in PWT1D (34,000+ participants by 2017) [23]. The Prospective Diabetes Follow-up Registry (DPV) contains anonymized data on diabetes treatment and outcome from 556,021 individuals with all types of diabetes, provided by 485 diabetes centres from Germany, Austria, Switzerland and Luxembourg [21]. Other registries originating from Sweden (Swedish National Diabetes Register; NDR) [22], Germany (German Diabetes Versorgungs-Evaluation; DIVE) [20], Denmark (Danish Adult Diabetes Registry; DADR) [24], Canada [19] and USA [25] are collecting data in PWT1D through hospitals or clinics medical files.

Across all age groups, 21.9% to 34.5% of BETTER participants met the Diabetes Canada A1C goal of ≤ 7.0% (Table 2) [26]. We have shown using data of the BETTER registry that self-reporting a range of A1C highly agrees with laboratory-measured A1C [27]. This may be an indication that engagement in such registry might capture individuals with an overall higher involvement in their T1D management. Indeed, in individuals living with type 2 diabetes, self-knowledge of A1C values is associated with better glucose control [28]. The proportion of individuals who reached the target of A1C ≤ 7% varies between databases, however the numbers from the BETTER registry are comparable to previously reported values. For example, in the DPV registry, 31.5% of adults had a A1C < 7% [21] while the LMC Diabetes Registry and T1D Exchange respectively reported that 22% and 21% of adults had an A1C ≤ 7% [19, 23]. Large cross-sectional real-life multinational study such as in the SAGE study have reported a lower proportion of patients reaching the less than 7% target: 24.3% [29]. Interestingly, a large fraction of participants is close to the A1C target as 41.1% reported levels between 7.1% and 8.0%, and therefore focusing on this large group could significantly improve the overall reported picture of diabetes control in this report. Reaching A1C targets is usually less prevalent in younger patients; indeed, only 21.9% of participants aged 14 to 25 years reportedly meet the A1C ≤ 7% goal. In the pediatric population, the recommended A1C goal is below 7.5% [26]. In a subsample of 52 participants aged 14-17 years old, only 13.7% reached that goal (data not shown). This is comparable to what was reported in the T1D Exchange for children and adolescents [23].

In our cohort, 78.4% of participants experienced at least one level-2-H episode (< 3.0 mmol/L) in the last month with a median number of five hypoglycemic episodes (Table 3). This observation differs from what was reported in the Canadian LMC registry, given that the hypoglycemia category was not specified and that participants were asked to report the frequency of ‘‘any hypoglycemia’’ (symptomatic and/or confirmed) in the previous week. In the Canadian LMC

registry, 63.1% of participants reported at least one hypoglycemic event per week with a mean incidence of 1.2 events [19]. Similarly, in the SAGE study, the proportion of affected patients was lower with 49.9% of patients reporting at least one level-2-H in the last 3 months [29]. Differences in the definition of hypoglycemia and in the proportion of participants using rtCGM/isCGM may largely explain different reported frequencies [12]. As for level-2-H, frequency of level-3-H varies depending on the definition used. In other registries, the definition used to define level-3-H varies from "the need of the assistance of another person" to "hypoglycemia resulting in seizure or loss of consciousness" [11, 19, 21, 30]. Diagnosis codes for hypoglycemia reported upon inpatient admission or at an emergency room visit was also used in the T1PCO study [21]. Using these definitions, severe hypoglycemia in the last 12 months was reported in 3.6% to 31.5% of participants [11, 19, 21, 30]. In the BETTER registry, level-3-H was defined as a low blood glucose levels requiring help from another person or use of glucagon or hospitalization or loss of consciousness which is the definition endorsed by ADA and Diabetes Canada [26, 31]. Based on this definition, 13.3% of participants experienced at least one level-3-H in the last 12 months with a median of 2 episodes per affected patient (Table 3). This result is close to what was reported by T1D Exchange [11], DPV registry [21] and SAGE study [29], suggesting that the definition we used allowed us to adequately capture severe hypoglycemic events. IAH is a major risk factor for level-3-H and available data suggest that it affects 20-25% of PWT1D [32]. Our results are in line with this as we observed that close to 20% of our participants had IAH.

