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DIABETES EPIDEMIOLOGY (E SELVIN AND K FOTI, SECTION EDITORS)

Patient-Reported Outcome Measures in Registry-Based Studies of Type 2 Diabetes Mellitus: a Systematic Review

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Abstract

Purpose of Review Patient-reported outcome measures (PROMs) and patient registries both play important roles in assessing patient outcomes. However, no study has examined the use of PROMs among registries involving patients with type 2 diabetes mellitus (T2DM). Our objective is twofold: first, to review the range of PROMs used in registry-based studies of patients with T2DM; second, to describe associations between these PROMs, T2DM and its complications.

Recent Findings The International Consortium for Health Outcomes Measurement (ICHOM) Diabetes Standard Set recommended routine usage of PROMs to assess psychological well-being, diabetes distress, and depression among patients with T2DM.

Summary A wide variety of PROMs were used among the 15 studies included in this review. Quality of life, depressive symptoms and treatment adherence were the most common aspects of T2DM that utilised PROMs for assessment. Adoption of PROMs among registries of patients with T2DM remains uncommon, non-routine and with few that are validated before use.

Keywords Diabetes mellitus · Patient-reported outcome measures · Registries · Quality of life · Depressive symptoms · Treatment adherence

Introduction

In recent years, patient-reported outcome measures (PROMs) have gained prominence in patient management and clinical decision-making since its initial uptake in the 1980s [1–4]. Patient-reported outcomes (PROs) are direct reports from patients about how they feel or function in relation to a health condition and its therapy without interpretation by any healthcare professionals [5], and can relate to symptoms, signs, functional status, perceptions or other aspects of care such as convenience and tolerability [4]. PROMs are important and advantageous for several reasons. First, PROMs provide a means for patients to effectively convey their day-to-day health experience, and can be useful in screening of underlying mental and functional problems to their providers [6, 7•]. Second, while the principal goals of healthcare are to maximise quality of life and minimise disability or symptoms, these aims can only be fully assessed by patients [1]. Third, domains, or question categories, in each PROM can provide insight on the aspects of patient health that have been most impacted by a condition or treatment [8]. For example,

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EuroQoL-5 Dimensions (EQ-5D), a validated PROM developed by the EuroQoL Research Foundation, consists of five questions and measures patients' perceived state of health across five domains, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression [8]. A patient's EQ-5D score therefore measures the impact of his/her medical condition according to the different domains, as well as the effectiveness of treatment in improving his/her quality of life. Monitoring of patient-reported symptoms may also help in improving care delivery or informing treatment decisions. Taken altogether, PROMs can bridge the gap between clinical concerns and patient perspectives, thereby enabling a holistic assessment of a condition or treatment [4]. Usage of information from PROMs has been found to not only improve doctor-patient communication and decision-making, but also lead to greater patient satisfaction and ultimately, improved clinical outcomes [6]. Routine PROM use also acts as a feedback loop which fosters learning and continuous improvement of care [7•, 9].

In a similar vein, the use of data from registries has been gaining traction over the years due to its unique and critical role in assessing patient outcomes. There is an increasing emphasis on real-world data (RWD) and real-world evidence (RWE) for regulatory approval and/or reimbursement of new drugs due to various limitations by the conduct of randomised controlled trials [10]. Patient registries is one of several sources of RWD alongside electronic medical records, patient surveys and trackers or mobile devices. As registries assess actual care that patients receive in the real-world setting, results from registries may hence better depict real-world outcomes as care is not assigned or dictated by trial protocol [11]. A potentially rich source of information, registry data may and should contain information regarding the many and different domains that make up the PROMs. Additionally, PROMs captured using registry data may indicate the actual well-being of the studied patient population without the influence of any specific intervention. While there have been reviews examining the use of PROMs among registries for other medical conditions such as knee and hip arthroplasty, renal conditions and rheumatoid arthritis [12–14], there is none thus far for type 2 diabetes mellitus (T2DM).

Type 2 diabetes mellitus has been associated with various macrovascular and microvascular complications. More importantly, T2DM has been found to impose significant psychological and emotional burden on the patient [15]. Assessing the impact of treatments and self-management strategies on PROs of patients with T2DM is therefore critical to quantify the success of these regimens [15]. Therefore, the aim of this systematic review is to first, describe the range of PROMs that have been used in studies involving registries of patients with T2DM and second, the association of these PROMs with T2DM and its complications. Through this review, we hope to highlight the importance of quality PROM data in the achievement of optimal patient outcomes in T2DM.

Data Collection

Search Strategy and Inclusion Criteria

We searched MEDLINE, Embase, CINAHL and OpenGrey for published studies on patient-reported outcomes in registries which include patients with T2DM since data inception and up to 4th of July 2019. Search terms included 'diabetes mellitus', 'registry', PRO terms 'quality of life', 'self-assessment', 'self-report', 'adherence' and 'patient experience'. The full search strategy is included in Appendix Table 2. We included studies which were registry-based, contained any type of PRO and focused on adults with T2DM or if the disease investigated is a complication and/or sequela of T2DM. Non-English studies, studies that focused on trials or on measurement development (e.g. focus group studies or evaluating psychometric properties ([i.e. validity, reliability, or factor structures]) were excluded. In addition, studies that did not differentiate between type 1 and type 2 diabetes were excluded.

Data Extraction

In alignment with PRISMA guidelines for systematic reviews [16], two authors (YTC and YZT) independently screened the titles and abstracts of included studies, with inter-rater reliability of 93.3%. Any disagreement was discussed to reach consensus or resolved by a third reviewer (HLW). YTC and HLW then performed full-text review and data extraction for studies which met inclusion criteria. Information such as the type of PRO (generic vs diabetes-specific), the construct of the PRO (e.g. depressive symptoms, health status, medication adherence) as described by the authors, frequency of assessment and study objectives related to the PRO were extracted to a pre-designed form. Studies that reported on different PROMs in the same registry by the same study team were included to capture the widest possible range of PROMs used in these studies.

