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A Systematic Review of the Effects of Sleeve Gastrectomy and Gastric Bypass on Type 2 Diabetes Control in the Middle East

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Abstract **Original Research Article**

Objective*:** The study aimed to explore the outcome of sleeve gastrectomy and gastric bypass in middle east patients with type 2 diabetes through the assessment of the weight trajectory postoperatively and its effect on the glycaemic control assessed by HbA1c. Where applicable, investigate the impact of sleeve gastrectomy and gastric bypass on the reduction of polypharmacy and postoperative Insulin requirements in patients with type 2 diabetes. ***Research Design and Methods: PubMed and Science Direct databases were searched. The obtained studies were screened for the title and abstract, followed by full-text reading and retrieved relevant studies. The data was extracted from the relevant papers using a united form according to the inclusion criteria. The articles' quality was assessed and critically appraised, and a narrative synthesis was conducted. ***Results*:** Eight studies met the inclusion criteria comprised the final review, and all had positive results. Four articles studied sleeve gastrectomy outcomes, and four compared sleeve gastrectomy and gastric bypass. All studies showed weight reduction postoperatively calculated as BMI, Total Weight Loss, or Excess Weight Loss sustained up to 5 years. The studies which assessed glycaemic control showed improvement of glycaemic parameters, reduction of HBA1C, and some achieved remission among prediabetes and diabetes patients. The review also indicated the reduction and cessation of antidiabetic medications following surgical interventions, which is attributed to achieving diabetes remission. A long-term follow-up cohort with a large sample size revealed that HBA1C reduction was more enunciated and sustained following gastric bypass in patients with diabetes. ***Conclusion*:** Sleeve Gastrectomy and Gastric Bypass positively affect type 2 diabetes control among obese adult patients in the Middle East. Both surgical interventions lead to weight reduction and improvement of glycaemic parameters postoperatively up to 5 years of follow-up. The review revealed limited evidence pertaining to the region. The available data was gathered from 6 out of 18 Middle East countries; nonetheless, overall data resembles the global statistics and outcomes. In the Middle East, bariatric surgery is well established as a reliable treatment for obesity. There is persuasive evidence that may drive its incorporation as a treatment option for Type 2 Diabetes.

Keywords: Bariatric surgery; Type 2 Diabetes; Middle East.

INTRODUCTION

Diabetes is a significant health crisis, with a global prevalence of 8.3% among the adult population in 2019 [1]. The exponential rise in obesity significantly contributes to the worldwide prevalence of type 2 diabetes (T2DM) and non-communicable diseases. Globally in adults, the prevalence of overweight (Body Mass Index (BMI) ≥25 kg/m²) is estimated at 39%, and the prevalence of obesity (BMI ≥30 kg/m²) is 13 % [2].

Obesity is a complex, multifactorial, chronic disease and a modifiable risk factor for developing type 2 diabetes. Weight management is proven to improve diabetes control [3] and prevent disease progression among high-risk patients [4].

Bariatric surgery interventions can be an effective tool for facilitating substantial weight loss, in association with support for behaviour change from a multi-disciplinary team before and after surgery. Improvement and remission of diabetes have been reported in more than 80% of patients post-bariatric operations [5]. 634,897 primary bariatric procedures were performed worldwide in 2016 [6].

In the past years, there has been more shift toward metabolic surgery (surgical procedures to

improve metabolic disease, especially diabetes). There is evidence that metabolic surgery is superior to intensive medical therapy for weight management and glycaemic control in patients with T2DM [7-9].

Malabsorptive bariatric surgery, also known as gastric bypass surgery, achieved better diabetes control and sustained resolution of metabolic syndrome compared to Gastric restrictive surgery; however, it carries the risk of more complications [10]. In particular, Roux en Y Gastric Bypass (Roux-en-Y) resulted in substantial weight loss and resolution of T2DM in up to 83% of patients [11].

