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The Impact of Hypoglycaemia on Quality of Life Outcomes Among Adults with Type 1 Diabetes: A Systematic Review

Abbreviated Running Title: Impact of Hypoglycaemia on Quality of Life

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Summary

Hypoglycaemia is a common barrier to optimal glycaemic management and often feared among adults with type 1 diabetes. The aim of this systematic review was to summarize current evidence regarding the impact of hypoglycaemia on quality of life (QoL) and related outcomes. Electronic searches of MEDLINE, PsycINFO, CINAHL, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials were conducted. Peer-reviewed empirical studies investigating the relationship between hypoglycaemia and QoL were eligible for inclusion. Thirty studies met the inclusion criteria. Extracted data was summarized in a narrative synthesis according to Synthesis Without Meta-Analysis guidelines. None of the studies examined the impact of hypoglycaemia on general QoL. There was no association between hypoglycaemia and diabetes-specific QoL in four of the 30 studies. Severe hypoglycaemia was associated with greater fear of hypoglycaemia and diabetes distress, and lower general emotional well-being, but not with depression, anxiety, or health status. Self-treated hypoglycaemia was associated with greater fear of hypoglycaemia. With the exception of fear of hypoglycaemia, this review shows mixed associations between hypoglycaemia and psychological outcomes. Further research is needed to investigate the impact of hypoglycaemia on other domains of QoL.

Keywords: Type 1 diabetes, T1DM, hypoglycaemia, low blood glucose, quality of life, psychology

Acronyms: ADA = American Diabetes Association; CGM = Continuous glucose monitoring; DQoL = Diabetes Quality of Life; EQ-5D = EuroQoL-5 Dimension; FoH = Fear of hypoglycaemia; HFS-II = Hypoglycaemia Fear Survey-Second Edition; IAH = Impaired awareness of hypoglycaemia; IHSG = International Hypoglycaemia Study Group; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROMs = Patient-reported outcome

measures; QoL = Quality of life; ScHARR = School of Health and Related Research; SWiM = Synthesis Without Meta-Analysis; T1DM = Type 1 diabetes mellitus; WHO-5 = World Health Organisation-Five Well-Being Index

1.1 Introduction

Self-management of type 1 diabetes (T1DM) is aimed at maintaining recommended glycaemic targets to avoid hyperglycaemia and prevent long-term diabetes complications. However, keeping glucose levels within target range is often associated with increased risk of hypoglycaemia (1). Hypoglycaemia represents the most common adverse event associated with intensive insulin therapy, with a two- to three-fold increase in severe hypoglycaemia for people with T1DM (2). Despite advancements in insulin analogs, insulin delivery devices, and continuous glucose monitors (CGM), many adults with T1DM experience difficulties with hypoglycaemia prevention and management, with prevalence studies indicating that current rates of severe hypoglycaemia are similar to rates reported almost 30 years ago (3).

Hypoglycaemic episodes are typically characterized by a range of autonomic symptoms (e.g., sweating, trembling, and palpitations) followed by neuroglycopenic symptoms (e.g., confusion and concentration difficulties) if low blood glucose is not reversed in time. Episodes can be self-treated if the individual's cognitive function remains sufficiently intact and they can ingest carbohydrates to restore glucose concentrations (4). Severe episodes require the assistance of another person due to cognitive impairment and can result in loss of consciousness, seizure, or death (5). The International Hypoglycaemia Study Group (IHSG) define glucose levels of <54mg/dL (<3.0mmol/L) as sufficiently low to indicate serious and clinically important hypoglycaemia, with concentrations of ≤70mg/dL (≤3.9mmol/L) defined as an alert level (6).

While some adults with T1DM may be unaffected or experience few episodes of hypoglycaemia, other individuals will experience many episodes (4). Long duration of T1DM and recurrent hypoglycaemia are risk factors for the development of impaired awareness of hypoglycaemia (IAH), which is associated with a three- to six-fold increased risk of severe hypoglycaemia (7). Regardless of episode severity, many adults with T1DM report that

hypoglycaemia is burdensome to their daily life and limits their functioning (8). Hypoglycaemia is associated with reduced sleep quality, decreased work productivity, and driving avoidance (9, 10). Many adults with T1DM greatly fear hypoglycaemia and may develop compensatory strategies, such as maintaining higher glucose concentrations to avoid hypoglycaemia (11). These behaviours can have clinical implications in terms of increased risk of hyperglycaemia and associated long-term complications (12).