Of the studies included after full-text screening, we checked each reference list to identify more relevant studies for inclusion. However, we were unable to find any additional studies using this supplementary approach. The PRISMA flow diagram (Fig. 1) summarises this data extraction process.

Quality Assessment

Two reviewers (YTC and MC) independently assessed the methodological quality of each article. As all included studies were cross-sectional studies, we used the NIH National Heart, Lung and Blood Institute quality assessment tool for cross-sectional studies [17].

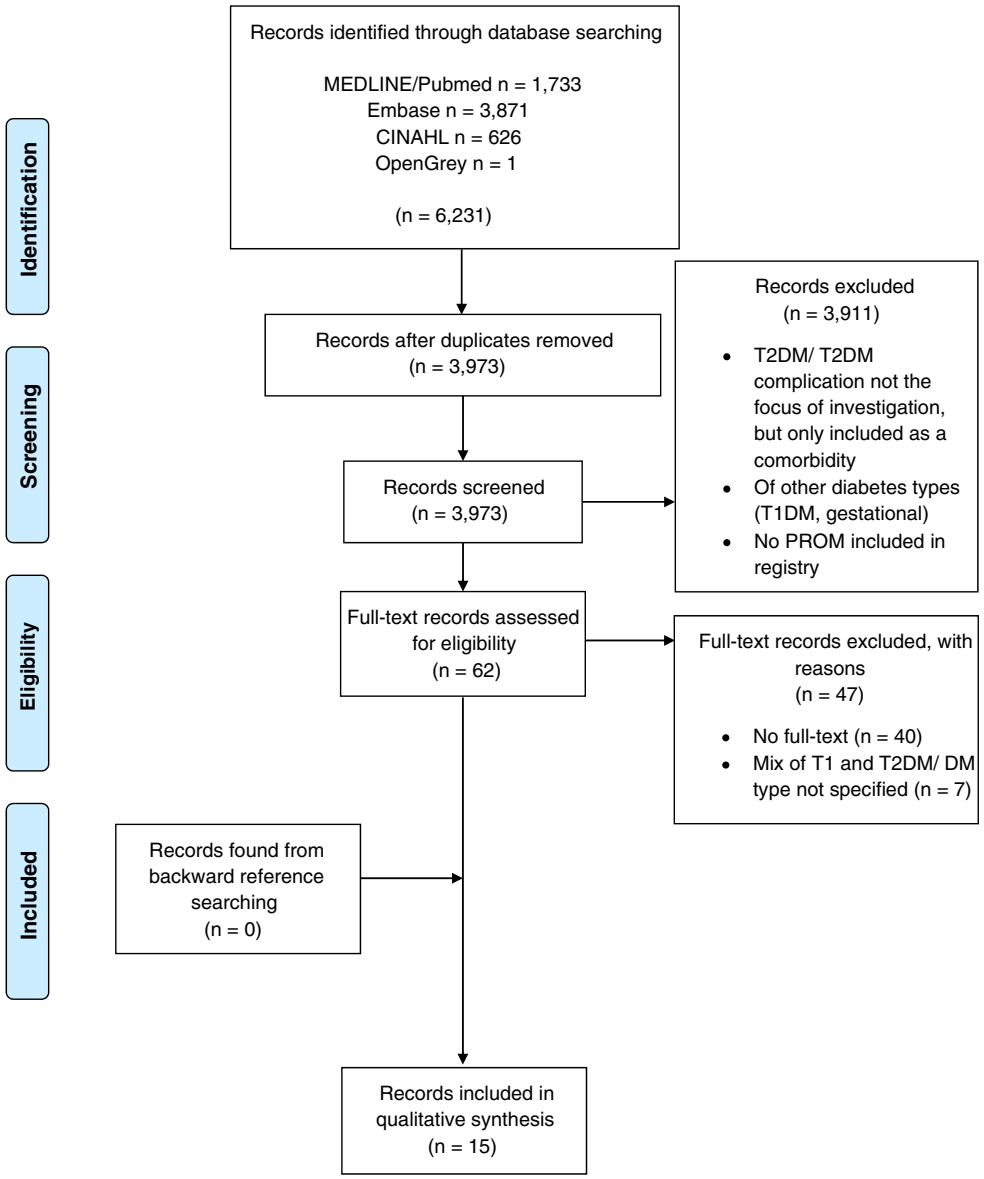

Fig. 1 PRISMA flow diagram

Results

A total of 3,973 articles were identified after duplicates were removed. Of these, 3,911 were excluded during the title and abstract screening phase. We reviewed the full text of 62 articles. Of these 62 studies, 47 were further excluded after full-text review due to insufficient details on how PROMs were utilised and interpreted, unclear specification of the type of diabetes being investigated, or the inclusion of both type 1 and 2 diabetes. Eventually, 15 studies were included in our analysis. The completed quality assessment is in Appendix Table 3.

Study characteristics of included studies are summarised in Table 1. Overall, studies were conducted in six countries and were based on ten unique registries of patients with diabetes: Japan (n = 7, 2 registries), USA (n = 2, 2 registries), Germany (n = 2, 2 registries), China (n = 1, 1 registry), Canada (n = 1, 1 registry), Denmark (n = 1, 1 registry), as well as an international study conducted across 9 European countries (n = 1, 1 registry). Six studies focused on T2DM complications, with four focusing specifically on depressive symptoms [18–21] and two focusing on all-cause mortality [22, 23].

