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The Association Between Body Mass Index and Glycemic Control in Patients with Type 2 Diabetes Across Eight Countries: A Literature Review

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Abstract

Objective: To investigate the association between obesity and glycemic control based on country-specific glycemic control data from the USA and selected European and Asian countries by body mass index (BMI), or BMI data by glycemic control (HbA_{1c}), in individuals with type 2 diabetes (T2D).

Methods: Literature search of databases and abstracts to identify real-world studies (2015-2020) reporting HbA_{1c} and BMI data.

Results: Seventeen articles (China, including Hong Kong, n=10; Japan, n=3; USA, n=2; Spain, n=1; UK, n=1) were identified from 6696 de-duplicated references. Of the 13 studies reporting by BMI mean rates of glycemic control or likelihood of achieving glycemic control, eight found that achieving control significantly declined as BMI increased; one reported a clear trend but no statistics; two reported glycemic control rates for those with obesity to be significantly worse than for one other group; and two reported no significant difference with BMI. Of the six studies reporting average HbA_{1c} levels by BMI, four reported HbA_{1c} to increase with BMI. Two of three studies reporting mean BMIs by glycemic control found these increased with HbA_{1c}.

Conclusions: This review consolidates recent evidence on the glycemic control status of individuals with T2D reported by BMI in selected countries. Studies generally reported a lower chance of achieving glycemic control targets in those with overweight or obesity. Most studies found greater HbA_{1c} in individuals with higher BMI, and average BMI greater in those with higher levels of HbA_{1c}. Focused efforts are needed to improve glycemic control in patients with T2D and overweight/obesity.

Keywords: Body mass index; China; Europe; Glycemic control; Japan; Type 2 diabetes; United States; Weight

Abbreviations: ADA: American Diabetes Association; BMI: Body Mass Index; CVD: Cardiovascular disease; EMR: Electronic Medical Record; FPG: Fasting Plasma Glucose; HbA_{1c}: Glycated Hemoglobin; ISPOR: Professional Society for Health Economics and Outcomes Research; NA: Not Applicable; OR: Odds Ratio; P: Percentile; RR: Relative Risk; RWE: Real-World Evidence; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; WHO: World Health Organization

Introduction

Type 2 diabetes (T2D) and obesity are intrinsically linked. Obesity is a major risk factor for developing T2D, and the progression of disease increases with obesity [1]. Obesity is also known to increase the odds of developing many common complications of diabetes, including heart disease, retinopathy, dyslipidemia, and hypertension [2].

Hyperglycemia is the defining feature of T2D, so achieving glycemic control is a fundamental aim of disease management. Inadequate control of T2D can result in the development of disabling and life-threatening complications [3,4]. However, a large proportion of individuals are still failing to achieve glycemic control and a significant proportion of those who are not achieving glycemic control have overweight or obesity [5]. Given the close relationship between T2D and obesity, weight reduction is a key therapeutic goal in both the prevention and management of type 2 diabetes [1,6], with weight management playing a prominent role in T2D guidelines. Such guidelines outline that all individuals with T2D and overweight or obesity should be advised of the health benefits of weight loss and be encouraged to engage in a program

of intensive lifestyle management to include dietary restrictions and increases in physical activity [4,7]. They also emphasize that when choosing a glucose-lowering agent for patients with overweight or obesity, careful consideration should be given to its impact on weight [4,7].

Weight loss is recognized to be associated with improvements in glycemic control among individuals with T2D [8]. However, weight reduction or maintaining a healthy weight can be challenging for many people with T2D. For example, in the United States it has been estimated that 89.0% of adults with diabetes had overweight or obesity [9].

With high rates of overweight and obesity in individuals with T2D, and the ongoing development of new diabetes therapies, having data from recent real-world studies on body mass index (BMI) and glycemic control would improve understanding of the patient population and could help to inform future decision-making. Therefore, the purpose of this review was to identify and report recent studies on the association between BMI and glycemic control through the identification of recently published country-specific (China, France, Germany, Italy, Japan, Spain, UK, USA) studies. The review is intended to serve as a resource of available studies for those working in or with those countries. There is no attempt to aggregate or pool data across the different studies, given the differences in study populations and also BMI cut-offs that are used in different countries.

Methods

Table 1: Eligibility criteria for the review.

Study Characteristic	Eligible	Ineligible
Patient population	Adult (≥18 years) patients with T2D Study undertaken in China, France, Germany, Italy, Japan, Spain, UK, or USA	Pediatric (<18 years) patients Study undertaken in a country other than China, France, Germany, Italy, Japan, Spain, UK, or USA
Outcomes	HbA_{1c}	Outcomes unrelated to HbA_{1c} or BMI/weight
	BMI	
	Weight	
Study type	Real-world cross-sectional study Real-world case–control study Real-world cohort study Administrative or claims database study Real-world electronic health record (EHR) Registry study representing real-world clinical practice Questionnaires and surveys relating to real-world clinical practice	Non-observational studies that do not reflect real-world clinical practice
		Case studies
		Pragmatic or randomized controlled trials
		Utility studies
		Preference or satisfaction studies based on hypothetical profiles
		Reviews
		Editorials/comments Economic evaluations
Time frame	Start January 2015 to end December 2019	Outside of included date range
Language	English (abstract)	Non-English abstract

BMI: Body Mass Index; HbA_{1c}: Glycated Hemoglobin; T2D: Type 2 Diabetes.

A literature review was conducted to identify studies reporting the relationship between BMI and glycemic control in adults with T2D. A robust and reproducible protocol was developed for the review that outlined the focus with respect to scope, patient population, appropriate study type, and outcomes of interest, and also provided details of the search strategy and data extraction methods. The protocol was developed to reduce the risk of introducing bias and for transparency.

Search strategy

Searches were undertaken for literature published in the English language from January 1, 2015, through January 8, 2020. The MEDLINE and EMBASE bibliographic databases were searched via OVID. A hand-search of the bibliographies of eligible publications was also undertaken to identify any relevant studies that, for whatever reason, were not found by the original search. EMBASE includes congress abstracts and all those indexed from 2019 until the search date were included to identify studies that may not have reached full publication. The main search strategy consisted of three concepts: T2D AND real-world evidence (RWE) and [(glycemic control OR BMI OR obesity levels/weight categories) AND countries]. These were captured using subject headings and text word searches in title, abstract, and keyword heading word fields. Search terms for the T2D concept included terms for non-specific diabetes and terms for explicit T2D. In the context of this search, 'RWE' was evidence based on real-world data derived from the following types of study: retrospective, cross-sectional, or prospective. Included were case–control studies, cohort studies, administrative or claims database studies, electronic medical record (EMR) studies, registry studies, questionnaires, and surveys relating to real-world clinical practice.

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Study eligibility criteria

Eligibility criteria were prespecified and are described in Table 1.