Many adults with T1DM report that hypoglycaemia compromises their quality of life (QoL) (13). Episodes and fear of hypoglycaemia (FoH) can impact various aspects of an individual's QoL, including occupational pursuits, leisure activities, relationships, and well-being. Quality of life is recognized as an important health outcome, with preservation or optimization of QoL a central goal of diabetes care (14). While there exists no universally agreed definition of QoL, this construct was conceptualized in the current study as an individual's subjective evaluation of physical, psychological, and social aspects of their lives (15, 16).

Previous studies of the impact of hypoglycaemia on QoL have employed many generic and diabetes-specific patient-reported outcome measures (PROMs) to assess and infer QoL (16). Systematic review of the current evidence base is needed to synthesize existing knowledge about the impact of hypoglycaemia on QoL in adults with T1DM, as previous reviews are non-systematic narrative reviews (17) or focused exclusively on economic outcomes (18). The aim of the current study was to summarize existing literature relating to hypoglycaemia and QoL-related outcomes among adults with T1DM. An additional aim was to identify knowledge gaps by determining which outcomes and domains of QoL have been examined with previous literature, and which domains require further investigation to better understand the impact of hypoglycaemia across all aspects of QoL. Findings of this review may identify QoL-related factors that could be prioritized in clinical care.

1.2 Methodology

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (CRD42020154023). This review was documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (19).

1.2.1 Search Strategy

Information specialists at the School of Health and Related Research (ScHARR) designed and conducted systematic database searches of MEDLINE including ePub Ahead of Print and In-Process (via Ovid), PsycINFO (via Ovid), CINAHL (via EBSCO), Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. Searches identified studies reporting on relationships between hypoglycaemia and QoL-related outcomes among adults with T1DM. Search terms related to three concepts: 1) T1DM; 2) hypoglycaemia; and 3) QoL-related outcomes (see Appendix A, Supplemental Digital Content, for the MEDLINE search string).

1.2.2 Article Screening

Empirical peer-reviewed studies were eligible for inclusion if they: 1) included adults with a diagnosis of T1DM; 2) were quantitative (including observational, experimental, and mixed-methods studies); 3) were published ≥2010 to reflect the current impact of hypoglycaemia on QoL, given recent advancements in diabetes treatments and technologies; 4) assessed hypoglycaemia frequency and severity; 5) administered any generic or diabetes-specific PROM that purported to measure self-reported physical, psychological, or social functioning or well-being; and 6) reported on the relationship between hypoglycaemia and PROMs. With exception to T1DM diagnosis, there were no further eligibility criteria relating to clinical characteristics. Studies were excluded if they:

1) were qualitative; 2) were not available in English; 3) did not report results separately for paediatric and adult samples or T1DM and type 2 diabetes groups; and 4) administered only clinician-rated measures of cognitive function, in line with the conceptualization of QoL in this review (i.e., QoL as an individual's subjective evaluation of functioning).

Following removal of duplicates, records were screened at title and abstract (AC and AS) and full-text (HC) levels. A random subset of 10% of the records were screened by an additional reviewer (MVJ). Inter-rater agreement between reviewers was 83%, with discrepancies resolved through discussion. Reviewers then conducted reference list-checking (via Web of Science) and citation-searching of included studies.

1.2.3 Data Extraction and Synthesis

Two reviewers (AC and HC) extracted data relating to study characteristics (e.g., PROMs administered and definition of hypoglycaemia), participant characteristics (e.g., baseline history of hypoglycaemia), and relevant findings. A random subset of 20% of extractions were independently verified by an additional reviewer (MC). The Joanna Briggs Institute Critical Appraisal Tool (20) was used to evaluate risk-of-bias in included studies and inform interpretations of the strength of evidence. Risk-of-bias evaluations were not used to determine inclusion or exclusion of studies in the review. Meta-analysis was not possible due to clinical and methodological diversity, including variation in study design, hypoglycaemia measurement, and QoL assessment. This variation precluded meta-regression or meta-analysis of multiple outcomes to address heterogeneity (21).