Range of PROMs Used in Published Studies Involving Registries of Patients with T2DM

Across 15 included studies, a total of 24 different PROMs were employed. The number of PROMs used in each study varied widely from one to six. Among studies that used multiple PROMs, the minimum number of PROM constructs covered is two (e.g. depressive symptoms and

Table 1 Studies included in the systematic review

Author	Year	Study location	Study design	Population	Total *N* (T2DM)	Mean (SD) age	No. of PROMs used	PROMs*
Fumagalli et al.	2018	9 European countries (Belgium, Denmark, Greece, Italy, Norway, Poland, Portugal, Romania, and The Netherlands)	Cross-sectional	EURObservational Research Programme-Atrial Fibrillation General Pilot (EORP-AF) Registry	638	68 (12)	1	AF-QoL
Woo et al.	2019	Canada	Cross-sectional	CANadian CAnagliflozin REgistry (CanCARE)	527	60.7 (10.8)	1	CHES-Q
Ji et al.	2015	China	Cross-sectional	Observational Registry of Basal Insulin Treatment (ORBIT)	18,995	55.4 (10.4)	4	EQ-5D, frequency of hypoglycaemia, serious adverse events, frequency of self-monitoring
von Arx et al.	2016	Denmark	Cross-sectional	Funens Diabetes Database (FDDB)	1,033	67.1 (10.4)	2	EQ-5D, questionnaire on diabetes treatment beliefs and health behaviour
Wasem et al.	2013	Germany	Cross-sectional	DiaRegis, an observational registry for T2DM	2,760	Median, 66.2 (57.6–73.0)	1	EQ-5D
Rathmann et al.	2018	Germany	Cross-sectional	DIAREG, an observational registry for T2DM	270	68.8 (10.2)	4	CES-D, SF-36, ADDQoL, DTSQ
Mashitani et al.	2013	Japan	Cross-sectional	Diabetes Distress and Care Registry at Tenri (DDCRT3)	1,441	65.4 (11.3)	1	Adherence to scheduled insulin injections
Mashitani et al.	2015	Japan	Cross-sectional	Diabetes Distress and Care Registry at Tenri (DDCRT5)	1,394	65.8 (11.8)	4	PHQ-9, DTR-QOL, IPAQ-SF, adherence to scheduled insulin injections
Tsujii et al.	2012	Japan	Cross-sectional	Diabetes Distress and Care Registry at Tenri (DDCRT1)	3,305	64.9 (11.2)	2	CES-D, PAID
Kikuchi et al.	2015	Japan	Cross-sectional	Fukuoka Diabetes Registry	4,218	65.5 (SD not given)	4	CES-D, frequency of severe hypoglycaemia, BDHQ, questionnaire on leisure-time physical activity
Hayashino et al.	2018a	Japan	Cross-sectional	Diabetes Distress and Care Registry in Tenri (DDCRT18)	3,305	64.9 (11.2)	3	SF-8, questionnaire on hypoglycaemia frequency, PAID
Hayashino et al.	2014	Japan	Cross-sectional	Diabetes Distress and Care Registry at Tenri (DDCRT6)	3,573	66.0 (11.4)	2	PHQ-9, IPAQ-SF
Hayashino et al.	2018b	Japan	Cross-sectional	Diabetes Distress and Care Registry in Tenri (DDCRT17)	2,970	65.8 (11.4)	2	DTR-QOL, IPAQ-SF
Shigaki et al.	2010	US	Cross-sectional	Two University Family Medicine clinic registries of University of Missouri	77	63 (17)	6	SF-36, SDSCA, questionnaire on understanding of diabetes, TSRQ-diabetes, PCDS, MOS-SSS
Berkowitz et al.	2014	US	Cross-sectional	Kaiser Permanente Northern California diabetes registry	14,357	58 (10)	1	Frequency of severe hypoglycaemia

*Please refer to Appendix Table 4 for the full names of PROMs

health status), and the maximum number of PROM constructs covered is five. Only a minority (four out of 24 PROMs) were validated for use among T2DM patients in the country where the study was conducted. The PROMs included in this review are summarised in Appendix Table 4.

The PROMs can be broadly categorised into three groups: first, general health status questionnaires (e.g. EQ-5D, Short Form 36 [SF-36]); second, diabetes-specific questionnaires (e.g. Audit of Diabetes-Dependent Quality of Life [ADDQoL], Diabetes Treatment Satisfaction Questionnaire [DTSQ]); and third, questionnaires that measure complications or comorbidities associated with diabetes. These include questionnaires that measure depressive symptoms (The Center of Epidemiological Studies Depression Scale [CES-D] and Patient Health Questionnaire-9 [PHQ-9]), or questions on the frequency of hypoglycaemia/severe hypoglycaemia. Each of these PROMs was included in 4 out of 15 studies.

Patient-Reported Health Status and Health-Related Quality of Life

Four studies evaluated the association between health-related quality of life (HRQoL) and T2DM-related outcomes. Overall, HRQoL among patients with T2DM was found to be significantly negatively associated with lower level of physical activity [24], lower level of adherence to insulin injections [25], higher frequency of hypoglycaemia, and presence of certain comorbidities including hypertension, clinical depression [26], or atrial fibrillation (AF) [23].

The role of anti-diabetic medication on health status or HRQoL is less clear, with one study reporting that a combination of insulin with an alpha-glucosidase inhibitor (AGI), or a combination of meglitinides/sulfonylurea with thiazolidinedione were associated with higher odds of poorer diabetes therapy-related quality of life (DTR-QOL) domain scores [24] and another study reporting no association [26]. In the exploratory analysis by Hayashino et al, the negative association with DTR-QOL scores was the strongest with the use of insulin compared to other anti-diabetic medications across all domains.

Patient-Reported Depressive Symptoms

Four studies evaluated the association between depressive symptoms and T2DM. In summary, depressive symptoms were associated with diabetes distress [19], severe hypoglycaemia [18], physical activity [18] and lower levels of HRQoL [20], as well as higher levels of high-sensitivity C-reactive protein (hs-CRP) among obese patients with T2DM [21]. On the other hand, no associations were found between depressive symptoms with treatment satisfaction [20].

Two studies had differing conclusions regarding the association of glycemia control and depressive symptoms [18, 19].

