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Research Article

The Effect of GLP-1 on the Incidence of Cardiovascular Events Compared to Bariatric Surgery: Systematic Review

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Abstract

Introduction: Worldwide obesity has become one of the most common public health concerns. In addition to being an increased mortality risk factor, it also contributes to type 2 diabetes, hypertension, heart disease, and some types of cancer. On aiming to reduce body mass index multiple measures are scientifically investigated such as lifestyle modification, pharmacological and surgical therapy. This review took a critical look on evaluating the scientific evidence of GLP-1 Vs bariatric surgery and the outcome of cardiovascular events.

Methods: PubMed, Google Scholar and Research Gate were searched for recent studies published in the period between 2010 and 2021.

Results: A total of 16 studies with 283983 patients were included in this review. Of these, 77316 patients were in the intervention groups representing 27.2% of the overall studied population. Around 9% of patients were in the bariatric surgery group, while 18% were in the GLP-1 group. Nine studies used bariatric surgery as their primary intervention, while seven used GLP-1. The mean age of participants ranged from 32.4 to 66 years.

Conclusion: In conclusion, GLP-1 showed similar event rates to the control group for MI and CVD but better stroke outcomes. Moreover, bariatric surgery, across studies demonstrated a significant reduction in the risk of the studied events. Thus, we recommend conducting high-quality trials comparing the two interventions to safely apply the results in everyday practice.

Keywords: Bariatric Surgery; GLP-1; Obesity; Cardiovascular Events; Myocardial Infarction; Cerebrovascular Accident

Introduction

Worldwide obesity has become one of the most common public health concerns. In addition to being an increased mortality risk factor, it also contributes to type 2 diabetes, hypertension, heart disease, and some types of cancer [1]. In the largest country on the Arabian Peninsula Saudi Arabia in 2013 unsurprisingly had an estimated obesity prevalence among healthy Saudi male adults of 24.1% and 33.5% female adults, mandating a multisectoral approach [2].

On aiming to reduce body mass index Multiple measures are scientifically investigated such as: lifestyle modification, pharmacological and surgical therapy.

Recently the medical therapy gaining more popularity especially after the novel Glucagon-like peptide-1 (GLP-1) receptor agonists a class of medications used initially for type 2 diabetes. And postulated role on weight loss. Acting as an incretin hormone stimulating the release of insulin from pancreatic beta cells in conjunction with carbohydrates that are absorbed from the gut.

On the other hand, surgical intervention i.e., bariatric surgery enormously has been offered as an effective strategy to reduce the weight, cardiovascular events, and deaths. With significant improvement in obesity-related comorbidities. This review took a critical look on evaluating the scientific evidence of GLP-1 Vs bariatric surgery and the outcome of cardiovascular events.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews (PRISMA) standers in our reporting.

Study design

This is a Systematic Review.

Eligibility criteria

The selected eligible studies should meet all the following criteria:

- Bariatric surgery/GLP-1 as primary procedure.
- Obesity as a primary indication for the procedure.
- Cardiovascular events as an outcome.
- Adult patients older than 18 years with no history of cardiovascular events.
- Recent study articles published from 2010 up to 2021
- Study design include Randomized controlled trial (RCT), Non-randomized controlled trial (non- RCT), cohort study, and case-control study
- Study articles with English language
- Free accessible Articles.

Literature search

We searched through PubMed, Google Scholar, and Research Gate for recent studies published in English Language, available free full text articles, in the period between 2010 and 2021. The search strategy combined free texts and MeSH terms. We used the following keywords "Bariatric surgery", "GLP-1", "Obesity", "Cardiovascular events", "Myocardial Infarction" and "Cerebrovascular Accident" to find the relevant studies.

Study screening and data collection

In order to determine eligibility and collect data from eligible articles, title and abstract were screened by two authors independently, after determining the potential eligible articles they screened the full text for final eligibility. From selected studies, data regarding study title, study design, patient characteristics, intervention (bariatric surgery or GLP-1), and outcomes was collected independently. The decision was adjudicated by a third reviewer if any discrepancies were found. A desktop version of Mendeley was used to check the search strategy's output for duplicates.