Both insulin delivery method as well as glucose monitoring method could affect observed results for both A1c and hypoglycemia. The proportion of participants using CSII was significantly higher in the 14-25 (52.8%) and 26-49 (42.7%) age groups (Table 2). These results reflect what was reported in the Canadian LMC registry as CSII use was more frequent in younger age groups: 43.5% in 18-25 years old, 42.0% in 26-49 years old and 36.1% in ≥ 50 years old [19]. In

the province of Quebec (Canada), reported percentages likely represent the impact of the governmental insulin pump access program available for those who start using CSII before the age of 18 years old [33]. These numbers differ from what was noted in T1D Exchange. Indeed, among participants aged 18-29 years old and 30-49 years old, the proportion of participants using CSII were respectively 59% and 65% [34]. According to Hermann et al. [34], the high percentage of CSII use in T1D Exchange could be in part attributable to the fact that participants receive their care at specialized diabetes clinics possibly overestimating the overall CSII use in the United States.

We observed that the proportion of participants using a rtCGM or isCGM was significantly higher in the 26-49 (82.2%) age group compared to the 14-25 (72.3%) and ≥ 65 (70.5%) age groups (Table 2). These results are notably different from the Canadian LMC Registry as CGM use varied from 16.4% to 23.8% across age groups [19]. Our proportion of participants using CGM technology is also higher from those of T1D Exchange and DPV registry as in both registries, 30% of participants were using a CGM [23, 35]. This difference could be related to the different periods of data collection and to access (e.g. public insurance coverage). Indeed, a US-based study also showed a sharp increase of CGM usage in recent years [36]. In the province of Quebec, there is a large access to isCGM for PWT1D with both public and private insurances as long as PWT1D have faced recurrent hypoglycemic episodes. However, we cannot exclude that a recruitment bias led to a higher proportion of participants using a CGM.

[19][11, 19, 21, 30][21][11, 19, 21, 30][26, 31][11][21][32]

The presence of reported diabetes chronic complications such as neuropathy and retinopathy has decreased over the last decades [37, 38] but remains significant and increases with age. For example, in participants aged ≥ 50 years, 30% of participants had neuropathy or retinopathy while 15% had nephropathy (Table 2). For comparable age groups, these percentages are different from the LMC registry reporting lower rate of neuropathy (11.6%) or retinopathy (21.2%) and higher

rate of nephropathy (31.6%) [15]. We also observed a marked increase in the proportion of participants having a macrovascular complication in the ≥ 65 age group (31.3% compared to 13.9% in the 50-64 age group). As a comparison, Aronson et al. [19] reported that 11.1% of participants aged ≥ 50 years old had a macrovascular disorder. The difference between our results and those of the Canadian LMC registry could be explained, at least in part, by the method used to collect information on diabetes-related complications. In the BETTER registry, the information was reported by participants while in the Canadian LMC registry the information was retrieved from medical records. Under- (e.g. not being aware of microalbuminuria) or over-reporting (e.g. interpreting leg pain related to mechanical problems as neuropathy) could be possible with patient-reported outcomes. Conversely, missing diagnosis could lead to underestimation of data from medical records.

As awaited, based on guidelines to introduce cardiometabolic preventive treatments (e.g. PWT1D > 30 years of age with a diabetes duration > 15 year) [39], in the BETTER registry, we observed that the proportion of participants taking medication for the treatment of hypertension or cardio-renal protection significantly increased after the age of 25 (Table 2). Accordingly, less than 5% participants aged ≤ 25 years old were taking medication while after the age of 25, this proportion increased to more than 20% and to more than 60% at the age of 50. Similarly, the proportion of participants using lipid-lowering medications was less than 5% when aged ≤ 25 and this proportion increased to more than 70% at the age of 50. Similar increases in the use of antihypertensive or lipid-lowering medications with age was also observed in the Canadian LMC registry [19].