Patient-Reported Treatment Adherence to Anti-diabetes Medications

Four studies examined the association between patient-reported treatment adherence and diabetes-related outcomes. Overall, higher levels of self-reported treatment adherence was associated with better glycaemic control (glycated haemoglobin, HbA_{1c}) [27, 28], better lipid profiles [27] and higher quality of life [25]. Patients' own motivation was also associated with treatment adherence [29].

Other Associations

Three studies reported other associations with T2DM. Woo and colleagues found that the use of canagliflozin improved patients' satisfaction towards their body weight and overall health, as well as improvement in CHES-Q domains of physical and emotional health [30]. Berkowitz's team found that low socioeconomic status was associated with higher risk of self-reported hypoglycaemia [31]. Hayashino and colleagues found that high Problem Area in Diabetes (PAID) scores, which indicate greater diabetes distress, was significantly associated with higher risk of all-cause mortality [22].

Discussion

In light of rising interests in using PROMs to better assess the effects treatment modalities have on patients with T2DM, and the growing importance and accessibility of registry-based data, we sought to understand the state of use of PROMs in existing registries and databases. This study, to the best of our knowledge, is the first of its kind in assessing the extent of PROMs reported in current literature of registry-based T2DM studies. In so doing, we attempted to summarise the common measurements that are being used to date. Our analysis has allowed us to discern possible associations between different aspects of diabetes care and their implications on relevant patient related endpoints that are often important but under-reported in trials and other studies. Moreover, the responses that we have gathered across registries from various countries offer a glimpse into current geographical practices within this growing contemporary field.

In this study, we identified 15 studies involving patients from 10 registries that included PROMs. We noted that a wide variety of PROMs are employed for T2DM registry-based research. Given the low number

of studies, it was evident that PROMs were largely not captured routinely and regularly.

We postulate the following reasons that may explain the limited number of PROMs used and reported in existing registry-based studies. First, administration of PROMs can be resource intensive. For traditional pen-and-paper administration, additional labour is required to perform data entry and data cleaning, thus adding to the administrative burden of maintaining registries [11, 32]. While electronic versions of PROMs (e.g. web-based or tablet-based administration) may be available, such modes may not be suitable for all types of patients, especially for those who may be unfamiliar with navigating such technology or are unable to use computing devices or smart phones due to physical limitations [11]. In addition, registries may not have the capability to invest in the equipment (e.g. laptops or tablets) and software (e.g. packages that specialise in the design and administration of PROMs) required for collecting data electronically [11]. Second, we found that many of the PROMs have not been validated in the specific T2DM patient populations although some may have been validated in the general or other clinical populations. This may thus hamper the adoption of PROMs in T2DM registry-based studies. Third, clinically meaningful interpretation of PROMs remains an impediment to its uptake, and the utility of such measurements are hence often questioned. Further, clinicians may be unfamiliar with the different measurements and its implications, and often report difficulty in interpreting PROM results [11]. Fourth, with the plethora of PROMs available, selection of appropriate PROMs for routine assessment may be challenging for clinicians and physicians. In this regard, the International Consortium for Health Outcomes Measurement (ICHOM) Diabetes Standard Set released on World Diabetes Day in 2018 included a section on PROMs with a clear purpose to identify a core, standard set of outcomes that reflects what matters most to people with diabetes, and that this set can be used globally [33•]. ICHOM recommended that psychological well-being (measured using WHO-5), diabetes distress (measured using PAID) and depression (measured using PHQ-9) should be routinely assessed among patients with diabetes [33•]. Cost may be a possible key factor for the low uptake of PROMs in registry; many PROMs charge fees for routine use outside of academic research [34]. As it is often costly to maintain registries, additional user charges may further discourage the inclusion of PROMs in registries. It is hence heartening to note that cost was a key consideration by ICHOM in its recommendation. Fifth, in countries where the government or health technology assessment agencies do not mandate the collection of PROMs for healthcare decision-making, the motivation to dedicate resources to the collection of PROMs may be low. In the UK, for instance, the National Institute for Health and Care Excellence recommends the use of EQ-5D for health technology assessment. As a result, the EQ-5D is included in population-based surveys and in the National Health Service (NHS) PROMs programme. The NHS PROMs programme has seen tangible benefits including health gains and reduction in procurement cost [34]. Hence, top-down non-financial incentives, recommendations from diabetes professional organisations or mandatory inclusions of these measurements by regulatory authorities may be useful in promoting the adoption of PROMs in T2DM registries.

It is interesting to note that ICHOM's recommendations of PROMs are consistent with our data where 7 out of 15 studies included CES-D, PAID or PHQ-9. Six of the studies that we reviewed also included generic health status questionnaires such as the SF-36, SF-8 and EQ-5D. While these questionnaires are widely used, we recognise several limitations when used in T2DM patients. Most importantly, other co-existing medical conditions may have a greater effect than diabetes on these questionnaires [35]. Hence, it is recommended that these should be used in combination with diabetes-specific HRQoL questionnaires such as the ADDQoL [35].

Our review provides an overview of the state of uptake for PROMs among registries of patients with T2DM. Encouragingly, we found that a few newly established T2DM registries, such as the DIAREG of Germany and ORBIT of China, are attempting to collect PROMs for all their patients. Uptake of PROMs is often slow; while the US Food and Drug Administration (FDA) has approved the use of PROMs in drug label claims since 2009, a recent study reported that among 11 novel anti-diabetic medications approved by the FDA between 2011 and 2017, none incorporated PROMs in their labelling. Furthermore, quality of life or treatment satisfaction data were collected for only 5 of these 11 novel medications [36]. Intuitively, most PROMs collected thus far arise mainly from single-centre, observational studies, which often only offer a snapshot of the landscape for the many PROMs that remain pertinent to patient care. With an increasing interest in the use of RWE for clinical, regulatory or reimbursement purposes, we believe that incorporation of PROMs in registries would facilitate assessment of temporal changes in these measures. This will be ideal for generating RWE that describes the real-time progress on T2DM patients.