Study selection and data extraction

Titles and abstracts of the search results were assessed for relevance to the research questions by two independent reviewers. Studies considered as meeting or possibly meeting the eligibility criteria were selected for further review using the full-text record. Any disagreements between reviewers were resolved by discussion until consensus was reached. Data extraction was performed on a standardized data extraction form by one reviewer, with the second undertaking a quality review.

Compliance with ethics guidelines

This article is a review of previously published studies and does not include any new research on human or animal subjects performed by any of the authors.

Results

Overview of search results

A PRISMA diagram of the study selection process is presented in Figure 1. Database searches yielded 6696 de-duplicated records and after initial abstract and full-text review 17 articles remained for inclusion in the final dataset.

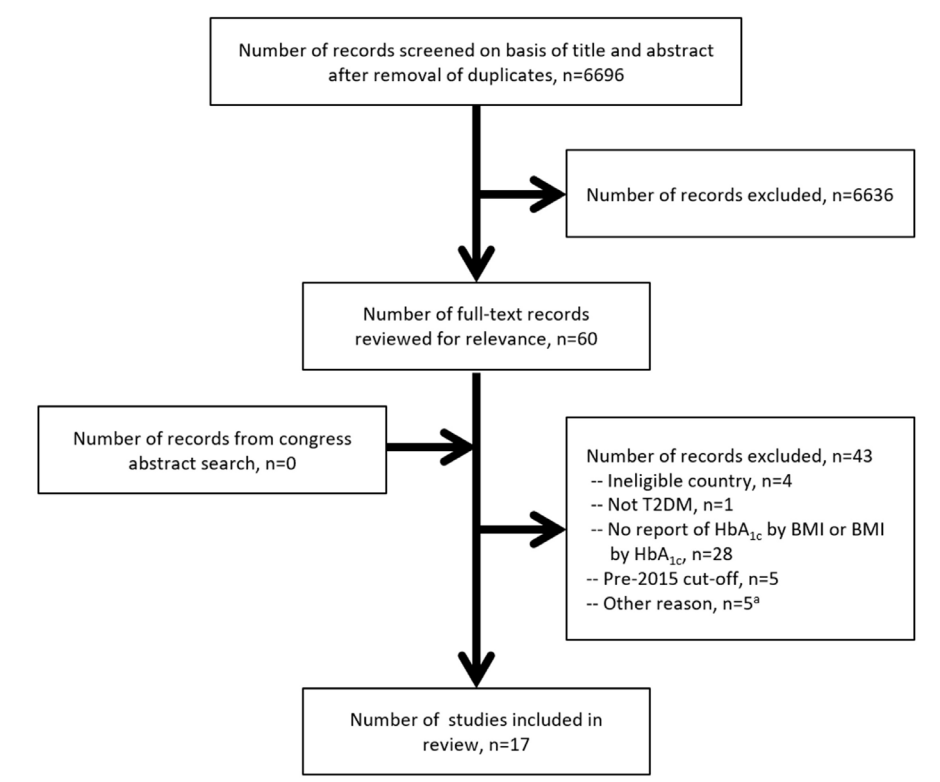

Figure 1: Study selection process.
[a]Other reasons (n=1 record each) included: evaluation of progression between glycemic stages across different levels of BMI; evaluation of weight loss only (no BMI or HbA_{1c}); population included individuals with T2D and acute coronary syndrome; individuals included all types of diabetes; studied association between onset of diabetic kidney disease, HbA_{1c} and BMI; evaluated glycemic level by percentage weight change rather than BMI
BMI: Body Mass Index; HbA_{1c}: Glycated Hemoglobin; T2D: Type 2 Diabetes

Study characteristics

There were 10 prospective studies and seven retrospective studies. Of the 10 prospective studies, six were cross-sectional and only gathered data at one time point [10-15]; four were longitudinal, but only baseline demographic data were used in our analysis [16-19]. Seven retrospective studies were identified [2,20-25]; in six of these, baseline data from the cohorts were used for our analysis; the other study [20] was different in that it looked at data over time, presenting the relative risk for having HbA_{1c} >7% presented by BMI category at 1-, 2-, 3-, and 5-year follow-up. Characteristics of included studies are summarized in Table 2.

A range of different sources were used to capture the data relevant to our analysis. These included medical records [2,12,20-25], study data [10,14-19], and data from the Diabetes Specific Programme [11]. Most studies were from were from Asia (China, n=9; Japan, n=3; Hong Kong, n=1), followed by the USA (n=2), Spain (n=1), and the UK (n=1). No studies were identified in the other included countries. Most of the studies reported no sponsorship (n=12); some reported pharmaceutical company sponsorship (n=5).

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The ways in which the data were reported varied (Table 2). The most common approach was to report glycemic control rates by BMI category (n=9 studies); some studies presented a regression analysis on higher BMI as a risk factor for worse glycemic control (n=8). There was some overlap, with 13 studies reporting either or both. Three of the studies that presented a regression analysis also reported categorical BMI distribution for HbA_{1c} categories (two studies for controlled vs uncontrolled; one study for HbA_{1c} ranges). Mean HbA_{1c} was reported by BMI category (n=6 studies). Three studies reported average BMI by glycemic control.

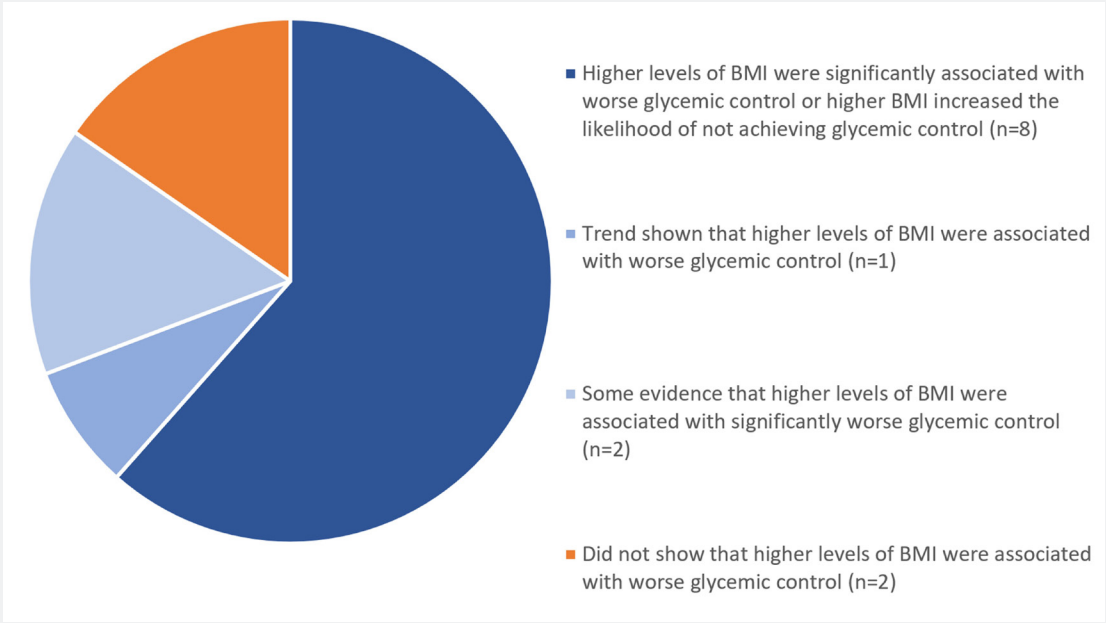

Figure 2: Studies reporting glycemic control rates by BMI, and BMI as a factor in regression analyses for poor glycemic control.