T1D is associated with a higher risk of mental health issues than in the general population [40]. Drug prescription for depression capture a fraction of mental health issues. In the BETTER registry, around 20% of our participants were taking medication for depression. This result is identical to the findings of Gendelman et al. [41] stating that among 458 PWT1D, 20.7% reported

using antidepressant medications. As depression in diabetes is associated with poorer glycemic control [42], greater risk of level-3-H [43] and poorer quality of life [44], these results suggest that greater attention should be given to depressive symptoms during PWT1D follow-up. A recent publication highlighted the positive impact of an intervention on diabetes distress with improvements in self-care behavior translating into positive glycemic outcomes [45].

When compared to the data of other registries, we believe that our data are representative of adolescents and adults living with T1D. However, since the participation is on a voluntary basis, participants may not be representative of the overall T1D population in Quebec. PWT1D included in the BETTER registry were mostly Caucasian, relatively affluent, well educated and with an overrepresentation of women. A lot of these characteristics mirror the overall province of Quebec diversity [46].

Conclusions

To our knowledge, we established the first PWT1D population surveillance system in Canada based on patient-reported outcomes. In the context of large adoption of modern treatment, our data show a persistently high hypoglycemia risk, a low percentage of participants reaching A1C targets and a high percentage of participants affected by chronic complications. Patient-reported outcomes are essential to understand the persistent burden of T1D and to undertake actions to reduce it.

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Authorship Contributions

A.S.B. designed the study and wrote the manuscript. V.M. prepared tables and figures and reviewed/edited the manuscript. M.T. performed statistical analysis and reviewed/edited the manuscript. C.G. reviewed/edited the manuscript. N.T. reviewed/edited the manuscript. I.F. reviewed/edited the manuscript. Z.W. reviewed/edited the manuscript. B.A.P. reviewed/edited the manuscript. A.C.C. reviewed/edited the manuscript. R.R.L. designed the study and reviewed/edited the manuscript. R.R.L. is the guarantor of this work, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Sharing

The list of variables of the BETTER registry can be found at https://www.maelstrom-research.org/mica/individual-study/better. De-identified individual participant data that underlie the results reported in this article can be available following acceptance by BETTER scientific committee and a duly authorized ethics board. Cost for providing access to data and maintenance of the registry must also be covered. To explore the possibility of having access to the BETTER registry data, please contact the research team at better@ircm.qc.ca.

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Table 1. Socio-demographics characteristics

	Total population (n=1430)	14-25 y.o. (n=271)[a]	26-49 y.o. (n=701)	50-64 y.o. (n=346)	≥ 65 y.o. (n=112)	P value
	N (%)	N (%)	N (%)	N (%)	N (%)	
Age in years mean ± SD	41.2 ± 15.7	19.9 ± 3.7	37.2 ± 6.6	56.6 ± 4.1	70.2 ± 4.2	<0.001
Sex, female	886 (62.0)	182 (67.2)†‡	468 (66.8)†‡	180 (52.0)	56 (50.0)	< 0.001
Ethnicity						
● White/Caucasian	1317 (92.1)	234 (86.3)†‡	643 (91.7)	330 (95.4)	110 (98.2)	
● Black	32 (2.2)	14 (5.2)†	16 (2.3)	2 (0.6)	0 (0.0)	0.001
● Arab	43 (3.0)	13 (4.8)	23 (3.3)	6 (1.7)	1 (0.9)	0.079
● Other[b]	51 (3.6)	16 (5.9)†‡	27 (3.9)‡	8 (2.3)	0 (0.0)	0.017
● I don't know/I prefer not to answer	27 (1.9)	11 (4.1)*†	9 (1.3)	5 (1.4)	2 (1.8)	0.034
Household income[c]						< 0.001
● <20,000 to $60,000	439 (32.7)	91 (49.2)*†	199 (28.4)‡	98 (28.3)‡	51 (45.5)	
● $60,000 to $100,000	352 (26.2)	27 (14.6)*†‡	192 (27.4)	102 (29.5)	31(27.7)	
● > $100,000	384 (28.6)	27 (14.6)*†	27 (35.5)‡	97 (28.0)‡	11 (9.8)	
● I don't know/I prefer not to answer	169 (12.6)	40 (21.6)*	61 (8.7)	49 (14.2)*	19 (17.0)*	
Education[c]						< 0.001
● Less than a high school diploma	57 (4.2)	11 (5.9)	23 (3.3)	19 (5.5)	4 (3.6)	
● High school diploma	156 (11.6)	37 (20.0)*†	56 (8.0)‡	39 (11.3)‡	24 (21.4)	
● Associate degree	533 (39.7)	99 (53.5)*‡	252 (35.9)†	155 (44.8)‡	27 (24.1)	
● Bachelor degree	374 (27.8)	30 (16.2)*‡	223 (31.8)	88 (25.4)	33 (29.5)	
● Master or doctorate degree	212 (15.8)	8 (4.3)*†‡	141 (20.1)†	41 (11.8)	22 (19.6)	
● I don't know/I prefer not to answer	12 (0.9)	0 (0.0)	6 (0.9)	4 (1.2)	2 (1.8)	
Employment status[c]						
● Full time	763 (56.8)	62 (33.5)*†‡	524 (74.8)†‡	174 (50.3)‡	3 (2.7)	< 0.001