With regard to the role of anti-diabetic medication on health status or HRQoL, we noted inconsistent findings in the two studies and considered that the inconsistent findings may be due to differences in the types of anti-diabetic medications that were used in the two studies [24, 26]. While close to half (46.9%) of patients in Hayashino et al.'s study were on insulin, Wasem et al.'s study only included patients who were on oral anti-diabetic medications.

Inconsistent findings were also observed for the relationship between glycaemic control and depressive symptoms, in two Japanese populations with similar mean age (65.5 [18] and 64.9 [19]). Findings by Kikuchi et al. showed that glycaemic control was significantly associated with depressive symptoms [18]. This differed from Tsujii et al.'s conclusion that glycaemic control was not associated with depressive symptoms [19]. We postulate that this difference may likewise be attributable to the types of anti-diabetic medications received by patients in both studies. In Kikuchi et al.'s study, all patients received some form of anti-diabetic medication with 26.5% of patients receiving insulin therapy. In contrast, in Tsujii et al.'s study, a sizeable 15% of patients were not on any medications while 41.6% were on insulin.

Shigaki et al. reported that adherence to diabetes-related self-care activities (diet and self-monitoring of blood glucose) was associated with autonomous motivation, which meant treatment needed to align with patients' personal interests and values for them to be intrinsically motivated [29]. This provides an understanding on how clinicians can help patients with T2DM become more adherent to their treatment and thus improve their treatment outcomes.

Although few, some studies highlight the importance of considering other potential confounders in the relationship between diabetes and PROMs. For example, given that lower socioeconomic status is associated with higher risk of hypoglycaemia and that socioeconomic status is associated with poorer HRQOL, it is important that socioeconomic status be adjusted for before any valid conclusions between hypoglycaemia and HRQoL may be drawn.

Our review has several limitations. First, we were not able to assess 40 studies (predominantly conference abstracts) which were initially included due to the unavailability of full texts. It is therefore possible that other potentially relevant registry-based studies were missed. Second, as 6 out of 15 studies came from a single registry (Diabetes Distress and Care Registry at Tenri), our findings may lack generalizability to other settings.

There are several areas of work which can be undertaken to improve PROM uptake among registries. First, validation of PROMs among patients with T2DM will help to ensure the validity of future registry-based studies. Second, a database of registries for T2DM, such as the Registry of Patient Registries (RoPR) in the USA, can foster collaboration and research among T2DM registries and can potentially facilitate PROM adoption. RoPR is a platform that not only serves as a collection of registries, it also encourages the use of common data variables and serves as a recruitment tool linking researchers and patients [37]. Such an initiative will also aid tracking of PROM adoption among registries. Third, presentation of PROMs data in a user-friendly format should improve the adoption of PROMs. Various approaches, such as representing PROM items using traffic light scheme [38] and image visualisation of each response option [39], as well as graphical presentations of results [36–38] have been tested, and more research are being conducted. Such research will improve the accessibility and utility of PROMs during routine clinical care.

Conclusions

Both PROMs and registries serve powerful and unique roles in assessing patient outcomes. Together, the usage of PROMs among registries has the potential to generate real world, population-based data with regard to patient experience which are of great clinical, regulatory and research value. Our review demonstrates that among registry-based studies of T2DM, adoption of PROMs among registries of patients with T2DM remains uncommon, non-routine and with few PROMs validated for use among patients with T2DM. Quality of life, depressive symptoms and treatment adherence were the most common aspects of T2DM that utilised PROMs for assessment in our review. The potential of PROMs in improving patient-centred care among people with T2DM remains untapped and should be more fully utilised.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any study with human or animal subjects performed by any of the authors.

Appendix

Table 2 Search strategy for this review

Database	Search strategy
MEDLINE/PubMed	((diabetes mellitus[mh] OR diabetes[tiab]) AND (register[tiab] OR registries[mh] OR registry[tiab]) AND (quality of life[mh] OR quality of life[tiab] OR QoL[tiab] OR health related quality of life[tiab] OR HRQoL[tiab] OR hrql[tiab] OR life quality[tiab] OR quality-adjusted life years[mh] OR quality-adjusted life year[tiab] OR QALY[tiab] OR health status[mh] OR health status[tiab] OR functional status[tiab] OR wellbeing[tiab] OR well-being[tiab] OR wellness[tiab] OR diabetes distress[tiab] OR symptom[tiab] OR instrument[tiab] OR measure[tiab] OR scale[tiab] OR patient compliance[tiab] OR adherence[tiab] OR compliance[tiab] OR persistence[tiab] OR self-evaluation[tiab] OR self-appraisal[tiab] OR self-assessment[mh] OR self-assessment[tiab] OR self-rate[tiab] OR self-rating[tiab] OR self-report[mh] OR self-report[tiab] OR self-perceive[tiab] OR self-perception[tiab] OR self-care[tiab] OR self-observation[tiab] OR self-test[tiab] OR patient-reported outcome[tiab] OR patient reported outcome measures[mh] OR PROM[tiab] OR PROMS[tiab] OR patient outcome assessment[tiab] OR patient based outcome[tiab] OR treatment outcome[tiab] OR patient-report[tiab] OR patient-centered[tiab] OR patient-centred[tiab] OR patient satisfaction[mh] OR patient satisfaction[tiab] OR personal satisfaction[tiab] OR consumer satisfaction[mh] OR consumer satisfaction[tiab] OR patient experience[tiab]) NOT trial[tiab])

Table 3 Quality assessment of included studies, using the NIH National Heart, Lung and Blood Institute quality assessment tool for cross-sectional studies