Risk of bias assessment

The Critical Appraisal Skills Programme risk of bias tool was used.

Results

Results of the literature search

A total of 526 records were identified through searching the 3 included databases, which resulted in 480 records after discarding duplicates. Forty-seven records resulted from title and abstract screening, and after full-text screening, 16 records were finally included in the qualitative and quantitative synthesis. The selection process is detailed in the PRISMA flow chart in Figure 1.

Characteristics of the included studies

Our systematic review included 16 studies with a total of 283983 patients; 77316 patients were in the intervention groups representing 27.2% of the overall studied population. Around 9% of patients were in the bariatric surgery group, while 18% were

Figure 1: PRISMA flowchart summarizes the study selection process.

in the GLP-1 group. Nine studies used bariatric surgery as their primary intervention, while seven used GLP-1. The mean age of participants in the intervention groups ranged from 32.4 to 66 years and from 36.3 to 66 years in the control group. The detailed characteristics of the included studies are illustrated in Table 1.

Cardiovascular events (CVE)

CVE was reported in 14 studies with 854 (3.4%) patients affected in bariatric surgery, while it was reported in 3215 (6.1%) patients who used GLP-1 as their primary intervention; however, CVE happened in 5497 (2.7%) patients in the control group [3-7,11-13,15-18]. CVE hazard ratio (CVE HR) ranged from (0.44, 95% CI [0.32,0.61]) in Näslund., *et al*. to (1.2, 95% CI [0.59,2.47]) in Hung., *et al*. in the bariatric surgery intervention arm while using GLP-1 resulted in HR ranged from (0.74, 95% CI [0.58,0.95]) in Marso., *et al*. to (0.90, 95% CI [0.83,0.98]) in Svanström., *et al*. [3,8,12,18]. The detailed CVE for each study in our systematic review is illustrated in Table 2.

Study	Study Design	Intervention	Total Sample Size (n)	Sample Size of Intervention Group (n)	Total Male	Male Intervention GX-DXroup	Mean Age of Intervention Group	SD of Age	Mean Age of Control Group	SD of Age
Hung, Shao-Lun., *et al*. [7]	Comprehensive National Cohort Study	Bariatric surgery	7801	1436	3075	568	32.39	8.63	36.25	7.35
Romeo, Stefano., *et al*. [9]	Prospective, nonrandomized, controlled study	Bariatric surgery	607	345	81	41	49	6	50	6
Scott, John D., *et al*. [10]	Retrospective cohort study	Bariatric surgery	9140	4747	1828	808	50.5	7.4	(Ortho*: 58.1), (GI*: 53.7)	(Ortho*: 9.3), (GI*: 9.3)
Sjöström, Lars., *et al*. [11]	Prospective, nonrandomized controlled study	Bariatric surgery	4047	2010	1180	590	NA	NA	NA	NA

Stenberg, Erik., *et al*. [13]	A nationwide matched cohort study	Bariatric surgery	38062	11863	13391	4053	52.1	7.46	54.6	7.12
Näslund, Erik., *et al*. [14]	A nationwide cohort study	Bariatric surgery	1018	509	582	291	53	7	53.2	7.4
Douglas, Ian J., *et al*. [15]	Retrospective cohort study	Bariatric surgery	7764	3882	1472	756	45	11	45	11
Alkharaiji, Mohammed., *et al*. [16]	Retrospective cohort study	Bariatric surgery	710	131	286	58	50.74	11	51.96	12.8
Pirlet, Charles., *et al*. [17]	Retrospective cohort study	Bariatric surgery	232	116	168	82	52.9	7.3	52.1	8.5
Marso, Steven P., *et al*. [3]	Randomized, double-blind, controlled trail	GLP-1	3297	1648	2002	1013	64.7	7.1	64.4	7.5
Marso, Steven P., *et al*. [4]	Randomized, double-blind controlled trail	GLP-1	9340	4668	6003	3011	NA	NA	NA	NA
O'Brien, Matthew J., *et al*. [18]	Retrospective cohort study	GLP-1	132737	11351	73802	4177	NA	NA	NA	NA
Guthrie, Robert. [19]	The LEADER program	GLP-1	9340	4668	NA	NA	NA	NA	NA	NA
Gerstein, Hertzel C., *et al*. [20]	Randomized, double-blind controlled trail	GLP-1	9901	4949	5312	2643	66.2	6.5	66.2	6.5
Husain, Mansoor., *et al*. [21]	Randomized, double-blind controlled trail	GLP-1	3183	1591	2176	1084	66	7	66	7
Svanström, Henrik., *et al*. [22]	Register-based cohort study	GLP-1	46804	23402	27408	13704	NA	NA	59	NA