Extracted data were classified by outcome and summarized in a narrative synthesis as per Synthesis Without Meta-analysis (SWiM) guidelines (22). Existing frameworks of QoL measurement were used to classify findings into outcome groups and physical, psychological, or

social domains of QoL (15, 16). Since effect sizes were inconsistently measured and reported across studies (see Table S4, Supplemental Digital Content, for available effect sizes), conclusions were drawn for each outcome using vote counting based on direction of effect (23). Vote counting involved comparing the number of effects showing a positive or negative association between hypoglycaemia and the outcome, with the number showing no association. For outcomes with limited findings (e.g., *n*=1) or findings from studies with risk-of-bias concerns, it was determined that there was insufficient evidence to draw conclusions. Preliminary conclusions were then tabulated by QoL domain (see Table 1) to determine which outcomes or domains have been examined with previous literature.

Findings from QoL-specific assessment tools are presented first in narrative synthesis, followed by diabetes-specific and generic outcomes. Synthesis was further structured by hypoglycaemia severity (e.g., self-treated versus severe episodes) and episode timing (e.g., daytime versus nocturnal). Findings related to mild, moderate, or symptomatic episodes that were defined in the original study as able to be self-treated or not requiring external assistance, were classified in this review as self-treated hypoglycaemia for the purposes of synthesis. Where definitions of mild episodes were not available or did not delineate the need for external assistance, severity labels were reported as they were in their respective studies.

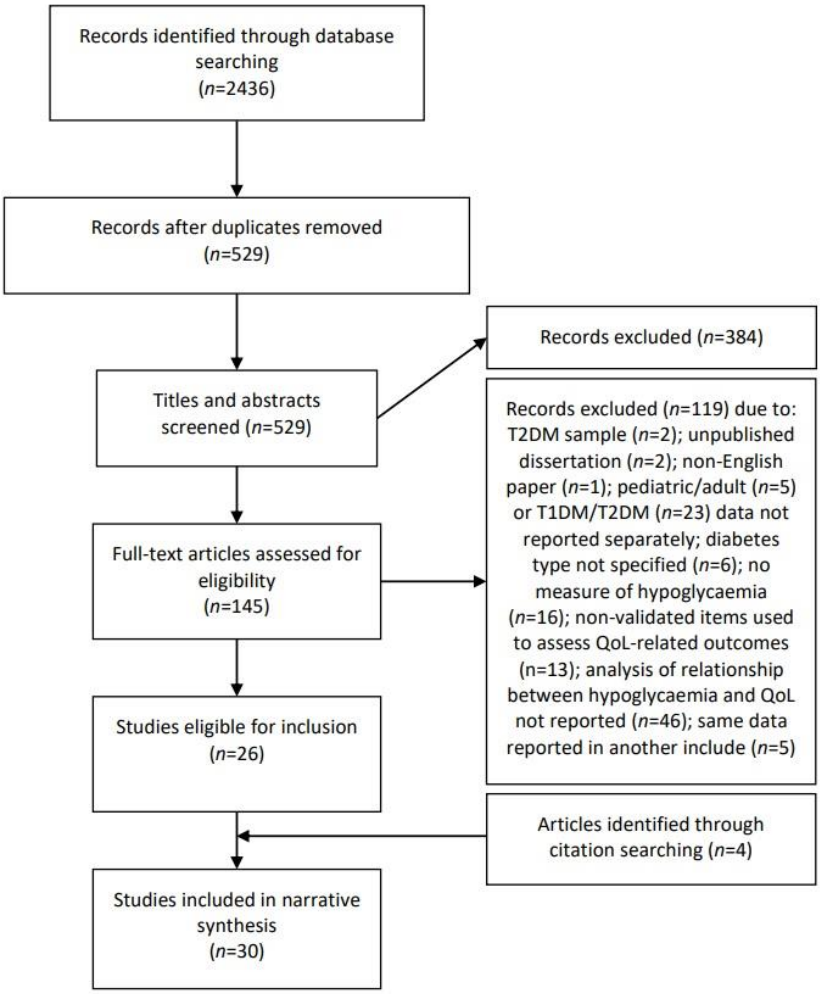
1.3 Results

Thirty studies were included in narrative synthesis (see Figure 1). Two papers reported on the same sample but presented data on different outcomes measured at two timepoints (2010 and 2014), so were not excluded (24, 25). Seventy-three percent (*n*=22) of studies were cross-sectional, 20% were prospective (*n*=6), and 7% (*n*=2) were case-control designs (24-41). Studies included a total of *N*=9,946 participants from 19 countries (see Table S1, Supplemental

Digital Content, for clinical characteristics of samples in included studies). Sample sizes ranged from *N*=33 to *N*=2,292. The average age of participants ranged from 21 to 69 years, and the average diabetes duration ranged from 6 weeks (in a study of adults with newly diagnosed T1DM) to 41 years.