Author (year)	Question number*														Quality rating
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	
Fumagalli et al. (2018)	Yes	Yes	Yes	Yes	No	No	No	NA	Yes	No	Yes	NA; self-assessment	Yes	No	Fair
Hayashino et al. (2014)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	NA; self-assessment	NA; no follow-up	Yes	Good
Hayashino et al. (2018a)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	NR	Yes	Yes	Good
Hayashino et al. (2018b)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	NR	NA; no follow-up	Yes	Good
Woo et al. (2019)	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	Yes	No	Good
Ji et al. (2015)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	NR	NA; no follow-up	No	Fair
Wasem et al. (2013)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	NA; self-assessment	NA; no follow-up	Yes	Good
Mashitani et al. (2013)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	NR	NA; no follow-up	Yes	Good
Tsujii et al. (2012)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	NA; self-assessment	NA; no follow-up	Yes	Good
Rathmann et al. (2018)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes	NA; self-assessment	NA; no follow-up	Yes	Fair
von Arx et al. (2016)	Yes	Yes	No	Yes	No	No	No	Yes	No	No	Yes	Yes	NA; no follow-up	Yes	Fair
Shigaki et al. (2010)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	NA; self-assessment	NA; no follow-up	Yes	Good
Berkowitz et al. (2014)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	NA; self-assessment	NA; no follow-up	Yes	Good
Kikuchi et al. (2015)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	No	NA; self-assessment	NA; no follow-up	Yes	Good

*Questions [18, 67]:

1. Was the research question or objective in this paper clearly stated?

2. Was the study population clearly specified and defined?

3. Was the participation rate of eligible persons at least 50%?

4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

5. Was a sample size justification, power description, or variance and effect estimates provided?

6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?

7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

10. Was the exposure(s) assessed more than once over time?

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

12. Were the outcome assessors blinded to the exposure status of participants?

13. Was loss to follow-up after baseline 20% or less?

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

(Data from the original NIH National Heart, Lung, and Blood Quality Assessment Tool: see https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.)

Table 4 List of PROMs included in the systematic review

Name	No. of items	Construct	Domains	Score interpretation	Studies that included	Has the PROM been validated among patients with T2DM in the country where the study was conducted?
Center of Epidemiological Studies Depression Scale (CES-D)	20	Depressive symptoms	1. Depressive symptoms (20 items)	Score can range from 0 to 60, with a cut-off score of 16 or higher generally used to suggest depressive symptoms in line with mild to moderate depression [20, 40].	*N* = 3 Rathmann et al. (2018) Tsujii et al. (2012) Kikuchi et al. (2015)	No Validity assessed among German general population [41] and Japanese workers [42], but not T2DM populations
Short Form 36/Short Form 36v2 (SF-36)	36	Generic, profile-based health status	1. General health perceptions (5 items) 2. Physical functioning (10 items) 3. Physical role limitations (4 items) 4. Bodily pain (2 items) 5. Vitality/energy (4 items) 6. Social functioning (2 items) 7. Mental health (5 items) 8. Emotional role limitations (3 items)	Each domain is treated as an independent scale, with each domain item scored from 0 to 100. Items are then averaged within the domain to give rise to the domain score, with higher scores indicating better health [43]. SF-36v2 uses the same format as SF-36, with minor differences in layout, wording and scaling system used [29].	*N* = 2 Rathmann et al. (2018) Shigaki et al. (2010)	No Validity not assessed for German and US T2DM populations
Short Form 8 (SF-8)	8	Generic, profile-based health status	1. General health perceptions (1 item) 2. Physical functioning (1 item) 3. Physical role limitations (1 item) 4. Bodily pain (1 item) 5. Vitality/energy (1 item) 6. Social functioning (1 item) 7. Mental health (1 item) 8. Emotional role limitations (1 item)	Each domain item is scored from 0 to 100 to form the domain score, with higher score indicating better health [44].	*N* = 1 Hayashino et al. (2018a)	No Validity assessed among Japanese general population but not T2DM population [45]
EuroQoL-5 Dimensions (EQ-5D)	5	Generic, preference-based health status	1. Mobility (1 item) 2. Self-care (1 item) 3. Usual activities (1 item) 4. Pain/discomfort (1 item) 5. Anxiety/depression (1 item)	Domains 1 to 5 are scored according to the patient-reported level of perceived problems, with a higher score indicating a greater level of perceived problems. The five domain scores can be summarised as a summary index by using population-specific value sets. The index ranges from 0 to 1, with 1 being full health [8].	*N* = 3 Ji et al. (2015) Wasem et al. (2013) Von Arx et al. (2016)	Yes EQ-5D-3 L validated among German patients with T2DM [46], but not among Chinese and Danish patients
Adherence to scheduled insulin injections	1	Medication adherence	1. 'How often did you omit insulin injections in the past month?' (1 item)	A PROM developed by study investigators, it utilises a scale ranging from 1 to 6, with 1 indicating never and 6 suggesting always. A higher score suggests poorer adherence [28].	*N* = 2 Mashitani et al. (2013) Mashitani et al. (2015)	No Developed by study investigators without validation
Audit of Diabetes-Dependent Quality of Life (ADDQoL)	21	Diabetes-specific, profile-based health-related quality of life	(2 introductory items on general QoL) 1. Family life (1 item) 2. Friendship and social life (1 item) 3. Close personal relationship (1 item) 4. Sex life (1 item) 5. Physical appearance (1 item) 6. Physical health (1 item) 7. Work/employment (1 item) 8. Holiday (1 item) 9. Leisure activities (1 item) 10. Local or long-distance journeys (1 item) 11. Self-confidence (1 item) 12. Motivation (1 item)	For each of the 19 domains, respondents rate the impact (on a scale of − 3 [greatest] to +1 [least]), as well as the importance (on a scale of 0 [least] to 3 [most]) of the domain to their diabetes-dependent quality of life. Scores from the two scales are then multiplied for each domain, and then summed to give rise to the overall Average Weighted Impact (AWI) score. A 'not applicable (N/A)' option is available for certain domains, so domains which respondents feels are not applicable to	*N* = 1 Rathmann et al. (2018)	No No ADDQoL validity studies among German population found

Table 4 (continued)