Table 1: Sociodemographic characteristics of the included studies.

*ortho: bariatric surgery compared to orthopedic surgery.

*GI: bariatric surgery compared to gastrointestinal surgery.

Study	Intervention	CVE in Intervention Group (n)	CVE in Control Group (n)	P value	HR of CVE	95% CI of CVE	CV Deaths in Intervention Group (n)	CV Deaths in Control Group (n)	P value	HR of CV Deaths	95% CI of CV Deaths
Hung, Shao-Lun., *et al.* [7]	Bariatric surgery	10	30	0.617	1.202	(0.585-2.472)	0	4	1	NA	NA
Romeo, Stefano., *et al.* [9]	Bariatric surgery	63	65	0.002	0.53	(0.35-0.79)	NA	NA	NA	NA	NA
Scott, John D., *et al.* [10]	Bariatric surgery	166	(Ortho: 364), (GI: 215)	0.001	(Ortho: 0.72), (GI: 0.48)	(Ortho: 0.6-0.9), (GI: 0.4-0.6)	NA	NA	NA	(Ortho: 0.81), (GI: 0.45)	(Ortho: 0.6-1.1), (GI: 0.3-0.6)
Sjöström, Lars., *et al.* [11]	Bariatric surgery	199	234	< 0.001	0.67	(0.54-0.83)	28	49	0.002	0.47	(0.29-0.76)
Stenberg, Erik., *et al.* [13]	Bariatric surgery	379	1125	< 0.001	0.73	(0.64-0.84)	108	283	0.017	0.84	(0.73-0.97)
Näslund, Erik., *et al.* [14]	Bariatric surgery	NA	NA	NA	0.44	(0.32-0.61)	NA	NA	NA	0.45	(0.29-0.70)
Douglas, Ian J., *et al.* [15]	Bariatric surgery	NA	NA	NA	NA	NA	3714	3774	0.87	0.97	(0.66-1.43)
Alkharaiji, Mohammed., *et al.* [16]	Bariatric surgery	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pirlet, Charles., *et al.* [17]	Bariatric surgery	37	50	0.049	0.65	0.42-1.0	9	11	0.55	0.77	0.31-1.85
Marso, Steven P., *et al.* [3]	GLP-1	108	146	<0.001 for non inferiority , 0.02 for superiority	0.74	0.58-0.95	44	46	0.92	0.98	0.65-1.48

Marso, Steven P., *et al*. [4]	GLP-1	608	694	0.01	0.87	0.78-0.97	219	278	0.007	0.78	0.66-0.93
O'Brien, Matthew J., *et al*. [18]	GLP-1	104	NA	NA	0.78	0.63-0.96	NA	NA	NA	NA	NA
Guthrie, Robert. [19]	GLP-1	608	694	0.01	0.87	0.78-0.97	NA	NA	0.007	0.78	0.66-0.93
Gerstein, Hertzel C., *et al*. [20]	GLP-1	594	663	0.026	0.88	0.79-0.99	317	346	0.21	0.91	0.78-1.06
Husain, Mansoor., *et al*. [21]	GLP-1	61	76	0.001	0.79	0.57-1.11	15	30	NA	0.49	0.27-0.92
Svanström, Henrik., *et al*. [22]	GLP-1	1132	1141	NA	0·90	0·83–0·98	323	371	NA	0·78	0·68–0·91

Table 2: Risk measure and comparison between study groups.