Figure 1.

PRISMA Flowchart



1.3.1 Risk-of-Bias Assessment

Eighty-five percent (*n*=25) of studies reported clearly defined inclusion and exclusion criteria. Samples and study settings were described in detail in 63% (*n*=19) of studies. All studies identified and measured common potential confounders of hypoglycaemia risk, such as age and diabetes duration. Seventy-three percent (*n*=22) of studies administered standardized PROMs that had been validated among adult T1DM samples. Seventy-seven percent (*n*=23) of studies used objective and standardized criteria to determine T1DM diagnoses (i.e., medical records), since most samples were recruited from diabetes clinics or registries.

Fifty-seven percent (*n*=17) of studies assessed hypoglycaemia severity with reference to published clinical practice guidelines (e.g., the American Diabetes Association Workgroup on Hypoglycemia Report (1) or the IHSG Position Statement (6)). There was significant variation between studies in hypoglycaemia measurement. Some studies (50%; *n*=15) used continuous scales (e.g., frequency of nocturnal hypoglycaemia in the past month). Other studies (43%; *n*=13) reported on categorical measurements (e.g., presence or absence of severe hypoglycaemia in the past year). Two studies (7%) used both continuous and categorical measurements. Most studies (83%, *n*=25) relied on self-report measures of hypoglycaemia, while five studies (17%) referred to CGM data or glucose logbooks. Recall periods ranged from a 48-hour data collection period (38) to lifetime incidence (39), with severe hypoglycaemia in the past 6-12 months the most common recall period (43%; *n*=13). Most studies (90%; *n*=27) referred to episodes of hypoglycaemia that occurred while awake, with three studies (10%) investigating episodes that occurred during sleep (25, 26, 42).

One study (36) was assessed to have high risk-of-bias and five studies were assessed to have moderate risk-of-bias (25, 30, 38, 43, 44). Risks related minimal reporting of sample characteristics, study settings, and hypoglycaemia definitions (see Table S2, Supplemental Digital Content, for risk-of-bias assessment results).

1.3.2 Impact of Hypoglycaemia on QoL

While none of the studies examined the impact of hypoglycaemia on QoL using generic or hypoglycaemia-specific measures of QoL, three studies investigated this relationship using a diabetes-specific measure of QoL (34, 40, 45). Two studies found no significant association between diabetes-specific QoL and self-treated or severe hypoglycaemia in the past one to six months (34, 45). One study showed that severe hypoglycaemia in the past year was negatively associated with overall diabetes-specific QoL and some of its domains (Impact and Diabetes-Related Worry subscales), but not other domains (Satisfaction and Social/Vocational Worry subscales) (40). While results were mixed, current evidence indicates that hypoglycaemia is not associated with diabetes-specific QoL for adults with T1DM. There is insufficient evidence to draw conclusions regarding the impact of hypoglycaemia on generic domains of QoL.

1.3.3 Fear of Hypoglycaemia

Seventeen of the 30 studies (57%) examined associations between hypoglycaemia and FoH, with 15 studies investigating severe hypoglycaemia and 7 studies investigating self-treated hypoglycaemia (3, 24, 25, 27-29, 33, 35, 38, 39, 41, 43, 44, 46-49).

1.3.3.1 Self-Treated Hypoglycaemia. Four studies found a significant positive correlation between FoH and self-treated hypoglycaemia (24, 25, 38, 44). Two of these studies (that investigated the same sample on different measures) reported that this association remained significant after adjusting for demographic, clinical, and psychological variables (including anxiety symptoms) (24, 25). In contrast, three studies showed no significant relationship between FoH and mild or symptomatic hypoglycaemia (39, 41, 48). Current evidence suggests a positive association between self-treated hypoglycaemia and FoH.