The Middle East and North Africa (MENA) region has the highest prevalence of diabetes among adults, at 12.8% [1]. In the Eastern Mediterranean region, the prevalence of overweight adults is 49%, and the prevalence of obesity is 20.8% [12]. A recent systematic review among adults in the Middle East found the prevalence of obesity at 21.17% and overweight prevalence at 33.14% [13]. The statistics make the Arab world region very distinct, and high numbers of weight management surgeries were performed. In this review, we considered the most common weight reduction surgeries in the MENA region 2015-2018, which are Sleeve Gastrectomy (SG), which accounts for 88%, and Roux en Y Gastric Bypass accounts for 4%. Followed by one Anastomosis/Mini-Gastric Bypass (OAGB/MGB), Gastric banding, and Duodenal switch with sleeve, all account for 8% [14].

Few studies evaluated the metabolic outcomes of bariatric surgery in the Middle East. Nonetheless, the contrast between the results of the two primary operations and their effect on pharmacological therapy has not been well investigated. This narrative review objectively assesses and compares regional outcomes with global findings.

RESEARCH DESIGN AND METHODS

Study design:

A systematic review of the available literature was carried out and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

PICo:

Population: Adult (more than 18 years) patients with diabetes in the Middle East
Interest: The effect on diabetes control
Context: Bariatrics surgery interventions

Inclusion criteria:

Randomised and observational studies published in English and conducted in the Middle East region between the years 2000 to 2022 are included. The study population is adult patients with T2DM who underwent SG or Gastric Bypass (GB) in the Middle East. Included studies have assessed the effect of SG and GB on type 2 diabetes, focusing on weight measurement, Glycosylated Haemoglobin (HBA1C) and medication changes on post-operative follow-up.

Excluded from the review were case series, reports, letters, and editorials. In addition, studies performed on children/adolescents and those with very short post-operative follow-ups were excluded.

Review question(s):

A preliminary search of PROSPERO was conducted, and no registered or ongoing systematic review on the topic was identified.

What are sleeve gastrectomy and gastric bypass effects on diabetes control among patients with type 2 diabetes in the Middle East?

Search strategy:

The search strategy aimed to locate the published studies. An initial search of PubMed, ResearchGate and Google Scholar was undertaken to identify articles on the topic. The reviewers used the text words in the titles and abstracts of relevant papers and the index terms used to describe the articles to develop a complete search strategy for PubMed and ScienceDirect databases. The search strategy is as follows:

Diabet* AND Middle east OR Arab world (MeSH) AND control OR metabolic outcome AND Bariatrics OR Gastric sleeve OR Sleeve Gastrectomy OR Roux en Y Gastric Bypass.

The included studies were published in English only since the year 2000. The timeline was meant to reflect the most recent evidence, and the data scoping process showed the evidence was scarce for the period before 2000.

Study selection:

Following the search, the identified citations were collated and uploaded into Zotero software. Then, the authors screened titles and abstracts for assessment against the inclusion criteria. The relevant studies were retrieved and imported into Joanna Brigg's Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) [16]. The authors then assessed the full text of the selected citations. Reasons for the exclusion of papers in full text that did not meet the inclusion criteria were reported in the systematic review. The search results and the study inclusion process are documented and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Figure 1).

Assessment of methodological quality:

The authors critically appraised eligible studies for methodological quality using the standard Joanna Briggs Institute (JBI) Critical Appraisal Checklist.

Five studies were methodologically appraised using the JBI checklist for analytical cross-sectional studies (Table 2 Appendix), and three cohort studies were appraised according to the JBI cohort appraisal tool (Table 3 Appendix).

All cross-sectional studies demonstrated clear inclusion criteria, a clear description of the study population and settings, and a reliable way of measuring the studied condition and the outcome. However, it did not address the matters around confounding factors, for example, the impact of age, gender and pre-operative BMI on the postoperative outcomes.

The strengths of the cohort studies were that they demonstrated similar characteristics of all participants with clear inclusion criteria. In addition, the interventions and the outcomes were measured reliably within an adequate follow-up time using appropriate statistical analysis methods. For the points mentioned above, the overall quality of the studies was deemed sufficient. However, the weakness of the pooled cohorts is not evidently addressing the confounding factors, and the follow-up was not complete and without the mention of straightforward strategies to address the issue.

Data Extraction:

The reviewers extracted and compiled the data in a data extraction form (Table 1). The data extracted included specific details about the country where the study was conducted, the study objective, populations, inclusion criteria, surgical operation intervention and the outcome of weight and or glycemic control parameters and medication use. The findings were extracted verbatim. Any missing or unclear information was accounted as Not Applicable to minimise errors during data extraction.