Table 2: Overview of study methods and data reporting (split by country).

Reference	Study Type (Sponsor)	Patient Population (Numbers)	Treatment Profile of Included Patients	Source of Data for Weight/ HbA_{1c} Analysis	Reporting by BMI Category		Reporting by Glycemic Control	Regression Analysis on Association Between BMI and Glycemic Control?	Notes
					Glycemic Control Rates (HbA_{1c} Used to Define Control)	Mean[a] HbA_{1c}	Mean[a] BMI		
CHINA									
Cai et al [16]	Observational prospective cohort study in 81 hospitals (Bristol-Myers Squibb)	Newly diagnosed individuals with T2D (<6 months) N=5770	Range of medications (including oral medications, herbal medicine and insulin)	Study records	✓ <7%			✓	

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Reference	Study Type (Sponsor)	Patient Population (Numbers)	Treatment Profile of Included Patients	Source of Data for Weight/ HbA_{1c} Analysis	Reporting by BMI Category		Reporting by Glycemic Control	Regression Analysis on Association Between BMI and Glycemic Control?	Notes
					Glycemic Control Rates (HbA_{1c} Used to Define Control)	Mean[a] HbA_{1c}	Mean[a] BMI		
Chen et al [10]	Observational prospective cross-sectional study in 26 medical centers	Adult outpatients with T2D N=9065	Range of medications (percentage of patients on oral medications and insulin reported, insulin use ranged from 35.05% to 52.43% of individuals, depending on BMI category)	Study records	✓ ≤7%	✓		✓	
Ji et al [11]	Observational prospective cross-sectional survey study (Diabetes Disease Specific Programme) (Lilly)	Individuals with T2D enrolled in Diabetes Disease Specific Programme N=2052	Range of medications (27.9% were insulin users)	Survey (Diabetes Disease Specific Programme – Patient Record Form)	✓ <7%	✓		✓	
Li et al [21]	Retrospective cross-sectional study using an existing database in one tertiary care center	Individuals with T2D receiving treatment at the diabetes center N=1387	Range of medications (between 37% and 51.2% were insulin users, dependent on level of glycemic control)	Electronic medical records				✓	Paper reports categorical BMI distribution for controlled and uncontrolled HbA_{1c} categories (for uncontrolled or controlled the paper reports the distribution across the BMI categories; e.g. for the population of individuals who are uncontrolled the paper reports what % of that population sits in each BMI category)
Liu et al [12]	Observational prospective cross-sectional study using face-to-face interviews in 50 medical centers	Individuals with T2D treated in medical centers N=5961	Range of medications (61.5% were insulin users)	Electronic medical records	✓ <7%			✓	

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Reference	Study Type (Sponsor)	Patient Population (Numbers)	Treatment Profile of Included Patients	Source of Data for Weight/ HbA_{1c} Analysis	Reporting by BMI Category		Reporting by Glycemic Control	Regression Analysis on Association Between BMI and Glycemic Control?	Notes
					Glycemic Control Rates (HbA_{1c} Used to Define Control)	Mean[a] HbA_{1c}	Mean[a] BMI		
Ma et al [22]	Retrospective cohort study in seven central hospitals (Jan–Dec 2010)	Individuals with T2D who have never been hospitalized for T2D N=17,259	Range of medications (6.6% were insulin users in the first year after diagnosis. Data for this report were baseline data)	Electronic medical records	✓ <7%	✓			
Wan et al [23] Note: study from Hong Kong	Retrospective cohort study in primary care patients from one territory	Individuals with T2D in primary care with no known CVD history N=115,782	Range of medications (1.32% were insulin users)	Electronic medical records			✓		
Wang et al [13]	Prospective cross-sectional questionnaire study undertaken in 27 centers	Individuals with T2D treated with insulin N=2787	Insulin-treated individuals	Study records				✓	Paper reports categorical BMI distribution within HbA_{1c} categories (in a defined HbA_{1c} group the paper reports distribution across BMI categories; e.g. for the population of individuals with an HbA_{1c} <7%, the paper reports what % of that population sits within each BMI category)
Zhang et al [25]	Retrospective study in a single hospital	Individuals with T2D N=3224	Range of medications (47% were insulin users)	Electronic medical records		✓			
Zhu et al [15]	Prospective cross-sectional study in a community-dwelling elderly population	Elderly (≥60 years) individuals with T2D N=918	Range of medication (82.2% to 88.5% were on anti-diabetic medications)	Study data (local diabetes management system)			✓		

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Reference	Study Type (Sponsor)	Patient Population (Numbers)	Treatment Profile of Included Patients	Source of Data for Weight/ HbA_{1c} Analysis	Reporting by BMI Category		Reporting by Glycemic Control	Regression Analysis on Association Between BMI and Glycemic Control?	Notes
					Glycemic Control Rates (HbA_{1c} Used to Define Control)	Mean[a] HbA_{1c}	Mean[a] BMI		
JAPAN									
Tobe et al [18]	Prospective postmarketing study (STELLA-LONG TERM) of ipragliflozin (Astellas)	Individuals with T2D being treated with ipragliflozin in real life N=11,053	Ipragliflozin treatment	Study records	✓ <8%				
Yamakawa et al [19]	Prospective multicenter diary study (Sleep and Food Registry)	Individuals with T2D participating in the Sleep and Food Registry in Kanagawa study N=3032	Range of medications (25.9% were insulin users)	Study records			✓		
Yokoyama et al [14]	Prospective cross-sectional nationwide survey	Individuals with T2D who attended primary care clinics N=9956	Range of medications (18.6% were insulin users)	Study records	✓ <7%				
SPAIN									
Salinero-Fort et al [17]	Longitudinal prospective outpatient study (MADIABETES)	T2D individuals N=3443	Not stated	Study records	✓ <7%	✓			
UK									
Aucott et al [20]	Retrospective longitudinal cohort study, linking Scottish Diabetes Care database records with hospital admission and mortality records	Individuals overweight/obese and newly diagnosed with T2D between 2002 and 2006 N=29,316 at baseline	Range of medications	Electronic medical records (Scottish diabetes database)				✓	
USA									
Bae et al [2]	Retrospective cohort study across 38 US states (Lilly)	Individuals diagnosed with T1D or T2D[b] N=248,567	Range of medications	Electronic medical records (Humedica® database)				✓	Paper reports categorical BMI distribution within HbA_{1c} categories (in a defined HbA_{1c} group the paper reports the distribution across the BMI categories; e.g. for the population of individuals with an HbA_{1c} <7%, the paper reports what % of that population sits within each BMI category)