• Part time	164 (12.2)	67 (36.2)*†‡	65 (9.3)	26 (7.5)	6 (5.4)	< 0.001
• Occasional or seasonal	29 (2.2)	15 (8.1)*†‡	12 (1.7)	2 (0.6)	0 (0.0)	< 0.001
• Self-employed	110 (8.2)	8 (4.3)	66 (9.4)	30 (8.7)	6 (5.4)	0.094
• Student	102 (7.6)	70 (37.8)*†‡	32 (4.6)†	0 (0.0)	0 (0.0)	< 0.001
• Unemployed	77 (5.7)	15 (8.1)	39 (5.6)	22 (6.4)	1 (0.9)	0.069
• Caregiver	7 (0.5)	0 (0.0)	6 (0.9)	1 (0.3)	0 (0.0)	0.330
• Volunteer	29 (2.2)	4 (2.2)	13 (1.9)‡	4 (1.2)‡	8 (7.1)	0.002
• Retired	211 (15.7)	0 (0.0)†‡	5 (0.7)†‡	105 (30.3)‡	101 (90.2)	< 0.001
• I don't know/I prefer not to answer	14 (1.0)	1 (0.5)	7 (1.0)	4 (1.2)	2 (1.8)	0.775
Insurance status						< 0.001
• Public	307 (21.5)	67 (24.7)*‡	105 (15.0)†‡	78 (22.5)‡	57 (50.9)	
• Private	963 (67.3)	156 (57.6)*†‡	547 (78.0)‡	247 (71.4)‡	13 (11.6)	
• Combined	126 (8.8)	25 (9.2)‡	41 (5.8)‡	19 (5.5)‡	41 (36.6)	
• I don't know/I prefer not to answer	34 (2.4)	23 (8.5)*†‡	8 (1.1)	2 (0.6)	1 (0.9)	

[a] 6.0% aged less than 18

[b] Includes South Asian, Chinese, Filipino, Latin American, South East Asian, West Asian, Korean, Japanese and Aboriginal (First Nation) people