Name	No. of items	Construct	Domains	Score interpretation	Studies that included	Has the PROM been validated among patients with T2DM in the country where the study was conducted?
			13. People's reaction (1 item) 14. Feelings about the future (1 item) 15. Financial situation (1 item) 16. Dependence on others (1 item) 17. Living condition (1 item) 18. Freedom to eat (1 item) 19. Freedom to drink (1 item)	them would not be included in the AWI score [47, 48].		
Diabetes Treatment Satisfaction Questionnaire (DTSQ)	8	Diabetes-specific, treatment satisfaction	1. Treatment satisfaction (6 items) 2. Burden of hyper/hypoglycaemia (2 items)	Expressed as a score ranging from 0 to 36, a higher DTSQ score indicates higher overall treatment satisfaction [20].	*N* = 1 Rathmann et al. (2018)	No
International Physical Activity Questionnaire, short form (IPAQ-SF)	7	Physical activities	1. Frequency of vigorous physical activity (2 items) 2. Frequency of moderate physical activity (2 items) 3. Frequency of walking (2 items) 4. Frequency of sitting (1 item)	IPAQ-SF can either be reported as continuous or categorical scores. For continuous scoring, median and interquartile ranges are calculated for each domain, based on response information. A standard set of formula can then be used to compute the metabolic equivalent (MET)-minutes per week. A higher score suggests greater level of physical activity. For categorical scoring, the IPAQ Group has set three standard categories (low, moderate, high) of physical activity and a list of criteria to meet for each category [49].	*N* = 3 Hayashino et al. (2014) Hayashino et al. (2018b) Mashitani et al. (2015)	No Validity assessed in Japanese elderly population but not T2DM population [50]
Questionnaire on leisure-time physical activity		Physical activities	1. Physical activity (number of items not provided)	Reported physical activities were converted to MET-hours per week using the Compendium of Physical activities [51], which provides the energy expenditures of activities.	*N* = 1 Kikuchi et al. (2015)	No Developed by study investigators without validation
Patient Health Questionnaire-9 (PHQ-9)	9	Depressive symptoms	1. Depressive symptoms (9 items)	Each item is scored on a scale of 0 (not at all) to 3 (nearly every day), resulting in a summary score with the range of 0–27. A higher score indicates more severe depressive symptoms. Cut-off scores of 5, 10, 15, 20 correspond with mild, moderate, moderately severe and severe depression [52].	*N* = 2 Hayashino et al. (2014) Mashitani et al. (2015)	No Validity assessed in Japanese population with psychiatric disorders but not T2DM population [53]
Problem Areas in Diabetes (PAID)	20	Diabetes-specific	1. Diabetes distress (20 items)	Each item is scored on a scale of 0 (no problem) to 4 (serious problem) and converted to a 0–100 scale. A cutoff score of 40 and above suggests significant emotional distress [19].	*N* = 2 Tsujii et al. (2012) Hayashino et al. (2018a)	Yes Validation done among Japanese T2DM population [54]
Current Health Satisfaction Questionnaire (CHES-Q)	14	Treatment satisfaction, treatment knowledge	1. Satisfaction with: - weight (1 item) - energy (1 item) - appetite (1 item) - sleep (1 item) - physical functioning (1 item) - social interactions (1 item)	For the satisfaction domain, each item is scored on a scale of 1 (strongly disagree) to 7 (strongly agree). On the other hand, each item is scored on a scale of 1 (not at all knowledgeable) to 5 (extremely knowledgeable). Each item score can be interpreted individually, with a higher	*N* = 1 Woo et al. (2019)	No Content validation done for patients with T2DM, but not among a Canadian population [56]

Table 4 (continued)

Name	No. of items	Construct	Domains	Score interpretation	Studies that included	Has the PROM been validated among patients with T2DM in the country where the study was conducted?
			- attitude (1 item) - mood (1 item) - blood sugar levels (1 item) - blood pressure (1 item) - current health (1 item) 2. Knowledge of: - current blood sugar levels (1 item) - blood pressure levels (1 item) - diabetes (1 item)	score suggesting greater health satisfaction or knowledge [55].		
Atrial fibrillation quality of life questionnaire (AF-QoL)	18	AF-specific health-related quality of life	1. Psychological (7 items) 2. Physical (8 items) 3. Sexual activity (3 items)	Each item is scored on a scale of 1 (totally agree) to 5 (totally disagree). Items within each domain are summed, resulting in a standardised score ranging from 0 to 100. A higher score indicates better AF-QoL [57].	*N* = 1 Fumagalli et al. (2018)	No Only validated for Spanish patients with AF [57]
Diabetes therapy-related quality of life (DTR-QOL) questionnaire	29	Diabetes-specific, treatment satisfaction	1. Burden on social activities and daily activities (13 items) 2. Anxiety and dissatisfaction with treatment (8 items) 3. Hypoglycaemia (4 items) 4. Satisfaction with treatment (4 items)	Each item is scored using a scale ranging from 1 (strongly agree) to 7 (strongly disagree). For the first three domains, items within each domain are totalled and transformed into a domain score between 0 and 100. For the fourth domain, item scores are reversed (7 represents highest QoL score) before being totalled and transformed like the other domains. Similarly, an overall DTR-QOL score can also be derived by summing all 29 items and transforming the sum on a scale of 0 to 100. For both domain and overall scores, a higher score indicates better diabetes therapy-related quality of life [58, 59].	*N* = 2 Hayashino et al. (2018b) Mashitani et al. (2015)	Yes Validated among Japanese patients with T2DM [58, 60]
Serious adverse events	1	Symptoms	1. Serious adverse events (1 item)	Developed by study investigators, a serious adverse event is defined in this study as any unfavourable and unanticipated medical event. This includes hospitalisation, injury, death as well as complication as a result of diabetes [61].	*N* = 1 Ji et al. (2015)	No Developed by study investigators without validation
Self-monitoring of blood glucose frequency	1	Treatment adherence	1. Frequency of self-monitoring of blood glucose (1 item)	Developed by study investigators, this PROM captures the number of times that blood glucose is self-monitored in a month [61].	*N* = 1 Ji et al. (2015)	No Developed by study investigators without validation
Questionnaire on diabetes treatment beliefs and health behaviour	28	Diabetes-specific, treatment adherence, treatment beliefs	1. Self-measured blood glucose after questionnaire completion (1 item) 2. Mental/physical health (7 items, including using EQ-5D) 3. Severe complications (2 items) 4. Minor complications (1 item) 5. Daily habits (3 items) 6. Self-efficacy (6 items)	A EQ-5D summary index for the five EQ-5D items is generated using the Danish EQ-5D valuation algorithm. Other items, which are devised by study investigators, are reported using a scale of 1 to 10, with 1 being very poor and 10 being very good [27].	*N* = 1 Von Arx et al. (2016)	No Developed by study investigators through two focus groups with 4 participants per group