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Reference	Study Type (Sponsor)	Patient Population (Numbers)	Treatment Profile of Included Patients	Source of Data for Weight/ HbA_{1c} Analysis	Reporting by BMI Category		Reporting by Glycemic Control	Regression Analysis on Association Between BMI and Glycemic Control?	Notes
					Glycemic Control Rates (HbA_{1c} Used to Define Control)	Mean[a] HbA_{1c}	Mean[a] BMI		
Weng et al [24]	Retrospective cross-sectional analysis of Quintiles database (covers 35 million individuals across America) (Novo Nordisk)	Individuals with T2D, excluding co-morbidities that were known to cause excessive weight changes N=414,266 (HbA_{1c} data available for)	Range of medications (~30% were insulin users)	Electronic medical records (Quintiles database)	✓ (See note) <8%	✓			Paper reports categorical HbA_{1c} distribution within BMI categories (in a defined BMI group the paper reports the distribution across the HbA_{1c} categories; e.g. for the population of individuals with a BMI <30 kg/m^2, the paper reports what % of that population sits within each HbA_{1c} category). No statistics undertaken in the paper
TOTAL (Number of studies)					9	6	3	8	

a Unless stated otherwise.

b We only present T2D data.

BMI: body mass index; CVD: cardiovascular disease; HbA1c: glycated hemoglobin; T1D: type 1 diabetes; T2D: type 2 diabetes.

The BMI and the glycemic control categories or ranges used in these studies are presented in Table 3. Importantly, the definition of overweight and obesity differs considerably between Eastern and Western countries. Within specific geographies, there were small inconsistencies with regards to BMI categories. Glycemic control was consistently defined as <7%, except in two studies [18,24] that used a cut-off of HbA_{1c} <8%.

Table 3: BMI and glycemic control categories, glycemic control ranges and supporting references.

Reference	BMI Range (kg/m^2)	Reference Source (BMI)	Glycemic Control Definition (Converted to HbA_{1c} if Needed)	HbA_{1c} Ranges	Reference Source (Glycemic Control)
CHINA					
Cai et al [16]	Normal: <24 Overweight: 24 to <28 Obese: ≥28	Reference source not explicitly stated	HbA_{1c} <7%	NA	Paper references both ADA (2017) [26] and Weng et al (2016) [27]
Chen et al [10]	Normal: 18–24 Overweight: 24–28 Obese: >28	BMI categories referenced to the Chinese BMI standard (Zhou et al, 2002) [28]	HbA_{1c} ≤7%	NA	References not given but <7% discussed with mention to 'ADA' and Chinese glycemia control level

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Reference	BMI Range (kg/m^2)	Reference Source (BMI)	Glycemic Control Definition (Converted to HbA_{1c} if Needed)	HbA_{1c} Ranges	Reference Source (Glycemic Control)
Ji et al [11]	Underweight: <18.5 Normal: 18.5 to <24.0 Overweight: 24.0 to <28.0 Obese ≥28.0	BMI categories endorsed by the National Health & Family Planning Commission of the People's Republic of China (2013) [29]	HbA_{1c} <7% Also provides data for HbA_{1c} ≥9%	NA	References not given
Li et al [21]	Underweight: <18.5 Normal: 18.5–23.9 Overweight: 24.0–27.9 Obese: ≥28	BMI categories referenced to the China Expert Panel of Medical Nutrition Therapy for Overweight/Obesity. Expert consensus on medical nutrition therapy for overweight/obesity in China (2016)	HbA_{1c} <7%	NA	Chinese Diabetes Society (2014) [30]
Liu et al [12]	Normal: 18.5–23.9 Overweight: 24.0–27.9 Obese: ≥28	BMI categories referenced to the Chinese Medical Association. Expert Consensus on Chinese adult obesity prevention (2011)	HbA_{1c} <7%	NA	ADA (2015) [31]
Ma et al [22]	Underweight: <18.5 Normal: 18.5–23.99 Overweight: 24.0–27.99 Obese: ≥28.0	BMI categories referenced to The Department of Disease Control Ministry of Health PRC. The guidelines for prevention and control of overweight and obesity in Chinese adults	<53 mmol/mol (equivalent to HbA_{1c} <7%)	NA	References not given
Wan et al [23]	NA	NA	NA	<6% 6–6.4% 6.5–6.9% 7–7.4% 7.5–7.9% 8–8.4% 8.5–8.9% 9–9.4% 9.5–9.9% ≥10%	Authors state: 'Most international guidelines provide a recommended optimal HbA_{1c} target as the goal for diabetic management. However, there is no clearly apparent consensus on the optimal HbA_{1c} target, which can vary from <6.5% to <8.0%. Recent guidelines including the American Diabetes Association and European Association for the Study of Diabetes are now advocating replacing rigid and uniform targets to one which is more nuanced and patient-centered, however more evidence is still needed to support the call for individualized HbA_{1c} targets'
Wang et al [13]	Underweight: <18.5 Normal: 18.5 to <24.0 Overweight: 24.0 to <28.0 Obese: ≥28.0	Reference source not explicitly stated	HbA_{1c} <7%		Diabetes Society of the Chinese Medical Association (2018) [32]

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Reference	BMI Range (kg/m^2)	Reference Source (BMI)	Glycemic Control Definition (Converted to HbA_{1c} if Needed)	HbA_{1c} Ranges	Reference Source (Glycemic Control)
Zhang et al [25]	BMI quintiles: <21.62 21.62–23.50 23.51–25.16 25.17–27.33 >27.33	NA	NA	NA	NA
Zhu et al [15]	NA	NA	HbA_{1c} ≤7%	NA	References two papers: Li et al (2018) [21] and Yang et al (2016) [33]
JAPAN					
Tobe et al [18]	<22.0 22.0 to <25.0 25.0 to <30.0 ≥30.0 *Note*: Label not attached to each category	Japanese Society for the Study of Obesity Diseases (2016) [34]	HbA_{1c} <8%	NA	Reference source not explicitly stated
Yamakawa et al [19]	NA	NA	NA	<6.5% 6.5–7.0% 7.0–7.5% 7.5–8.0% >8.0%	Reference source not explicitly stated
Yokoyama et al [14]	<25.0 25 to <30 ≥30.0	Reference source not explicitly stated	HbA_{1c} <7%	NA	Haneda et al (2018) [35]
SPAIN					
Salinero-Fort et al [17]	Reference categories based on distribution of the data by percentiles P5: <23.0 P5–25: 23.0–26.8 P25–75: 26.9–33.1 P75–95: 33.2–39.4 P>95: >39.4	NA	HbA_{1c} <7%	NA	ADA (2011) [36]
UK					
Aucott et al [20]	25–29.9 30–34.9 35–39.9 ≥40	Reference source not explicitly stated	HbA_{1c} ≤7%	NA	Authors state: 'Glycaemic control definitions vary. While <48 mmol/mol (or 6.5%) is an absolute target, we defined "control" as HbA_{1c} ≤53 mmol/mol (or 7%), a commonly used clinical classification'. They reference two papers: Chiu et al (2013) [37] and Berkowitz et al (2014) [38]
USA					