Cardiovascular death (CVD)

CVD was reported in 13 studies with 3859 (15.4%) patients affected in bariatric surgery, while it was detected in 827 (1.6%) patients who used GLP-1 as their primary intervention; however, CVD happened in 5192 (2.4%) patients in the control group [3,6,7,9,11-13,16-18]. The HR for bariatric surgery intervention ranged from (0.45, 95% CI [0.29,0.70]) to (0.97, 95% CI [0.66,1.43]), with Näslund., *et al*. reporting the lowest HR and Douglas., *et al*. reporting the highest. When using GLP-1, the HR ranged from (0.49, 95% CI [0.27,0.92]) to (0.98, 95% CI [0.65,1.48]), with Husain., *et al*. reporting the lowest HR and Marso., *et al*. reporting the highest [8,9,17,12]. Table 2 provides a detailed summary of CVD outcomes for each study in our systematic review.

Myocardial infarction (MI)

MI was reported in 15 studies, with 3907 (15.6%) patients affected in bariatric surgery, while it was detected in 1174 (2.2%) patients who used GLP-1 as their primary intervention; however, MI happened in 5181(2.5%) patients in the control group [3,4,6,9-13,16-18]. The MI hazard ratio (MI HR) for bariatric surgery intervention ranged from (0.24, 95% CI [0.14,0.41]) to (1.09, 95% CI [0.47,2.58]) with Näslund., *et al*. reporting the lowest HR and Pirlet., *et al*. reporting the highest. When using GLP-1, the HR ranged from (0.74, 95% CI [0.51, 1.08]) to (1.18, 95% CI [0.73,1.90]) with Marso., *et al*. reporting the lowest HR and Husain., *et al*. reporting the highest [8,11,12,17]. Table 3 provides a detailed summary of the MI outcome for each study in our systematic review.

Study	Intervention	MI in Intervention Group (n)	MI in Control Group (n)	P value	HR of MI	95% CI of MI	Stoke in Intervention Group (n)	Stroke in Control Group (n)	P value	HR of Stroke	95% CI of Stroke
Hung, Shao-Lun., *et al*. [7]	Bariatric surgery	3	11	0.09	1.086	0.298-3.960	7	19	0.602	1.26	0.528-3.005
Romeo, Stefano., *et al*. [9]	Bariatric surgery	38	43	0.025	0.56	0.34 - 0.93	34	24	0.29	0.73	0.41-1.30

Scott, John D., *et al.* [10]	Bariatric surgery	NA	NA	NA	(Ortho: 0.59), (GI: 0.49)	(Orho: 0.4-0.8), (GI: 0.4-0.7)	NA	NA	NA	(Ortho: 0.69), (GI: 0.49)	(Ortho: 0.4-1.3), (GI: 0.2-0.9)
Sjöström, Lars., *et al.* [11]	Bariatric surgery	122	136	0.02	0.71	(0.54-0.94)	39	111	0.008	0.66	(0.49-0.90)
Stenberg, Erik., *et al.* [13]	Bariatric surgery	NA	NA	0.001	0.52	(0.41-0.66)	NA	NA	0.063	0.81	(0.63-1.01)
Näslund, Erik., *et al.* [14]	Bariatric surgery	NA	NA	NA	0.24	(0.14-0.41)	NA	NA	NA	0.91	(0.38-2.20)
Douglas, Ian J., *et al.* [15]	Bariatric surgery	3618	3732	0.01	0.28	(0.10-0.74)	3683	3748	0.86	0.91	(0.47-1.76)
Alkharaiji, Moham-med., *et al.* [16]	Bariatric surgery	114	30	0.95	0.98	(0.54-1.77)	47	16	0.76	0.87	(0.36-2.10)
Pirlet, Charles., *et al.* [17]	Bariatric surgery	12	10	0.85	1.09	0.47-2.58	3	2	0.67	1.47	0.24-11.2
Marso, Steven P., *et al.* [3]	GLP-1	47	64	0.12	0.74	0.51-1.08	27	44	0.04	0.61	0.38-0.99
Marso, Steven P., *et al.* [4]	GLP-1	292	339	0.046	0.86	0.73-1.00	173	199	0.16	0.86	0.71 - 1.06
O'Brien, Matthew J., *et al.* [18]	GLP-1	NA	NA	NA	0.91	0.67-1.24	NA	NA	NA	0.65	0.44-0.97
Guthrie, Robert. [19]	GLP-1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gerstein, Hertzel C., *et al.* [20]	GLP-1	223	231	0.63	0.96	0.79-1.15	158	205	0.01	0.76	0.62-0.94
Husain, Mansoor., *et al.* [21]	GLP-1	37	31	NA	1.18	0.73-1.90	12	16	NA	0.74	0.35-1.57
Svanström, Henrik., *et al.* [22]	GLP-1	575	554	NA	0·94	0·84–1·06	424	436	NA	0·88	0·77–1·01