1.3.3.2 Severe Hypoglycaemia.

Twelve studies found a significant positive correlation between FoH and severe hypoglycaemia in the past 6-12 months (3, 24, 25, 27-29, 35, 41, 43, 46-48), with one study reporting a large effect size (48) and others demonstrating weak associations (25, 35, 41, 43, 47). Six of the 12 studies showed that the association between severe hypoglycaemia and FoH remained significant after adjusting for demographic, clinical, and psychological variables (including anxiety and depressive symptoms, loneliness, and Type D personality) (3, 24, 25, 28, 41, 47), including one study with a large effect size (41). In contrast, five studies reported that severe hypoglycaemia in the past 6-12 months was not significantly associated with FoH (27, 33, 39, 41, 49). Current evidence suggests a positive association between severe hypoglycaemia and FoH.

1.3.3.3 Nocturnal Hypoglycaemia.

One study found a weak positive correlation between nocturnal hypoglycaemia and FoH, which remained significant after adjusting for demographic and psychological factors (including anxiety symptoms) (25). There is insufficient evidence to draw conclusions regarding the impact of hypoglycaemia during sleep and FoH.

1.3.4 Diabetes-Specific Distress

Eight studies examined associations between hypoglycaemia and diabetes distress, with seven studies investigating severe hypoglycaemia and four studies investigating self-treated hypoglycaemia (3, 30, 32, 37, 45, 48-50).

1.3.4.1 Self-Treated Hypoglycaemia.

Three studies reported no significant correlation between mild hypoglycaemia and diabetes distress (45, 48, 50). Two of these studies excluded individuals with psychiatric difficulties and comorbidities (45, 50). An additional study showed a weak positive correlation between mild hypoglycaemia and diabetes distress (37) in a sample reporting severe diabetes burnout (as indicated by scores of 87.5 out of 100 on the diabetes

distress measure, and 14.4% reporting that hypoglycaemia was a serious problem), which may reflect a more distressed sample. There is insufficient evidence to draw conclusions regarding the impact of self-treated hypoglycaemia on diabetes distress.

1.3.4.2 Severe Hypoglycaemia. Five studies found a significant positive association between severe hypoglycaemia and diabetes distress (3, 30, 32, 48, 49), with one study reporting a medium effect size (48). Two of the five studies showed that severe hypoglycaemia in the past 6-24 months remained significantly associated with higher diabetes distress after adjusting for demographic and clinical variables (32, 49). By contrast, two studies reported no significant association after controlling for clinical variables (3, 50), with one of these studies being a nine-month prospective study (50). Two additional studies demonstrated no significant association between severe hypoglycaemia and diabetes distress, in populations with a higher mean age (54.5 years) relative to other studies in this review (37, 45) and in a small sample (*N*=50) where individuals with depression and anxiety were excluded (45). Current evidence suggests a positive association between severe hypoglycaemia and diabetes distress.

1.3.5 Diabetes-Specific Positive Well-Being. One study reported a significant negative correlation between the occurrence of severe hypoglycaemia in the past six months and diabetes-specific positive well-being (3), which remained significant after controlling for clinical variables. There is insufficient evidence to draw conclusions regarding the impact of hypoglycaemia on diabetes-specific positive well-being.

1.3.6 Psychological Distress

Nine studies examined the impact of hypoglycaemia on general psychological functioning, with four studies investigating depressive symptoms and four studies investigating

anxiety symptoms (24, 30, 33, 36, 39, 46, 50, 51). One study reported a significant positive association between the occurrence of severe hypoglycaemia in the past two years and overall psychological distress (30).

1.3.6.1 Depressive Symptoms. Three studies found no significant association between depressive symptoms and the occurrence of severe hypoglycaemia (46, 51) or frequency of self-treated hypoglycaemia (50). An additional study found that frequency of self-treated hypoglycaemia in the preceding two weeks (but not severe hypoglycaemia in the past year) was significantly associated with depressive symptoms, with a large effect size (39). Current evidence suggests that hypoglycaemia is not associated with depressive symptoms.

1.3.6.2 Anxiety Symptoms. One study reported weak positive associations between mild or nocturnal hypoglycaemia (but not severe hypoglycaemia) and generalized anxiety or social phobia symptoms (25) in a sample where the majority (75%) reported no episodes of severe hypoglycaemia in the previous year. Two additional studies found no significant association between severe hypoglycaemia and anxiety symptoms (33, 39), with one of these studies having excluded individuals with psychiatric problems limiting their ability to participate (39). One study reported positive associations (with small effect sizes) between severe hypoglycaemia in the past month and post-traumatic stress disorder symptom severity and diagnoses (36), although these findings should be interpreted with caution due to risk-of-bias concerns. While results were mixed, current evidence suggests that hypoglycaemia is not associated with anxiety symptoms.