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Reference	BMI Range (kg/m^2)	Reference Source (BMI)	Glycemic Control Definition (Converted to HbA_{1c} if Needed)	HbA_{1c} Ranges	Reference Source (Glycemic Control)
Bae et al [2]	Normal: 18.5 to <25 Overweight: 25 to <30 Obesity I: 30 to <35 Obesity II: 35 to <40 Obesity III: ≥40	WHO (2015), BMI classification [39]	NA	<7% ≥7 to <8% ≥8 to <9% ≥9%	Authors note that glycemic control cut-offs were based on clinical guidelines that recommend a treatment target of HbA_{1c} <7% for many non-pregnant adults with diabetes and suggest that a target of <8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, or diabetic complications or comorbidities [31]. Furthermore, results from an observational study among the elderly suggest that a target HbA_{1c} of 8–8.9% may be appropriate [40] and that an HbA_{1c} value of >9% is associated with increased mortality risk among patients with type 2 diabetes [41]
Weng et al [24]	<30 30 to <35 35 to <40 ≥40 *Note*: Label not attached to each category	Reference source not explicitly stated	NA	≤6.5 >6.5% to <8% ≥8% ≥9% *Note*: The ≥8% includes the ≥9% category	Authors state that ≥8% is considered a lower limit of poor glycemic control, patient BMI distributions within the categories of HbA_{1c} ≥8% and ≥9% was more closely examined to determine whether a relationship between glycemic control and BMI could be ascertained. ≤6.5% is considered to represent good glycemic control

ADA: American Diabetes Association; BMI: body mass index; HbA1c: glycated hemoglobin; NA: not applicable; P: percentile; WHO: World Health Organization.

Patient characteristics

The included studies varied in terms of population numbers and individual characteristics. Population numbers ranged from 918 in a study of community-dwelling elderly people with T2D [15] to 414,266 in the Quintiles EMR database [24].

Some of the study populations were relatively specific and focused – for example, the study by Zhu et al. [15] was undertaken in elderly adults aged ≥60 years and the study by Cai et al. [16] was in newly diagnosed individuals. Other studies were much broader – for example, Bae et al. [2] had few exclusion criteria; data were sourced from EMRs from the Humedica database, which comes from a US network of provider organizations that treat ~30 million individuals in 38 states who may be uninsured or insured via commercial insurance, Medicare, or Medicaid.

In those studies that reported gender across the whole cohort, approximately 50% were male (range, 45.31–55.70%). There was little age differentiation between studies: where an overall figure was given, mean age ranged from 55.7 to 65.0 years. Mean BMI was reported in around half the studies. There were clear differences between geographic regions, with BMI levels in China and Japan lower than in Western countries. For example, in the largest US study (N=626,386) [24], the mean BMI was 33.2 kg/m^2, compared with the largest (N=115,782) study from Asia (Hong Kong) [23], where mean BMI was 25.57 kg/m^2.

The use of anti-diabetic medications varied across studies. Most of the studies (15 out of 17) included individuals on a wide range of therapies. The proportion of individuals on the different medications varied across studies, from 1.32% [23] to over 85% [15].

Study findings

Reported by BMI category

Glycemic control rates

Studies either reporting glycemic control rates by BMI category or where BMI was explored as a factor in regression analysis for poor glycemic control are summarized in Table 4 & Figure 2. Eight [2,10,12,14,17,18,20,22] of the 13 studies that focused on achieving glycemic control (generally defined as HbA_{1c} <7%) reported by BMI category demonstrated that the percentage of patients achieving glycemic control significantly declined as BMI increased, and/or that the likelihood of achieving glycemic control was lower. Just one study focused explicitly on association between BMI and glycemic control, noting that little research had previously explored this in a large, insured US patient population.

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In this study, multinomial logistic regressions examined the association while controlling for a range of confounders including patient demographics, general health, comorbid conditions, and anti-hyperglycemic medication use. The authors reported that for T2D patients, there were positive and statistically significant associations between being overweight or obese and having suboptimal glycemic control. For example, individuals in obesity class III were found to have a 37% increase in the probability of having an HbA_{1c} ≥7% and <8%, a 60% increase in the probability of having an HbA_{1c} ≥8% and <9%, and a 62% increase in the probability of having an HbA_{1c} ≥9% [2].

Table 4: Studies reporting glycemic control rates by BMI, and BMI as a factor in regression analyses for poor glycemic control.

Reference	N	Findings	
		Glycemic Control Rates Reported by BMI	Regression Analyses Exploring BMI as a Factor for Poor Glycemic Control
Studies showing that glycemic control worsens with increasing BMI (statistically significant)			
Aucott et al (UK) [20]	15,757 (at Year 1) to 12,401 (at Year 5)		Higher diagnosis BMI was one of the factors associated with poor glycemic control (HbA_{1c} >7%) Significantly higher risk of not being in control for each increasing BMI category, vs being overweight (25–29.9 kg/m^2) at 1-year follow-up. For example, the relative risk for not achieving glycemic control at Year 1 (HbA_{1c} >7%) was 1.17 (95% CI, 1.09–1.26) for someone with a BMI of 30–34.9 kg/m^2 vs 25–29.9 kg/m^2 (p<0.001) Significant associations were also shown at 2-, 3-, and 5-year follow-up
Bae et al (USA) [2]	248,567		There were positive and statistically significant associations between being overweight or obese and having suboptimal glycemic control (HbA_{1c} ≥7%) Significantly higher probability of having above-target glycemic control (HbA_{1c} ≥7% to <8%; ≥8% to <9%; ≥9%) for each BMI category (25 to < 30, 30 to <35, 35 to <40; ≥40 kg/m^2) vs the reference state of being normal weight or underweight (BMI <25 kg/m^2) For example, individuals in obesity class III (≥40 kg/m^2) were found to have a 37% increase in the probability of having an HbA_{1c} ≥7% and <8%, a 60% increase in the probability of having an HbA_{1c} ≥8% and <9%, and a 62% increase in the probability of having an HbA_{1c} ≥9% There was no statistical difference in the probability of having above-target glycemic control when comparing alternative classes of obesity
Chen et al (China) [10]	9065	Glycemic control rates differed among BMI groups, with 33.7% of individuals in the <24 kg/m^2 group, 33.8% in the 24–28 kg/m^2 group, and 30.2% in the >28 kg/m^2 group having an HbA_{1c} of ≤7% (p=0.005) This held even after partial correction analysis adjusting for age, degree of education, duration of diabetes, HbA_{1c}, and FPG (p=0.006)	Higher BMI reported to be an independent risk factor for poor glycemic control defined as HbA_{1c} >7% (p=0.026 in multivariate analysis)