Table 3: Risk measure and comparison between study groups.

Stroke

Stroke was reported in 15 studies, with 3813 (15.2%) patients affected in bariatric surgery, while it was detected in 794 (1.5%) patients who used GLP-1 as their primary intervention; however, stroke was unfortunate outcome in 4820 (2.3%) patients in the control group [3,4,6,9-13,16-18]. The HR ranged from (0.49, 95% CI [0.20,0.90]) in Scott., *et al*. to (1.47, 95% CI [0.24,11.20]) in Pirlet., *et al*. in the bariatric surgery intervention arm, while using GLP-1 resulted in HR ranged from (0.61, 95% CI [0.38,0.99]) in Marso., *et al*. to (0.88, 95% CI [0.77,1.01] in Svanström., *et al*. [5,11,12,18]. The detailed findings about stroke for each study in our systematic review are shown in Table 3.

Discussion

Our review entailed 16 studies searching the available literature about cardiovascular events accompanying bariatric surgery and GLP-1 use. Although it is not a direct comparison between the two interventions, we tried to reveal each cardiovascular event and HR between each interventional arm and the control group. Across the included studies in the review, GLP-1 mostly showed similar event rates to the control group regarding MI and CVD with better stroke outcomes. On the contrary, HR in most studies significantly favored bariatric surgery over control. Moreover, bariatric surgery over the searched studies, demonstrated significant decrease in the risk of the studied events. However, in some of the literature, it showed more adverse events than the control group. Still, the large discrepancies between cardiovascular events in bariatric surgery groups compared to the GLP-1 group could be justified by multiple comorbidities and severe obesity that make bariatric surgery indicated. So, the high event rates may not be attributed to the surgery itself but could be due to the confounders accompanying the studied patients in this group.

Despite the absence of randomized, controlled trials investigating the effects of bariatric surgery on cardiovascular events as a primary prevention measure, certain observational studies have discovered a connection between bariatric surgery and a reduced incidence of cardiovascular events. For example, *Aminian., et al.* found that bariatric surgery had a significantly lower cardiovascular events outcome in patients with severe obesity and type 2 DM, similar findings were reported by *Moussa., et al.* concluding a significantly lower occurrence of cardiovascular events in patients who had undergone bariatric surgery compared to unoperated severely obese patients [19,20]. Moreover, a matched cohort study of severely obese patients with type 2 DM found that bariatric surgery was associated with decreased incidence of macrovascular events and coronary artery disease [21]. Furthermore, previous studies have evaluated cardiovascular events after bariatric surgery in patients with a history of cardiovascular disease and showed their protective effect on survival after MI and stroke [19,22,23].