[c] Participants aged ≥ 18 years old; data available for 1344 participants

* Significantly different from the 26-49 y.o. group

† Significantly different from the 50-64 y.o. group

‡ Significantly different from the ≥ 65 y.o. group

Table 2. Diabetes-related characteristics and use of other medication

	Total population (n=1430)	14-25 y.o. (n=271)	26-49 y.o. (n=701)	50-64 y.o. (n=346)	≥ 65 y.o. (n=112)	P value
	N (%)	N (%)	N (%)	N (%)	N (%)	
Type of diabetes						< 0.001
• Type 1 diabetes	1319 (92.2)	267 (98.5)*†‡	653 (93.2)†‡	304 (87.9)	95 (84.8)	
• LADA[a]	111 (7.8)	4 (1.5)*†‡	48 (6.8)†‡	42 (12.1)	17 (15.2)	
Diabetes duration in years[b] mean ± SD	22.0 ± 14.7	8.8 ± 5.9*†‡	19.5 ± 10.7†‡	32.2 ± 14.3‡	37.8 ± 17.9	< 0.001
A1C[c]						< 0.001
• ≤ 7.0%	423 (29.7)	59 (21.9)*	241 (34.5)†	92 (26.7)	31 (27.7)	
• 7.1% to 8.0%	586 (41.1)	101 (37.4)	277 (39.7)	154 (44.6)	54 (48.2)	
• 8.1% to 9.0%	214 (15.0)	49 (18.1)*	86 (12.3)†	66 (19.1)	13 (11.6)	
• ≥ 9.1%	105 (7.4)	28 (10.4)†	57 (8.2)†	15 (4.3)	5 (4.5)	
• I don't know/I prefer not to answer	97 (6.8)	33 (12.2)*†	37 (5.3)	18 (5.2)	9 (8.0)	
Pump use[d]	585 (40.9)	143 (52.8)*†‡	299 (42.7)†	110 (31.9)	33 (29.5)	< 0.001
rtCGM or isCGM use[e]	1115 (78.0)	196 (72.3)*	576 (82.2)‡	264 (76.5)	79 (70.5)	0.018
Self-monitoring of blood glucose (number of tests per day)[f] mean ± SD	4.8 ± 2.4	4.6 ± 2.0	4.7 ± 2.5	5.0 ± 2.7	4.7 ± 1.6	0.073
Healthcare providers for diabetes[g]						
• Endocrinologist	1251 (87.5)	237 (87.5)	617 (88.0)	297 (85.8)	100 (89.3)	0.713
• Family doctor	475 (33.2)	79 (29.2)	248 (35.4)	109 (31.5)	39 (34.8)	0.253
• Internist	153 (10.7)	22 (8.1)	81 (11.6)	36 (10.4)	14 (12.5)	0.417
• Pediatrician	32 (2.2)	28 (10.3)*†‡	3 (0.4)	0 (0.0)	0 (0.0)	< 0.001
• None	9 (0.6)	3 (1.1)	5 (0.7)	1 (0.3)	0 (0.0)	0.490
• Other	46 (3.2)	7 (2.6)	32 (4.6)†	6 (1.7)	1 (0.9)	0.032

• I don't know/I prefer not to answer	4 (0.3)	3 (1.1)†‡	1 (0.1)	0 (0.0)	0 (0.0)	0.038
Reported diabetes-related complications						
• Cardiovascular disease	105 (7.3)	3 (1.1)†‡	19 (2.7)†‡	48 (13.9)‡	35 (31.3)	< 0.001
• Nephropathy	153 (10.7)	14 (5.2)†	73 (10.4)	52 (15.0)	14 (12.5)	0.009
• Neuropathy	241 (16.9)	10 (3.7)*†‡	83 (11.8)†‡	104 (30.1)	44 (39.3)	< 0.001
• Retinopathy	288 (20.1)	9 (3.3)*†‡	124 (17.7)†‡	114 (32.9)	41 (36.6)	< 0.001
• Gastroparesis	97 (6.8)	8 (3.0)†‡	43 (6.1)	34 (9.8)	12 (10.7)	0.039
Reported medication for						
• Hypertension	442 (30.9)	11 (4.1)*†‡	151 (21.5)†‡	209 (60.4)	71 (63.4)	< 0.001
• Dyslipidemia	560 (39.2)	5 (1.8)*†‡	215 (30.7)†‡	253 (73.1)	87 (77.7)	< 0.001
• Depression	294 (20.6)	36 (13.3)*	169 (24.1)	67 (19.4)	22 (19.6)	0.001
First-degree family member with T1D	454 (31.7)	93 (34.3)‡	219 (31.2)‡	122 (35.3)‡	20 (17.9)	0.006

[a] LADA: latent autoimmune diabetes in adults

[b] Available for 1420 participants

[c] Available for 1425 participants

[d] Available for 1429 participants

[e] rtCGM: real time continuous glucose monitoring; isCGM: intermittent scanning continuous glucose monitoring; available for 1429 participants