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Reference	N	Findings	
		Glycemic Control Rates Reported by BMI	Regression Analyses Exploring BMI as a Factor for Poor Glycemic Control
Liu et al (China) [12]	5961	Individuals with lower levels of BMI had significantly ($p<0.01$) higher rates of achieving glycemic control (HbA_{1c} <7%) The percentage of patients achieving control (HbA_{1c} <7%) who were classified as normal, overweight, or obese was 36.4%, 31.3%, and 26.7%, respectively	BMI reported to be one of the factors associated with attainment of HbA_{1c} (and blood pressure and cholesterol goals) (OR 0.584; $p=0.001$)
Ma et al (China) [22]	17,259	The proportion of individuals achieving glycemic control (HbA_{1c} <7%) was significantly ($p<0.001$) lower in individuals with obesity or overweight vs individuals of normal weight The percentage of patients achieving control (HbA_{1c} <7%) who were classified as normal, overweight, or obese was 58.6%, 50.7%, and 45.5%, respectively	
Salinero-Fort et al (Spain) [17]	3443	The percentage of individuals achieving glycemic control (HbA_{1c} <7%) reduced significantly ($p=0.001$) with higher levels of BMI The percentage of patients achieving control ranged from 58.1% in the 5th percentile to 45.5% in the 95th percentile	
Tobe et al (Japan) [18]	11,053	As BMI increased, the proportion of individuals achieving glycemic control (HbA_{1c} <8%) was significantly reduced ($p<0.001$) The percentage of patients achieving control (HbA_{1c} <8%) ranged from 58.9% in those with a BMI <22 kg/m^2 to 51.7% in those with a BMI ≥30 kg/m^2	
Yokoyama et al (Japan) [14]	9956	Higher BMI levels were associated with reduction of the rates of achieving therapeutic HbA_{1c} target of <7%. The authors concluded that increasing BMI levels correlated with decreasing rates of achieving all targets ($p<0.001$); HbA_{1c} was one of these targets (along with blood pressure and lipids) The percentage of individuals achieving control (<7%) was 57.1% those with a BMI <25 kg/m^2, 48.6% in those with a BMI 25 to <30 kg/m^2, and 44.7% in those with a BMI ≥30 kg/m^2	

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Reference	N	Findings	
		Glycemic Control Rates Reported by BMI	Regression Analyses Exploring BMI as a Factor for Poor Glycemic Control
Studies showing a trend of glycemic control worsening with increasing BMI			
Weng et al (USA) [24]	626,386	The prevalence of poor glycemic control increases as BMI increases The proportion of patients in the category of good glycemic control (HbA_{1c} ≤6.5%) decreased as BMI category increased. In those individuals with a BMI <30 kg/m^2, it was reported that 40.1% had an HbA_{1c} ≤6.5%; this compared with 30.1% of individuals with a BMI ≥40 kg/m^2 Conversely, the proportions of patients with poor glycemic control (HbA_{1c} ≥8%) increased with increasing BMI category. In those individuals with a BMI <30 kg/m^2, it was reported that 21% had an HbA_{1c} ≥8%; this compared with 30.2% of individuals with a BMI ≥40 kg/m^2 No statistical tests for differences were used to differentiate among patients in the four BMI categories	
Studies showing some evidence that some statistically significant evidence that glycemic control worsens with higher levels of BMI			
Cai et al (China) [16]	5770	At baseline, the percentage of individuals achieving glycemic control (HbA_{1c} <7%) with a BMI of <24, 24 to <28, and ≥28 kg/m^2 was 35.7%, 39.1%, and 33.7%, respectively At 1 year, the percentage of individuals achieving glycemic control with a BMI of <24, 24 to <28, and ≥28 kg/m^2 was 70.3%, 69.2%, and 62.0%, respectively	Patients with obesity were found in the multivariate model to have a significantly higher probability (RR 1.05; p=0.0044) of failing to achieve glycemic control (HbA_{1c} <7%) than individuals of normal weight (in overweight individuals, the RR was not significant) at 1-year follow-up The global p-value (for overweight/obesity vs normal) was significant (p=0.02)
Ji et al (China) [11]	2052	With regards to an HbA_{1c} target of <7.0%, it was found (using unadjusted analyses) that significantly more individuals in the overweight group than in the obese group achieved an HbA_{1c} target of <7.0% (39.8% vs 27.3%; p=0.001). Also, significantly fewer individuals in the normal BMI group than in the overweight group achieved an HbA_{1c} target of <7.0% (33.3% vs 39.8%; p=0.006) When looking at the population with an HbA_{1c} ≥9.0%, it was reported that significantly fewer individuals in the normal BMI group than the obese group had an HbA_{1c} ≥9.0% (4.3% vs 10.2%; p=0.002). In addition, significantly more individuals in the obese group had an HbA_{1c} ≥9.0% vs the overweight group (10.2% vs 5.5%; p=0.024)	Using adjusted methods, the results were not fully confirmed
Studies that did not show that glycemic control worsens with increasing BMI (statistically significant)			
Li et al (China) [21]	1387		Simple logistic regression analysis found no between-BMI group differences in the achievement of HbA_{1c} <7.0% (p=0.817)
Wang et al (China) [13]	2787		The standard used in this paper for a statistically significant result appears to be p<0.0001, with a p-value of 0.0133 for BMI; this is interpreted here to mean that the relationship between BMI and glycemic control was not sufficiently clear to warrant further investigation using machine learning techniques

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The largest study included in this review (N=626,386) [24] did not undertake any statistical testing to differentiate among the four BMI categories, as the analysis was intended to be exploratory. In those individuals with a BMI <30 kg/m^2, it was reported that 40.1% had good glycemic control (HbA_{1c} ≤6.5%), compared with 30.1% of individuals with a BMI ≥40 kg/m^2. Conversely, the proportions of patients with poor glycemic control (HbA_{1c} ≥8%) increased with increasing BMI category. In those individuals with a BMI <30 kg/m^2, it was reported that 21% had an HbA_{1c} ≥8%, compared with 30.2% of individuals with a BMI ≥40 kg/m^2.

Two studies reported some evidence that higher levels of BMI were associated with significantly worse glycemic control: one study [16] found that individuals with obesity had a significantly higher probability of failing to achieve glycemic control than those of normal weight, but in those who were overweight the probability was not significant. The global p-value for the combined overweight/obesity group compared to normal was significant. The other study [11] found that the use of adjusted methods did not fully confirm the findings from the unadjusted analyses.