A recent study examined mortality rates after MI or stroke in patients who had previously undergone bariatric surgery and those who had not [24]. The study found that patients who had undergone bariatric surgery before experiencing an MI or stroke had a lower mortality rate (odds ratio [OR], 0.62 [95% CI, 0.44–0.88]) compared to matched controls who had not undergone bariatric surgery [24]. It is unlikely that weight loss alone is responsible for the observed association between surgery and a lower risk of cardiovascular events. Many patients in the previously mentioned study experienced clinical remission of type 2 DM, hypertension, and dyslipidemia, which may have contributed to the lower risk of cardiovascular events [24]. This contrasts with the AHEAD (Action for Health in Diabetes) trial, which found that weight loss through lifestyle intervention was not associated with reducing cardiovascular events in patients with type 2 DM [25]. However, another recent study found that cardiovascular events were significantly reduced after bariatric surgery in patients with type 2 DM [19].

Näslund and colleagues proposed that the positive impact of bariatric surgery on cardiovascular events is not just due to significant and sustained weight loss but also to other cardiometabolic effects resulting from changes in the anatomy and physiology of the gastrointestinal system that occur after surgery, as the alteration in the release of gastrointestinal peptides [14,26]. After modern bariatric surgery, the postprandial plasma concentrations of GLP-1 increase significantly [27]. A recent meta-analysis showed that using GLP-1 receptor agonists in patients with type 2 DM led to a 10% decrease in the relative risk of CVD, nonfatal MI, and nonfatal stroke [26]. This finding indicates that increased plasma GLP-1 concentrations may play a role in the observed association between bariatric surgery and cardiovascular events [28]. However, the extent to which GLP-1 is responsible for the cardiometabolic benefits of bariatric surgery is currently being debated [29].

Various explanations could explain why GLP-1 receptor agonists have beneficial effects on cardiovascular outcomes. These include lowering HbA1c, LDL cholesterol, blood pressure, and weight [30]. New evidence also suggests that these drugs might improve endothelial function, how endothelial cells respond to ischemia, and platelet function independently [30]. They might also have direct neuroprotective effects. Additionally, these drugs could slow the progression of atherosclerosis, vascular inflammation, and vasoconstriction [31]. Regardless of how GLP-1 works, various trials' results explained the cardiovascular impacts of GLP-1 receptor agonists [12,13,16,32]. These trials imply that most middle-aged or older patients with type 2 diabetes can experience cardiovascular advantages from GLP-1 receptor agonists [12,13,16,32]. Furthermore, they showed that these drugs had a more significant effect on reducing the incidence of stroke than myocardial infarction [12,13,16,32].

This review aimed to give an overview of cardiovascular events in GLP-1 and bariatric surgery. It spotted the gap in the literature that lacks a direct comparison between GLP-1 and bariatric surgery, so we cannot pool evidence efficiently and analyze it. The limitations we faced in our study could be summarized in the following points: 1) Being this study without meta-analysis, and most studies included were not RCTs make the evidence pooled from of limited use in the clinical field; 2) Many confounders could bias our findings as there were different bariatric surgeries conducted without mentioning which operation had been conducted in each study. 3) Our studies have different study designs such as cohort, RCT, and non-randomized trials; this makes the evidence of each study does not stand on equal footing with each other.4) As we stated above, GLP-1 level alteration after bariatric surgeries may be a key role in their cardiovascular benefit, so we need more studies to stratify their results in bariatric surgeries regarding GLP-1 levels. 5) Different study designs and clinical heterogeneity, e.g., as the included studies used different GLP-1 agents, thus complicate the relation further making it difficult and of low value to do qualitative analysis for included studies. For all the previously mentioned drawbacks, we recommend conducting high-quality trials comparing GLP-1 directly with bariatric surgeries regarding their safety profile, especially their cardiovascular outcomes on treated patients. So, we could generalize the results and apply them safely in everyday practice.

Conclusion

Our review of 16 studies investigated the occurrence of cardiovascular events in patients undergoing bariatric surgery and treatment with GLP-1. While there was no direct comparison between the two interventions, the incidence of cardiovascular events and HRs in each group has been examined compared to the control. GLP-1 showed similar event rates to the control group for MI and CVD but better stroke outcomes. The majority of studies favored bariatric surgery with significant HRs. Moreover, bariatric surgery, across studies demonstrated a significant reduction in the risk of the studied events. By thus we recommend conducting high-quality trials comparing the two interventions to safely apply the results in everyday practice.

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