1.3.7 Generic Emotional Well-Being

Four studies found significant correlations between severe hypoglycaemia in the past six to 24 months and lower emotional well-being (3, 30, 32, 48), including one study that indicated the relationship remained significant after adjusting for demographic and clinical variables (32).

One of these studies reported that the association was no longer significant after accounting for age at diabetes onset, diabetes duration, and IAH, although each of these factors was independently related to severe hypoglycaemia (3). One of the studies showed no significant relationship between symptomatic hypoglycaemia in the preceding month and emotional well-being (48). Current evidence suggests that severe hypoglycaemia is associated with reduced emotional well-being.

1.3.8 Health Status

Five studies examined relationships between hypoglycaemia and health status (31, 33, 48, 49, 52). Three of the five studies found no significant association between frequency or severity of hypoglycaemia and health status (31, 33, 52), with a two-year prospective study reporting that hypoglycaemia was not a significant predictor of health status (52). One of the three studies found a significant negative association between severity of hypoglycaemia and EuroQol 5-Dimension (EQ-5D) Usual Activities subscale scores, which may indicate that hypoglycaemia is only related to certain aspects of health status (33). A prospective study found that severe hypoglycaemia in the two years following islet transplantation was a significant predictor of emotional functioning but not physical functioning, after adjusting for demographic and clinical covariates (49). One study showed a significant negative association between the occurrence of severe hypoglycaemia in the past year and health status (medium effect size), but no significant correlation between symptomatic hypoglycaemia in the past month and health status (48). Current evidence suggests that hypoglycaemia is not associated with health status.

1.3.9 Sleep Quality

Two of the 30 studies reported no significant correlation between sleep quality and hypoglycaemia during sleep (26, 42). Both studies were characterized by small sample sizes (*N*=48

and *N*=64) comprised of younger adults (mean ages 22 and 27 years) with shorter diabetes durations (12 and 14 years), compared to other studies in this review. There is insufficient evidence to draw conclusions regarding the impact of hypoglycaemia on sleep quality.

1.3.10 Summary of Main Findings

Table 1 provides an overview of conclusions drawn from narrative synthesis.

Table 1. Relationships between Hypoglycaemia and QoL-Related Outcomes, Presented by QoL Domain.

Outcome	*n*	Relationship
Psychological		
Diabetes-specific QoL	3	No association
Fear of hypoglycaemia	17	Severe hypoglycaemia and self-treated hypoglycaemia associated with higher fear of hypoglycaemia Insufficient evidence for nocturnal hypoglycaemia
Diabetes distress	8	Severe hypoglycaemia associated with higher diabetes distress Insufficient evidence for self-treated hypoglycaemia
Diabetes-specific positive well-being	1	Insufficient evidence
Depressive symptoms	4	No association
Anxiety symptoms	4	No association
Emotional well-being	4	Severe hypoglycaemia associated with reduced well-being

Physical		
Health status	5	No association
Sleep quality	2	Insufficient evidence

n=Number of studies that reported on outcome

1.4 Discussion

Of the 30 studies included in this review, 73% (*n*=22) reported a significant positive association between hypoglycaemia and negative psychological outcomes. Severe hypoglycaemia is associated with greater fear of hypoglycaemia and diabetes distress, and reduced general emotional well-being. Self-treated hypoglycaemia is associated with greater fear of hypoglycaemia. Current evidence suggests that hypoglycaemia is not associated with diabetes-specific QoL, depressive or anxiety symptoms, or health status. There is insufficient evidence to draw conclusions regarding the relationships between hypoglycaemia and generic QoL, diabetes-specific positive well-being, diabetes distress (for self-treated episodes), or sleep outcomes, due to the limited number of studies investigating these outcomes.

For several outcomes, there were discrepant findings that may be explained by methodological and sample across studies. Firstly, hypoglycaemia definitions and measurements were inconsistent across studies, with some studies referring to severity labels that do not align with practice guidelines and clinical care (e.g., “moderate” hypoglycaemia). Current evidence is limited by its reliance on self-report measures of hypoglycaemia, in terms of recall bias. Future studies on the impact of hypoglycaemia on QoL would benefit from a standardized measure of hypoglycaemia that integrates self-report, proxy-report, and glucometer-based data. Future studies could utilise ecological momentary assessment with CGM to collect real-time data on daily hypoglycaemic

events, hyperglycaemic events, glucose variability, and QoL, to determine relationships among these variables more precisely.