Li et al. [21] did not report any significant between-BMI group differences in the achievement of glycemic control (HbA_{1c} <7.0%), and the relationship between BMI and glycemic control was not significant in the study by Wang et al. [13].

Mean HbA_{1c}

Four of six studies that reported average levels of HbA_{1c} reported them to be greater in patients with higher BMI (Table 5). In one of these studies, it should be noted that no statistical analysis was undertaken [24], while in another, the mean HbA_{1c} in the lowest 5th BMI percentile was slightly higher than the mean HbA_{1c} for the 25th BMI percentile, but otherwise HbA_{1c} increased as BMI increased [17]. In this study when median HbA_{1c} values were used, the values increased with BMI percentiles consistently across all percentiles. In two studies [20,25], the mean HbA_{1c} significantly decreased as BMI increased.

Table 5: Studies reporting mean levels of HbA_{1c} by BMI status.

Reference	N	Normal	Over-weight	Obese	Notes
Aucott et at (UK) [20]	29,316	Not included in study	8.3%	8.2%[a]	Individuals who were overweight had slightly higher mean baseline HbA_{1c} (8.3%) than those who were obese, where it was 8.2% (p<0.001) *Note*: Individuals with normal weight were not included in the study and most studies have compared vs normal, which was not possible here
Ji et al (China) [11]	2052	7.3%	7.3%	7.6%	Mean HbA_{1c} was significantly different between normal BMI and obese group (7.3% vs 7.6%; p<0.001), as were the differences between the overweight and obese groups (7.3% vs 7.6%; p≤0.002)
Ma et al (China) [22]	17,259	6.7%	7.2%	7.7%	Mean HbA_{1c} was significantly (p<0.001) worse in individuals with obesity (7.7%) and overweight individuals (7.2%) vs normal-weight individuals (6.7%)
Salinero-Fort et al (Spain) [17]	3443	HbA_{1c} reported by percentiles – see notes			Mean (and median) HbA_{1c} levels significantly (p<0.001) increased with higher BMI versus the reference BMI category (BMI 23-26.8 kg/m^2) Mean HbA_{1c} ranged from 7.0% in BMI <23 kg/m^2 to 7.3% in BMI >39.4 kg/m^2 Median HbA_{1c} ranged from 6.8% to in BMI <23 kg/m^2 to 7.1% in BMI >39.4 kg/m^2
Weng et al (USA) [24]	626,386	BMI <30 kg/m^2 = 7.2% Note: This is a wider range than would be considered 'normal'		BMI 30 to <35 kg/m^2 = 7.4% BMI 35 to <40 kg/m^2 = 7.5% BMI ≥40 kg/m^2 = 7.5%	Mean HbA_{1c} ranged from 7.2% in individuals who did not have obesity to 7.5% in those in the two highest obesity categories No statistical tests for differences were used to differentiate among patients in the four BMI categories
Zhang et al (China) [25]	3224	Five different BMI categories. Mean HbA_{1c} declined with increasing BMI, ranging from 9.37% in those with a BMI of <21.62 to 8.69 in those with a BMI of >27.33 kg/m^2			Mean HbA_{1c} declined with increasing BMI (p<0.001) Paper also reports underweight categories: BMI <21.62 kg/m^2 = 9.37% BMI 21.62–23.50 kg/m^2 = 9.35%

[a] Included.

BMI: body mass index; HbA_{1c}: glycated hemoglobin.

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Reported by glycemic control category

Mean BMI

Three studies [15,19,23] reported average BMI levels by glycemic control. One [15] reported median BMI, with the HbA_{1c} categories defined as controlled (≤7%) and uncontrolled (>7%), and two reported mean BMI across a range of HbA_{1c} categories: 10 in Wan et al. [23], and five in Yamakawa et al. [19].

Both studies [19,23] found significant differences in mean BMI between the different HbA_{1c} categories, and BMI was observed to increase with HbA_{1c}. BMI values ranged from 24.95 kg/m^2 (HbA_{1c} <6%) to 25.60 kg/m^2 (HbA_{1c} ≥10%) [23], and from 24.6 kg/m^2 (HbA_{1c} <6.5%) to 26.7 kg/m^2 (HbA_{1c} >8%) [19].

Another study [15] reported that the difference in median BMI between the controlled (24.44 kg/m^2) and uncontrolled groups (24.10 kg/m^2) was not significant (p=0.498), and in both the univariate and multivariate regression analysis higher BMI was not identified as a risk factor for poor glycemic control (HbA_{1c} >7%).

Discussion

This review was undertaken to identify studies from real-world settings that quantified the association between BMI and glycemic control. The topic was explored in various ways, including reporting glycemic control (average values, percentage achieving control, distribution across categories) by BMI and average BMI by HbA_{1c}.

The datasets included in this review were often very large, and in most cases represented very broad populations. The evidence base was, however, dominated by studies from Asia (13/17), with only four studies from Europe or the USA. Most studies included in this review reported an association between BMI and glycemic control. Eight out of 13 studies found that the rates of achieving glycemic control in individuals with T2D were significantly lower with higher levels of BMI, or that the risk of not achieving glycemic control significantly increased with higher BMI. The largest study (N=626,386) [24] did not undertake any statistical testing to differentiate among the four BMI categories, as the analysis was intended to be exploratory. The authors did, however, report that the prevalence of poor glycemic control increased as BMI increased. With regards to statistical analysis, it is also pertinent to note that an observed statistically significant difference does not necessarily indicate a clinically significant difference.

In those studies that reported average HbA_{1c} levels by BMI, it was also found that these were generally greater in individuals with higher levels of BMI in most (4/6) studies. The two studies that reported BMI by HbA_{1c} level found that mean BMI was significantly higher as HbA_{1c} increased, although in the study that just grouped individuals into controlled or uncontrolled according to HbA_{1c} (<7% defined as controlled) there was no reported difference in median BMI.

The evidence base was relatively limited, in that few recent studies specifically focused on this topic. In the wider literature there are numerous studies that report HbA_{1c} and BMI data, but we found few that reported one of these by the other. It was the case that most of the included studies reported the relationship between BMI and glycemic control as part of a wider analysis, such as the study by Ma et al. [22] on the impact of BMI on mortality. One of the few studies to focus in detail on the association between BMI and glycemic control was by Bae et al. [2].