[f] Excluding rtCGM and isCGM users; calculated on 305 participants

[g] Participants were allowed to choose more than one answer

* Significantly different from the 26-49 y.o. group

† Significantly different from the 50-64 y.o. group

‡ Significantly different from the ≥ 65 y.o. group

Table 3. Self-experience with hypoglycemia

	Total population (n=1430)	14-25 y.o. (n=271)	26-49 y.o. (n=701)	50-64 y.o. (n=346)	≥ 65 y.o. (n=112)	P value
	N (%)	N (%)	N (%)	N (%)	N (%)	
Last level-2-H[a]						0.077
• Less than 1 month ago	1121 (78.4)	204 (75.3)	547 (78.0)	292 (84.4)	78 (69.6)	
• 1 to 6 months ago	181 (12.7)	40 (14.8)	91 (13.0)	31 (9.0)	19 (17.0)	
• More than 6 months ago	82 (5.7)	15 (5.5)	40 (5.7)	11 (4.6)	11 (9.8)	
• Never had a level-2-H	35 (2.4)	8 (3.0)	19 (2.7)	6 (1.7)	2 (1.8)	
• I don't know/I prefer not to answer	11 (0.8)	4 (1.5)	4 (0.6)	1 (0.3)	2 (1.8)	
Among those reporting at least one, Number of level-2-H in the last month[b] median (IQR)	5.0 (3.0 - 10.0)	5.0 (2.0 – 8.2)	5.0 (3.0 -10.0)	5.0 (3.0 – 10.0)	4.0 (2.0 – 7.7)	0.098
Last level-3-H[c]						< 0.001
• In the last 12 months	190 (13.3)	20 (7.4)*†	99 (14.1)	53 (15.3)	18 (16.1)	
• More than 12 months ago	461 (32.2)	52 (19.2)*†‡	218 (31.1)†	143 (41.3)	48 (42.9)	
• Never had a level-3-H	761 (53.2)	195 (72.0)*†‡	377 (53.8)†‡	144 (41.6)	45 (40.2)	
• I don't know/I prefer not to answer	18 (1.3)	4 (1.5)	7 (1.0)	6 (1.7)	1 (0.9)	
Among those reporting at least one, Number of level-3-H in the last year[d] median (IQR)	2.0 (1.0 - 3.0)	2.0 (1.0 – 2.0)	2.0 (1.0-3.0)	2.0 (1.0 – 3.0)	2.0 (1.0 – 2.5)	0.941
Impaired awareness of hypoglycemia[e]	281 (19.7)	37 (13.7)†‡	128 (18.3)†‡	84 (24.3)	32 (28.6)	0.001
Threshold for symptoms of hypoglycemia						< 0.001
• > 3.8 mmol/L	383 (26.8%)	90 (33.2%)†‡	202 (28.8%)†	70 (20.2%)	21 (18.8%)	
• 3.3 to 3.8 mmol/L	644 (45.0%)	133 (49.1%)	329 (46.9%)	137 (39.6%)	45 (40.2%)	
• 2.8 to 3.3 mmol/L	253 (17.7%)	39 (14.4%)	115 (16.4%)	73 (21.1%)	26 (23.2%)	
• 2.2 to 2.7 mmol/L	69 (4.8%)	3 (1.1%)†	28 (4.0%)†	32 (9.2%)	6 (5.4%)	
• < 2.2 mmol/L	40 (2.8%)	0 (0.0%)†‡	16 (2.3%)	18 (5.2%)	6 (5.4%)	

• No symptoms	32 (2.2%)	4 (1.5%)	7 (1.0%)†‡	15 (4.3%)	6 (5.4%)
• I don't know/I prefer not to answer	9 (0.6%)	2 (0.7%)	4 (0.6%)	1 (0.3%)	2 (1.8%)

[a] Blood glucose < 3.0 mmol/L that the participant was able to treat himself.

[b] Available for 1084 participants..

[c] Defined as a low blood glucose level requiring help from another person or use of glucagon or hospitalization or loss of consciousness.

[d] Available for 162 participants..