Table 4 (continued)

Name	No. of items	Construct	Domains	Score interpretation	Studies that included	Has the PROM been validated among patients with T2DM in the country where the study was conducted?
			7. Treatment adherence (1 item) 8. Health belief: susceptibility to health risk (4 items) 9. Health belief: severity of diabetes (1 item) 10. Barriers toward treatment (1 item) 11. Benefit of treatment (1 item)			
Summary of Diabetes Self-Care Activities—Revised (SDSCA)	5	Treatment adherence	1. Adherence to blood sugar testing (2 items) 2. Adherence to exercise (2 items) 3. Adherence to diet (1 item)	An 8-point scale is used for respondents to indicate the number of days (0–7) in the past week they completed a diabetes self-care activity (i.e. blood sugar testing, exercise and diet). Items in each domain are summed to give a domain score, or can also be totalled to give an overall SDSCA score [62]. In their study, Shigaki and colleagues had shortened the PROM to a 3- domain, 5-item measure, instead of the original 5-domains, 11-item questionnaire [29].	*N* = 1 Shigaki et al. (2010)	Yes Validated among US T2DM population [62]
Questionnaire on understanding of diabetes	2	Diabetes knowledge	1. Understanding of diabetes (1 item) 2. Attendance of diabetes education classes (1 item)	Devised by study investigators, understanding of diabetes is scored using a scale ranging from 1 to 7, with a higher score indicating a better self-rated understanding of diabetes. A yes/no answer is used to report the item on attendance of diabetes education classes [29].	*N* = 1 Shigaki et al. (2010)	No Developed by study investigators without validation
Treatment Self-Regulation Questionnaire-diabetes (TSRQ-diabetes)	32	Motivation	1. Motivation for testing blood glucose (12 items: 7 autonomous, 5 controlled) 2. Motivation for following diet recommendations (10 items: 6 autonomous, 4 controlled) 3. Motivation for exercise (10 items: 6 autonomous, 4 controlled)	Each domain consists of items for two different regulation mechanisms: autonomous regulation and controlled regulation. Each item is rated using a scale ranging from 1 (not at all true) to 7 (very true). A summary score for each regulation system is computed by averaging all items attributed to that mechanism [29].	*N* = 1 Shigaki et al. (2010)	No Validation only done for the theoretical structure for tobacco, exercise and diet in US [63]
Perceived Competence for Diabetes Scale (PCDS)	4	Diabetes-specific, self-efficacy	1. Self-efficacy in managing diabetes (4 items)	Each item is scored using a scale of 1 (not at all true) to 7 (very true). Item scores are then averaged to form a summary score. A higher summary score indicates higher perceived competence in diabetes self-management [29].	*N* = 1 Shigaki et al. (2010)	No No PCDS validity studies for T2DM found
Medical Outcomes Survey-Social Support Scale (MOS-SSS)	19	Profile-based social support	1. Emotional/ informational support (8 items) 2. Tangible support (4 items) 3. Affectionate support (3 items) 4. Positive social interaction (3 items) (Additional item: 'Someone to do things with to help you get your mind off things')	Each item is scored on a scale of 1 (none of the time) to 5 (all of the time). Scores of all 19 items are averaged to form an overall social support index. A higher index score suggests better social support [64].	*N* = 1 Shigaki et al. (2010)	No No MOS-SSS validity studies for T2DM found

Table 4 (continued)

Name	No. of items	Construct	Domains	Score interpretation	Studies that included	Has the PROM been validated among patients with T2DM in the country where the study was conducted?
Frequency of hypoglycaemia /severe hypoglycaemia	1	Symptoms	1. Frequency of hypoglycaemia/severe hypoglycaemia in the 1 month/3 months/12 months prior to survey response (1 item)	Developed by study investigators, respondents provide the number of hypoglycaemic/severe hypoglycaemic episodes experienced in the time parameter set by investigators [18, 31, 61].	*N* = 3 Ji et al. (2015) Kikuchi et al. (2015) Berkowitz et al. (2014)	No Developed by study investigators without validation
Questionnaire on hypoglycaemia frequency	4	Symptoms	1. Frequency of hypoglycaemia in the past 90 days (2 items) 2. Severity of hypoglycaemic episodes (2 items)	Developed by Hayshino and colleagues, the reported hypoglycaemia frequency is classified into three severity levels: non-nocturnal hypoglycaemia (NNH), non-nocturnal disabling hypoglycaemia (NNDH), and non-nocturnal severe hypoglycaemia (NNSH) [65].	*N* = 1 Hayashino et al. (2018a)	No Developed by study investigators without validation
Brief-type self-administered diet history questionnaire (BDHQ)	58	Dietary intake	1. Intake frequency of 46 food and non-alcoholic beverage items (46 items) 2. Daily intake of rice and miso soup* 3. Frequency of drinking and amount per drink for alcoholic beverages* 4. Usual cooking methods* 5. General dietary behaviour* *Number of items for each domain unknown	For each item in the first three domains, respondents select their intake frequency out of the 7 options, ranging from 'more than twice a day' to 'almost never'. A BDHQ computer algorithm is then used to estimate the nutrient intake based on reported intake [66].	*N* = 1 Kikuchi et al. (2015)	No Validation only done for Japanese general population [66]

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