It is important to note, as pointed out by several researchers, that the exploratory nature of the analyses included in this review that use cross-sectional data do not allow for a direct explanation of causation and leave some questions unanswerable. Nevertheless, some studies attempted to explore what is driving the association between BMI and glycemic control. Weng et al. [24] suggested two possibilities: (1) individuals with T2D and higher BMI may be more difficult to treat than those with lower BMI, as weight loss has been correlated with improved glycemic control; or (2) patients with more poorly controlled T2D may, as a result, have higher BMIs. Cai et al. [16] proposed that individuals with obesity may be more likely to fail to achieve glycemic control because they lack the self-management skills or the resources necessary for adherence (similarly, active smokers were less likely than non-smokers to achieve glycemic control). So, patients with higher levels of BMI have a greater unwillingness or inability to make lifestyle decisions that will improve their HbA_{1c}. There may also be clinical inertia from the physician to initiate more aggressive therapy in those with higher BMIs. Yurgin et al. [42] reported that individuals with obesity had a lower likelihood insulin initiation than that of patients without obesity (hazard ratio 0.814, p=0.01). The treatment characteristics of patients were not always provided by studies. This is an important consideration as, for example, patients who are treated with insulin may have good glycemic control yet experience weight gain [43].

In contrast to most of the included studies, Zhang et al. [25] reported using descriptive statistics that patients with a higher BMI had lower HbA_{1c} measurements. The study findings are inconsistent with most of the included studies; this was also one of the smallest in the review (N=3224). They state that the results are likely not to be causal or reverse causal. They also note individuals can be lean because of the chronic accumulation of metabolic, inflammatory, and pathological conditions caused by lifestyle behaviors such as long-term exposure to smoking, drinking, and unhealthy diets.

Overall, the studies presented in this review suggest that there is an association between higher BMI and worse glycemic control. We cannot conclude from the design of these cross-sectional studies that glycemic control is improved through reducing BMI. However, weight loss is known to directly impact insulin sensitivity and to preserve β-cell function [6]; and there is evidence from several longitudinal studies that the glycemic control of patients

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with T2D improves with weight loss. For example, a study by McAdam-Marx et al. [44] reported that participants initiating a new glucose-lowering agent who lost ≥3% of their body weight from baseline to 6 months were more likely to attain their HbA_{1c} goal of <7% (odds ratio [OR] 3.02; 95% confidence interval [CI] 1.94–4.70) versus those who gained weight (p<0.001). Of those who lost ≥3% of their body weight, 64.2% reached HbA_{1c} targets compared with 33.1% who remained weight stable and 38.8% who gained weight (p<0.001). Another example comes from an analysis of the observational Look AHEAD study (N=5145) [45], which found that the magnitude of weight loss at 1 year was strongly (p<0.0001) associated with improvements in glycemic control. Those who lost 5% to <10% of their body weight had increased odds (compared with weight-stable participants) of achieving a 0.5% reduction in HbA_{1c} (OR 3.52; 95% CI 2.81–4.40). Results from a literature review and meta-analysis of clinical trials of lifestyle weight-loss interventions [46] seem to suggest that a weight loss of >5% appears necessary for beneficial effects (including to HbA_{1c}), although the authors did acknowledge that achieving this level of weight loss requires intensive work and might not be a realistic primary treatment strategy for improved glycemic control.

A recent literature review [6] on the impact of weight change in adults with T2D reported mixed findings, concluding that further real-world studies were needed to advance understanding of the incremental benefits of weight loss in individuals with T2D. A key observation was that in studies included in their review, the weight-loss period evaluated was concurrent with the change in glycemic control; so the same time period was used to evaluate both the predictor and outcome variables – whereas to demonstrate a causal effect between weight change and glycemic control, the weight change would have to precede the measurement of glycemic control. They outline various considerations that should be reflected in study design – such as exploring potential biases that may occur because of differences in participants' baseline characteristics, assessing the impact of varying weight-loss interventions, and determining how best to measure changes in these parameters and their relationships over time.

It should be recognized that there are benefits of reducing weight in patients who have overweight or obesity, beyond any impact on glycemic control. In those with T2D, weight loss has been shown to reduce cardiovascular risk factors and improve quality of life, mobility, and physical and sexual function [47].

Limitations of our review relate to the search itself and to the evidence base. Although the search was undertaken using a robust and reproducible protocol that retrieved >7000 original 'hits', it is possible that other studies relevant to the research questions were missed because it was unclear from the title or abstract that the reference held data of value. The search was restricted to English-language papers, but it is likely that other relevant studies could have been published in foreign-language journals. It also possible that further relevant studies could inevitably have been published since our searches were undertaken. The syntax used to limit studies to those undertaken in 'real-world' settings and in certain countries, and to identify studies on HbA_{1c} and weight, could have resulted in some relevant studies being missed. However, it should be noted that reference lists were reviewed for all included publications and no additional references were identified. As noted earlier, the geographic distribution of the included studies in this review was limited. The results from China are not generalizable to Western populations, and vice versa, with population characteristics and categories of overweight and obesity having different definitions. The prevalence of obesity in different populations also varies considerably: as shown in the review by Colosia et al. [48], prevalence rates were 6.7% in China and 64.2% in the United States. There were also differences across studies in the threshold to determine glycemic control and some used ranges rather than a cut-off in response to the call for individualized HbA_{1c} targets.

An advantage of many of the included studies was that the datasets were sourced from large EMR databases; but medical records cannot capture all the variables that impact glycemic control (e.g. self-monitoring of blood glucose, adherence to T2D therapy, physical activity), so these factors could not be included in the analyses. Furthermore, much of the data came from studies that addressed different research questions; many did not attempt to control for confounders (e.g. the use of different anti-diabetic medications) in exploring the specific relationship between BMI and HbA_{1c}. Furthermore, although the focus of this study was on the link between BMI and glycemic control, it is possible that other measures warrant closer attention; for example, Chen et al. [10] found waist circumference to be an independent risk factor for poor glycemic control.

Conclusion

This review is intended as a resource that consolidates and reports the recent evidence base on glycemic control in individuals with T2D reported by BMI in real-life settings in selected countries. Most of the identified studies demonstrated that rates of achieving glycemic control in individuals with T2D were lower with higher levels of BMI, or that the risk of not achieving glycemic control increased with higher BMI. Average HbA_{1c} levels were generally higher in individuals with greater BMI, and individuals with higher HbA_{1c} tended to have higher BMI.

Given that the evidence base is dominated by studies from China and Japan (13/17 studies), there is a real need for additional studies in Europe and the United States to represent local populations, especially given the increasing prevalence of obesity and T2D. Most of the included studies had wider objectives than our specific study question, highlighting the need for large, robust, focused studies to bridge this gap.

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Nevertheless, this review consolidates data from several studies and helps to identify patients at risk of poor glycemic outcomes; in doing so, it may enable targeted healthcare strategies to reduce the burden of T2D. Focused efforts are needed – particularly in individuals with T2D and obesity who, for a range of reasons, can be particularly challenging to manage. Weight management should be an integral part of the management and treatment of T2D, and the weight effects of pharmacotherapy should be considered when treatment decisions are being made.

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Conflict of Interest

Kristina S Boye is an employee and minor shareholder of Eli Lilly and Company. Tessa Kennedy-Martin and Matthew Kennedy-Martin are employees of KMHO, who received funding from Eli Lilly for time spent conducting this research.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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