Table 1: Summarized Data extraction form

Author(s)	Objective(s)	Study design	Setting of intervention	Study population	Measures	Main findings
Al Kadi *et al*., 2017 [17]	To compare the efficacy of various standard bariatric surgical procedures	prospective cohort study	159 patients (58.9%) had Laparoscopic Sleeve Gastrectomy (LSG) ,, 97 patients (29.3%) underwent Laparoscopic Roux-en-Y GB	270 morbidly obese adult Saudi patients body mass index (BMI) of >40, physically and mentally fit	post-operative weight, BMI, major comorbidities cure, or improvement postoperatively, including type II diabetes	The average EWL was 75.8% in LSG and 67.9% and in Laparoscopic Roux-en-Y GB
Barzin *et al*., 2017 [24]	evaluating and comparing several surgical bariatric procedures	prospective cohort study	319 patients underwent SG, 106 patients underwent GB	425 morbidly obese adult patients, Body mass index (BMI) ≥ 40 kg/m2 or a BMI between 35 and 40 kg/m2 plus a medical comorbidity	Trend of BMI, MetS parameters and glycated hemoglobin (HbA1C)	Average EWL% at 12 months postoperatively was 75 ± 20.1% for the SG and 75.2 ± 23.4%for the GB. At 12 months MetS prevalence decreased from 60% to 16% in the SG group, and from 64% to 10% in the GB group
Nimeri *et al*., 2013 [21]	To report and compare the local bariatric surgery with outcomes of The American College of Surgeons National Surgical Quality Improvement Programme (ACS NSQIP)	Cross sectional study	275 bariatric operations, of which 69.8% (192) Roux-en-Y GB and 24.8% (68) SG	Young adults mean age 36 years, mean BMI 47.4	Short-term outcomes of bariatric surgery	Weight-loss at 12 months shows 77% EWL for RYGB and 76% for LSG.
Dicker *et al*., 2016 [19]	To compare weight loss, glucose control, and diabetes remission in individuals with type 2 diabetes, after three types of	cohort study	Operations performed 1027. (47%) Gastric Banding, 1023 (47%) SG, and 140 (6%)	2190 Patients with diabetes who underwent bariatric surgery	Changes in BMI and HbA1c. The achievement of diabetes remission (defined as	At 1 year of follow-up, mean BMI decreased by 10.1, 9.2 units, for RYGB, SG respectively. At 5 years, decreases in BMI were similar among the procedures at 8.8 and

Author(s)	Objective(s)	Study design	Setting of intervention	Study population	Measures	Main findings
	bariatric surgery		RYGB		HbA1c <6 %, without the use of a diabetes medication except metformin)	8.3. Mean HbA1c decreased by 2.0 % in the first year following RYGB, significantly more than following SG. At 5 years was 1.4 % lower than the baseline mean. At 1 year 53.2 % had achieved remission; at 5 years, 54.4 %
Al Khalifa *et al*., 2018 [22]	To examine the short and midterm outcomes of patients who underwent SG	Cross sectional study	59 patients with IGT or T2DM who underwent LSG between 2011 - 2014	Patients with impaired glucose tolerance and T2DM who underwent SG	Pre and post-surgery weight, BMI, HbA1c, and fasting blood glucose were compared	Mean Total Weight Loss (TWL) was 30.8%, and mean EWL was 65.52%. Mean HBA1C reduced by 1.9% postoperatively. 18 patients (75%) with Diabetes showed normalization of both HbA1c and FBG levels. 97.14 % of the 34 patients with prediabetes had complete resolution.
Zaki *et al.*, 2021 [18]	To evaluate the effect of LSG on glycemic control through assessment of reduction in HbA1C associated with weight loss following LSG	Cross sectional study	LSG between January 2017 and December 2019	102 patients with Body mass index (BMI) of ≥30 kg/m2 and age ≥18 years patients, with HbA1c ≥ 5.7% who underwent LSG between January 2017 and December 2019	Pre and postoperative BMI and HbA1c	Mean difference of BMI reduction 14.2%. Mean HBA1C reduction 1.67 %.
Sakran *et al.*, 2016 [20]	To report the outcome of LSG operations	Cross sectional study	LSG between May 2006 and December 2014	3003 patients with body mass index (BMI) > 40 kg/m2 or BMI < 35 kg/m2 with significant weight-related comorbidities, who underwent LSG	Pre and postoperative weight and glycemic parameters	Mean EWL was 72% (n = 937) at 1 year. Resolution for diabetes 51.4% (n = 697).
Dakour Aridi *et al.*, 2015 [23]	To assess the efficacy and safety of laparoscopic sleeve gastrectomy (LSG)	Cross sectional study	LSG between April 2007 and March 2015	76 patients who underwent LSG at a tertiary referral hospital between April 2007 and March 2015	BMI, presence of medical co-morbidities, and postoperative complications	EWL was 69.8% at 5 years. TWL was 26.5% at 5 years. At 5 years, 3 out of 8 patients (37.5%) had complete remission of Diabetes. 1 patient (out of 8) (12.5%) stopped their diabetes medication and 3 patients (37.5%) decreased their antidiabetic medications.