Studies included in this review were conducted across 19 countries; thus, cultural differences could have contributed to conflicting findings between studies, based on previous research demonstrating significant inter-country variation in work productivity following episodes of hypoglycaemia (9). Future studies should examine cultural differences in QoL-related outcomes of hypoglycaemia, to determine whether findings are stable across countries and cultural groups. Some studies excluded individuals with depression, anxiety, and other psychiatric diagnoses; thus, findings of this review may not represent more distressed adults with T1DM. Few studies (17%; *n*=5) reported participant hypoglycaemia awareness status, despite IAH being a known predictor of severe hypoglycaemia (and in turn, reduced QoL). Further research should compare QoL impacts of hypoglycaemia for individuals with intact versus impaired awareness.

There was considerable variation in QoL measurement across studies, which was expected since there is no single validated measure of the impact of hypoglycaemia on QoL. The Hypoglycaemia Fear Survey was the only hypoglycaemia-specific measure identified, and with 57% (*n*=17) of studies administering some form of the HFS, this measure dominated assessment across studies. Most studies focused on the impact of hypoglycaemia on psychological well-being or distress using generic and diabetes-specific measures. Some studies purported to assess QoL using measures of health status that likely tap in to physical aspects of QoL, to the exclusion of other important aspects of QoL (e.g., interpersonal relationships or vocational pursuits) (15). Further research is needed to determine whether existing measures of QoL are sensitive to, and completely capture, the impact of hypoglycaemia across domains of QoL. A standardized measure of the impact of hypoglycaemia on QoL could have important research and clinical applications.

Database searches retrieved few studies of QoL-related outcomes for self-treated or nocturnal episodes of hypoglycaemia. Future studies could examine whether severe episodes have a greater impact on QoL compared to self-treated and nocturnal events, or whether the impact of hypoglycaemia is comparable between severity levels. Database searches indicated a skewness in the literature, whereby most of the evidence was related to psychological or emotional outcomes. Qualitative data has shown negative impacts of hypoglycaemia on romantic and family relationships (53, 54), an aspect of QoL that is important to adults with T1DM but not reflected in the current evidence. Further research is needed to examine the impact of hypoglycaemia on other domains of QoL that have not been investigated in past studies, such as interpersonal and vocational domains. A more balanced representation of QoL domains would assist in identifying which domains are most affected by hypoglycaemia.

1.4.1 Strengths and Limitations

This review is the first of its kind to summarize evidence relating to the impact of hypoglycaemia on QoL among adults with T1DM. Most studies were assessed to have low risk-of-bias, such that conclusions of the review can be interpreted with some confidence. Narrative synthesis identified outcomes that have been examined with previous literature (i.e., psychological or emotional aspects of QoL), as well as knowledge gaps that require further investigation. This review synthesized findings relating to any severity or type of episode and was not limited to severe hypoglycaemia only. It is possible that relevant studies were not identified in database searches due to the inherent complexity in defining QoL and thus selecting search terms that adequately capture all potential facets of this construct. Exclusion of non-English papers published more than 10 years ago has implications for relevant findings potentially being omitted from this synthesis.

Due to the lack of consensus regarding definition and measurement of hypoglycaemia and QoL, classification methods used in this review may be idiosyncratic, despite the use of published practice guidelines and QoL frameworks in classifying findings. While vote counting based on direction of effort is recognized as an acceptable synthesis approach in these circumstances (21), this method provided limited information on the magnitude of effects and did not account for differences in the relative sizes of studies.

1.4.2 Implications and Conclusions

Findings of this study highlight potential support needs of adults with T1DM. This review found that hypoglycaemia increases fear of hypoglycaemia and diabetes distress, and reduces general emotional well-being in adults with T1DM. These factors are not only strongly associated with QoL, but have also been shown to predict clinical outcomes such as HbA_{1c} (55). Specific approaches to identify and address these QoL-related factors (i.e., fear of hypoglycaemia, diabetes distress, and emotional well-being) in routine clinical practice may improve glycaemic outcomes, reduce complications, and help people to live well with their condition.

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