[e] Based on a Gold score [18] ≥ 4

* Significantly different from the 26-49 y.o. group

† Significantly different from the 50-64 y.o. group

‡ Significantly different from the ≥ 65 y.o. group

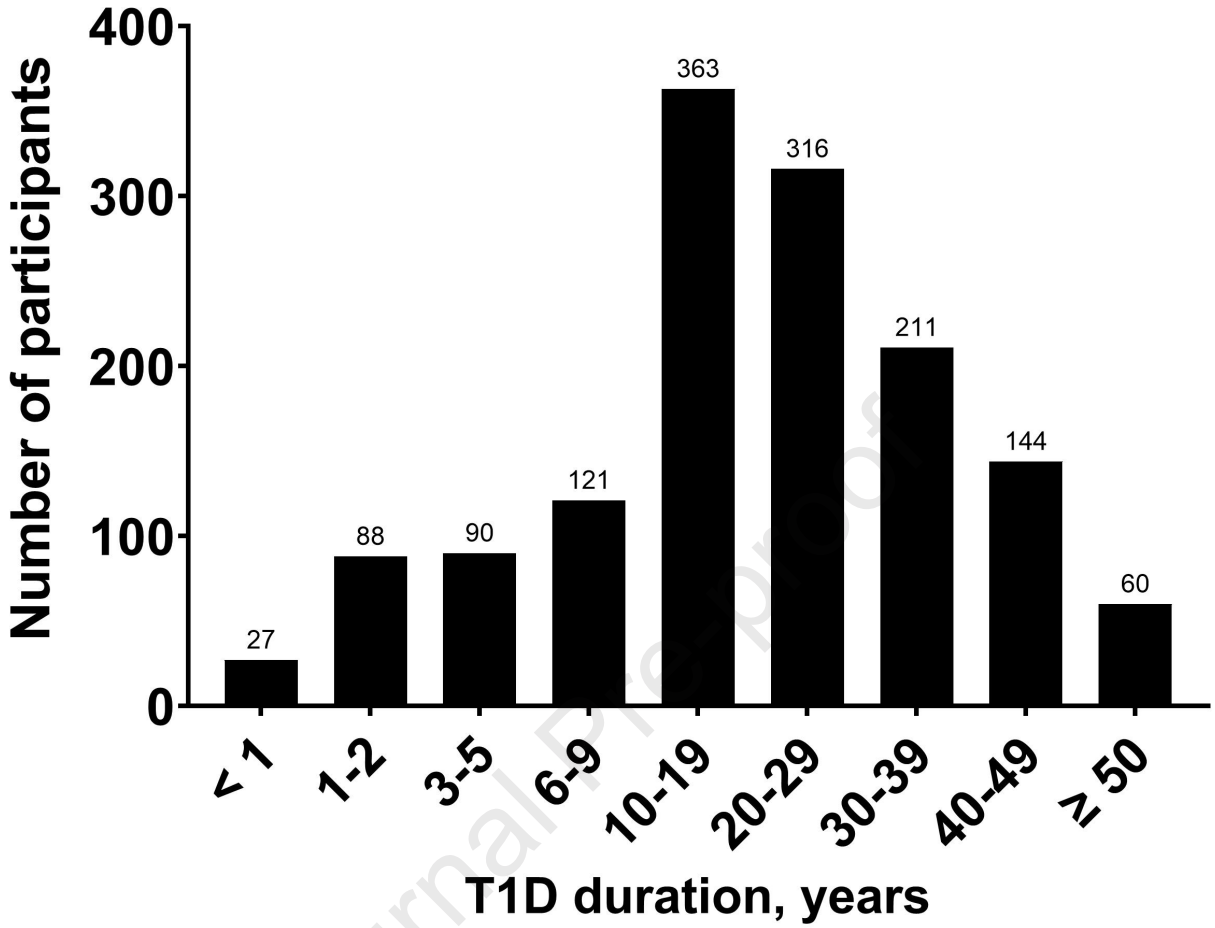

Figure legends

Figure 1. Duration of T1D across the BETTER registry. T1D: type 1 diabetes

Supplementary Figure 1. A1C according to age groups. The number of participants in each age group is as follow: 14-25 y.o. = 270; 26-49 y.o. = 698; 50-64 y.o. = 345; ≥ 65 y.o. : 112.