RESULTS

The primary data search yielded 167 studies. 11 studies were duplicates and 5 non-English language publications. 140 studies were excluded from the Abstract and title screening. The majority of exclusions were unrelated topics or performed outside the Middle East. Few studies assessed adolescent obesity and type 1 diabetes or addressed a different type of bariatric procedure. Three more studies were excluded after the full-text reading. One study displayed a short follow-up period, and 2 studies were performed in a non-western society outside the Middle East region. Consequently, 8 studies were covered in this review after fulfilling the inclusion criteria [17-24].

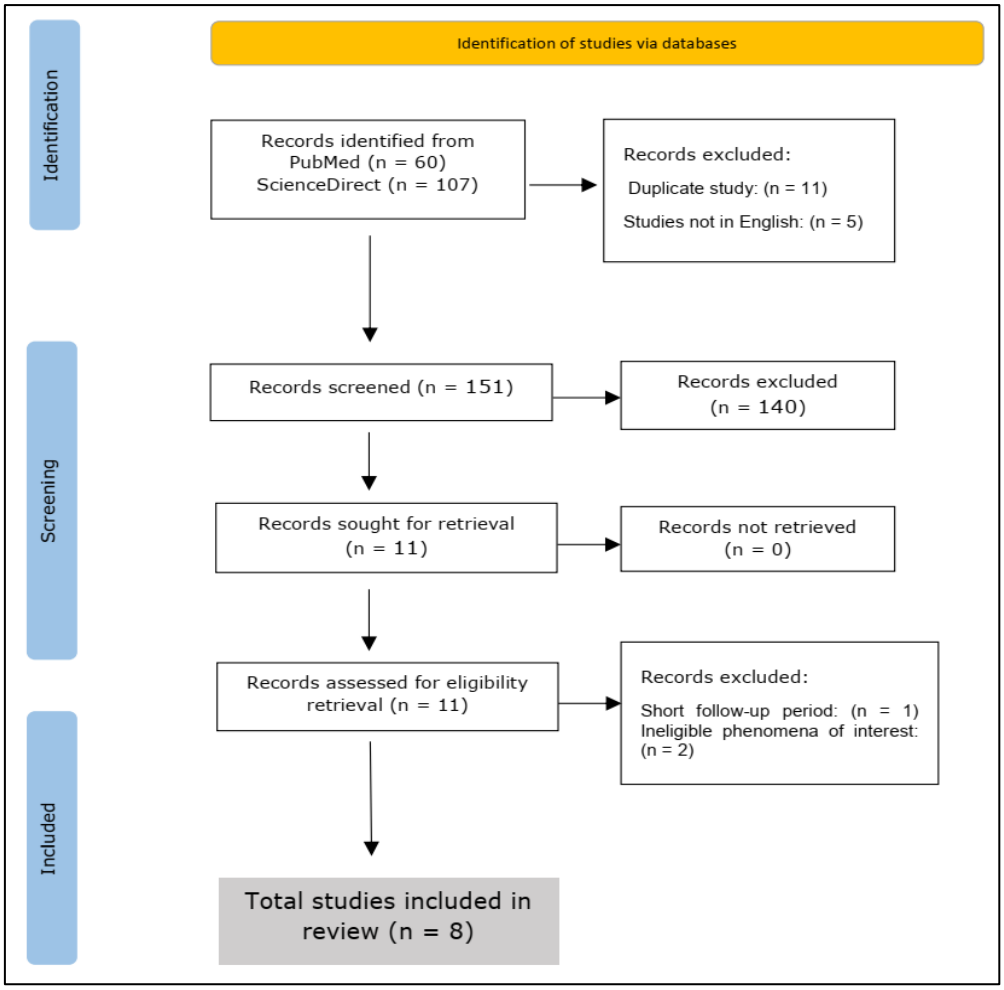

Figure 1: Study screening and data extraction process

All the Middle East studies retrieved in this review were published from 2013 onward. Two studies were performed in Saudi Arabia [17, 18] and two in Israel [19, 20]. One study each conducted in the United Arab Emirates [21], Bahrain [22], Lebanon [23] and Iran [24]. Five studies were described as analytical cross-sectional reviews [18, 20-23] and three studies were cohort reviews [17, 19, 24].

Zaki *et al*., [18], Sakran *et al*., [20], and Dakour Aridi *et al*., [23] assessed the outcomes of Laparoscopic Sleeve Gastrectomy (LSG). The studies pooled data comprised 3181 adult patients with obesity (BMI of ≥30 kg/m2) who underwent LSG. All studies demonstrated weight reduction. Zaki *et al*., revealed a baseline mean BMI reduced from 47.3 ± 7.73 to 33.1 ± 6.72 kg/m2 postoperatively with a mean difference of 14.2. Sakran *et al*., and Dakour Aridi *et al*., revealed a comparable marked Excess Weight Loss (EWL) of 72 % and 69.8%, respectively. The EWL achieved by Dakour Aridi *et al*., was maintained for up to 5 years.

In terms of glycemic control, all studies demonstrated improvement. Zaki *et al*., showed a baseline mean HbA1c reduction from 7.45 ±1.66 to 5.78 ± 0.92 postoperatively. Mean difference 1.67(%). The reduction in HbA1c following the procedure was 27.4% for patients with diabetes. The mean follow-up period for the study was ten months. The resolution of diabetes post-LSG was demonstrated by two studies [20, 23]. Sakran *et al*., showed a 51.4 % (n = 697) resolution rate, defined as maintaining normal glucose values without medications. The study had a large population of 3003 patients; however, the 1-year follow-up rate was only 57 %. At five years post-LSG, Dakour Aridi *et al*., demonstrated that out of eight patients with diabetes, three patients (37.5%) had complete remission, one patient (12.5%) managed to stop their diabetes medication, and three patients (37.5%) decreased their antidiabetic medications. In the study, diabetes remission was defined as HbA1C < 6% or fasting blood glucose (FBG) < 100 mg/dL without the use of anti-diabetic medications.

Al Khalifa *et al*., [22] conducted in the Kingdom of Bahrain studied the metabolic effects of LSG on patients with diabetes and prediabetes. The mean Total Weight Loss (TWL) was 30.8 %, and the mean EWL was 65.52 % postoperative. There was reciprocated reduction of mean HBA1C from 6.27 ± 2.25 at baseline to 4.37 ± 2.39 postoperatively; 18 patients (75%) with known diabetes showed

normalization of both HbA1c and Fasting Blood Glucose (FBG) levels. Also, 97.14 % of the 34 patients with prediabetes had complete remission, which was also defined as HbA1c less than or equal to 6.0 % and FBG <100 mg/dL without using antidiabetic medications.

Al Kadi *et al*., [17], Nimeri *et al*., [21] and Barzin *et al*., [24] are three methodologically equivalent studies that compared the effects of SG and GB on weight and glycemic control. Population characteristics were similar in all studies: morbidly obese adult patients with BMI ≥ 40 kg/m2 or a BMI between 35 and 40 kg/m2 in addition to the presence of medical comorbidity. The cumulative numbers of bariatric procedures were 546 SG and 395 GB operations. At 12 months follow-up, all three studies showed an almost identical average EWL post SG 75.8%, 75 ± 20.1% and 76%. For the GB, the reported EWL was 67.9%, 75.2 ± 23.4% and 77%. Barzin *et al*., addressed the effects of the surgical procedures on Metabolic Syndrome (MetS) parameters, showing that at 12 months, MetS prevalence decreased from 60% to 16% post SG and from 64% to 10% following Bypass Surgery.

Dicker *et al*., [19] is a long-term follow-up observational study that evaluated the bariatric surgery interventions on a large sample size of morbidly obese patients with diabetes. During the first year of follow-up, mean BMI decreased by 10.1 and 9.2 units for GB and SG, respectively. At five years of follow-up, the mean decreases in BMI from baseline plateaued among the procedures at 8.8 and 8.3 for GB and SG. In terms of glycemic control, HBA1C decreased by 2.0 % in the first year following GB compared to a modest reduction following SG. At five years, HBA1C was 1.4% lower than the baseline mean for the post-Gastric Bypass group. For all the studied patients with diabetes, remission rates of 53.2% and 54.4% were observed at 1-year and five years follow-ups, respectively. There was no difference in the remission rate between GB and SG groups at five years. The characteristics profile of the patients who underwent GB could explain this. They were older adults with higher baseline HbA1c and high baseline insulin use. All these factors were found to predict lower diabetes remission rates.

DISCUSSION

Sleeve gastrectomy and gastric bypass are the most common bariatric procedures performed worldwide. These procedures are proven to positively impact type 2 diabetes control through substantial weight loss, leading to better glycaemic control [10]. A large meta-analysis assessed the long-term effects of bariatric surgery on T2DM with a similar outcome [25]. This review considered studies that explored the assessment of glycaemic parameters in obese patients with diabetes who underwent SG or GB surgeries. This review focused on the Middle East region, given the high prevalence of obesity and the exponential rise in bariatric operation numbers in recent years. Despite the collected evidence from only six countries, it reveals that SG is the region's most commonly performed bariatric procedure.

The results demonstrate the post-operative weight loss measured as EWL ranging between 65.5% to 76% for SG and 67.9% to 77% for GB. Studies that assessed mean BMI reduction revealed a range of 9.2 to 14.2 for SG and 10.1 Mean BMI reduction in one study that assessed GB. This review concluded a comparable weight loss post both surgical procedures, and similar results were echoed globally. A randomised clinical trial showed excess BMI loss in morbidly obese patients to be 61.1% post laparoscopic sleeve gastrectomy and 68.3% post laparoscopic Roux-en-Y gastric bypass. It also proved the excess BMI loss difference for the two operations was not statistically significant [26]. SLEEVEPASS is another randomised control study that showed a more significantly different mean EWL of 57% for laparoscopic Roux-en-Y gastric bypass, compared to 49% EWL after Laparoscopic sleeve gastrectomy still, similarly, the difference was not statistically significant [27]. These results demonstrate that the global outcomes concerning weight loss are similar to the Middle East.

Regarding the improvement of glycaemic parameters, an HBA1C mean difference of 1.67(%) post-LSG was achieved in one study [18]. Al Khalifa *et al*., [22] showed a reduction of mean HBA1C of 1.9(%), leading to 75% of known diabetes patients normalising both HbA1c and FBG levels. In addition, 97.14 % of the 34 patients with prediabetes had complete remission sustained one year postoperatively.

51.4% of T2DM resolution was observed one-year post-LSG [20]. At five years of follow-up, 37.5% of patients had complete remission of T2DM [23]. As achieved by Dicker *et al*., HBA1C decreased by 2.0 % in the first year following GB compared to a lower reduction following SG. At five years, HBA1C was 1.4% lower than the baseline mean for the post-GB group. In addition, 53.2% and 54.4% remission rates were observed at 1-year and five years follow-ups, respectively. The studies defined Diabetes remission/resolution as normalisation and maintenance of glycemic indices (HBA1C, FBG) without the use of antidiabetic medications [20, 22, 23] or maintenance of normal glycaemic values with no diabetes medications or metformin only [19].

Dakour Aridi *et al*., detailed the post-operative pharmacological changes. Five years post-LSG, one patient (12.5%) managed to stop their diabetes medication, and three (37.5%) decreased their antidiabetic medicines. As detailed above, few studies achieved diabetes remission, defined as normal glycemia with no medication use, which suggests that bariatric operations reduce the need for medications.

Antidiabetic medications require adjustment, reduction and even discontinuation post-surgery, and the type of operation guides the changes [28-30]. More research is needed to explore the effects of different surgeries on medication requirements.

Glycaemic control post-bariatric surgery (Restrictive or Malabsorptive) is not merely related to weight loss, and complex structural, hormonal and behavioural changes lead to glycaemic improvement and early diabetes resolution [31-33]. The recent evidence also favours the structural changes, especially post GB operations, to be the most beneficial for T2DM remission and control [34, 35]. It remains debatable which bariatric procedure is more advantageous for T2DM management. Historically more GB operations are performed worldwide, and it is believed that GB is the paradigm for achieving glucose control and diabetes remission [10, 36]. A large population-based data analysis in the UK found the chance of T2DM remission post bariatric surgery increased 18 folds compared to medical management alone. It also found a higher remission rate post GB than SG [10]. Nevertheless, it is notable that over recent years, more SG operations have been performed worldwide as it is regarded as a less complex and safer procedure with comparable beneficial cardiometabolic effects [37]. A recent notion on an evidence-based selection of bariatric operations in patients with diabetes is that it should be selected depending on diabetes severity [38].

In summary, this review demonstrated clear evidence that SG and GB can achieve sustained weight loss, glycaemic control and remission of T2DM.

CONCLUSIONS

Bariatric surgical interventions are gaining rapid popularity in Middle East countries. This review demonstrated that Sleeve Gastrectomy and Gastric Bypass surgeries substantially influence weight reduction, leading to better glycemic control and a decrease in HBA1C. More studies are needed to evaluate the long-term glycemic effect further and to explore the area of polypharmacy and medication requirements post interventions. The review revealed relatively limited evidence pertaining to the Middle East region and only data available from a few countries; nonetheless, overall data resembles the global statistics and outcomes. This review concludes that Laparoscopic Sleeve Gastrectomy is the most common weight reduction procedure in the Middle East. In the Middle East, bariatric surgery is well established as a reliable treatment for obesity. There is persuasive evidence that may drive its incorporation as a treatment option for Type 2 Diabetes.

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Appendices:
Critical Appraisal Results

Table 2: Analytical Cross-Sectional Study

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Al Khalifa *et al*., 2018	Y	Y	Y	Y	N	N	Y	U
Dakour Aridi *et al*., 2015	Y	Y	Y	Y	N	N	Y	U
Nimeri *et al*., 2013	Y	Y	U	Y	N	N	Y	Y
Sakran *et al*., 2016	Y	Y	Y	Y	N	N	Y	Y
Zaki *et al*., 2021	Y	Y	U	Y	U	N	Y	U
%	100.0	100.0	60.0	100.0	0.0	0.0	100.0	40.0

Q1 Were the criteria for inclusion in the sample clearly defined?
Q2 Were the study subjects and the setting described in detail?
Q3 Was the exposure measured in a valid and reliable way?
Q4 Were objective, standard criteria used for measurement of the condition?
Q5 Were confounding factors identified?
Q6 Were strategies to deal with confounding factors stated?
Q7 Were the outcomes measured in a valid and reliable way?
Q8 Was appropriate statistical analysis used?

- Y: Yes N: No U: Unclear N/A: Not applicable

Table 3: Cohort Study

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Al Kadi *et al*., 2017	Y	Y	Y	N	N	N/A	Y	Y	N	N	Y
Barzin *et al*., 2017	Y	Y	Y	U	N	Y	Y	Y	N	U	Y
Dicker *et al*., 2016	Y	Y	Y	U	N	Y	Y	Y	U	U	Y
%	100.0	100.0	100.0	0.0	0.0	66.66	100.0	100.0	0.0	0.0	100.0

Q1 Were the two groups similar and recruited from the same population?
Q2 Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3 Was the exposure measured in a valid and reliable way?
Q4 Were confounding factors identified?
Q5 Were strategies to deal with confounding factors stated?
Q6 Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7 Were the outcomes measured in a valid and reliable way?
Q8 Was the follow up time reported and sufficient to be long enough for outcomes to occur?
Q9 Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
Q10 Were strategies to address incomplete follow up utilized?
Q11 Was appropriate statistical analysis used?

- Y: Yes N: No U: Unclear N/A: Not applicable