The effect of bariatric surgery in comparison with the control group on the prevention of comorbidities in people with severe obesity: a prospective cohort study

Amir Ebadinejad1, Maryam Barzin1*, Behnaz Abiri1, Maryam Mahdavi1, Alireza Khalaj2, Danial Ebrahimi3, Farhad Hosseinpanah1 and Majid Valizadeh1*

Abstract
Background: Obesity is a global health priority, particularly in developing countries. The preventive effect of bariatric surgery against obesity-related diseases in the developing countries of the Middle East and North Africa region, where type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia prevail, has not been examined.

Method: Severely obese participants who underwent bariatric surgery were compared with their counterparts who underwent no intervention. These patients had been followed up in two prospective cohort studies for three years. We here determined the incidence of new-onset T2DM, HTN, and dyslipidemia and reported absolute and relative risks for the incidence of these comorbidities in the two groups.

Results: In this study, 612 participants in the bariatric surgery group were compared with 593 participants in the control group. During the follow-up period, T2DM developed in eight (2.9%) people in the surgery group and 66 (15.0%) people in the control group (P < 0.001). New-onset HTN and dyslipidemia showed significantly lower frequencies in the surgery group compared to the control group (4 (1.8%) vs. 70 (20.4%) and 33 (14.3%) vs. 93 (31.5%), respectively). Regarding a less favorable metabolic profile in the surgery group at the baseline, the relative risk reductions associated with bariatric surgery were 94, 93, and 55% for the development of T2DM, HTN, and dyslipidemia, respectively.

Conclusion: The risk reduction of obesity-related comorbidities after bariatric surgery should be considered in the decision-making process for public health in the region, which bariatric surgery could result in the prevention of comorbidities.

Keywords: Bariatric surgery, Diabetes, Hypertension, Dyslipidemia
trend, reached 4.5% and 10.9% in 2016, respectively. [3, 4]. Obesity is an established risk factor for overall all-cause mortality and obesity-related comorbidities, including type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia [5, 6].

Therapeutic options for severe obesity include nonsurgical treatments and bariatric surgery. The non-surgical approach usually encompasses a multicomponent strategy comprising behavioral therapy, dietary recommendations, increased physical activity, and pharmacotherapies, which often fails [7, 8]. Notable recent studies, however, indicate that pharmacological therapy for optimal weight loss in overweight or obese patients offers promising results [9–11]. Compared with the non-surgical treatment of obesity, bariatric surgery offers a safe, efficient, and permanent approach for weight loss and delivers higher remission rates for T2DM and metabolic syndrome [8, 12, 13]. Compared to non-surgical and pharmaceutical treatments, bariatric surgery has shown protective effects against obesity-related diseases, which is related to significant weight loss and physiological changes [14]. A recent meta-analysis reported that bariatric surgery was associated with the relative risk reductions of 61%, 64%, and 77% for the development of T2DM, HTN, and dyslipidemia, respectively; however, the number of studies was insufficient in the recent meta-analysis, and all the studies included had been conducted in developed countries [15]. To our knowledge, no study has examined the preventive effects of bariatric surgery against obesity-related diseases in the developing countries located in the Middle East and North Africa region (MENA), where T2DM, HTN, and dyslipidemia prevail and people have less tendency for bariatric surgery compared to other communities [16, 17]. In this cohort study, we examined the preventive effects of bariatric surgery against obesity-associated T2DM, HTN, and dyslipidemia over a mid-term follow-up.

**Methods and materials**

**Study design and participants**

In this study, we prospectively investigated the incidence of new-onset comorbidities in two cohorts of people living in Tehran during a specific period of time. As the control group, individuals with severe obesity and over 18 years of age were included from a population-based cohort, the Tehran Lipid, and Glucose Study (TLGS). As the surgery group, individuals with severe obesity and over 18 years of age participating in another ongoing cohort, the Tehran Obesity Treatment Study (TOTS), who underwent bariatric surgery for the first time were included. All the individuals selected from the two studies were in the same time period and lived in the same state. Those who were under treatment with glucocorticoids were excluded. Patients who initially had all three T2DM, HTN, and dyslipidemia were excluded. In order to evaluate the incidence of one comorbidity, patients who did not initially have it in each group were followed up. Therefore, the sum of participants without one comorbidity is greater than the total number because some patients may have two comorbidities from the beginning. The participant selection process in the two groups has been illustrated in Fig. 1.

**TLGS**

TLGS is a prospective study initiated in 1999 as a large-scale community-based study aiming to determine the prevalence of non-communicable disease risk factors in a representative sample of the residents of District 13 of Tehran, the capital city of Iran. Its data are collected prospectively at 3-year intervals. The sampling and follow-up methods have been described previously [18]. Among 11,025 eligible individuals entering phase V of the study (2011–2014) and continuing to phase VI (2015–2018), after applying the exclusion criteria, 593 people with a mean age of 49.0 years and a BMI of 38.6 kg/m² were finally selected.

**TOTS**

TOTS is an ongoing single-institution prospective study initiated in March 2013, in which the participants undergoing a bariatric procedure based on an individualized clinical decision plan are registered. The participants entering TOTS are referred to one of three university-affiliated hospitals for clinical assessments and surgical procedures. All TOTS participants undergo bariatric surgery, including sleeve gastrectomy (SG), one-anastomosis gastric bypass (OAGB), and Roux-en-Y gastric bypass (RYGB). More information regarding the study’s protocol is available elsewhere [19]. Out of 4640 eligible individuals, we finally included 612 participants from March 2013 to March 2019, with a mean age of 39.2 years and a BMI of 45.0 kg/m² (364 cases of SG, 210 cases of OAGB, and 38 cases of RYGB).

The incidence of new-onset T2DM in both surgical and control groups was evaluated in participants who did not have T2DM at baseline (272 vs. 440). Also, participants without HTN (224 vs. 343) and dyslipidemia (230 vs. 295) at the beginning of the study were evaluated for the incidence of new-onset HTN and dyslipidemia.

The Ethics Committee of Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved all procedures concerning human participants (IR.SBMU.ENDOCRINE.REC. 1400.050). This study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its later amendments or comparable ethical
guidelines. Written informed consent was obtained from all the participants included in the study.

Clinical and biochemical measurements
The details of data collection (demographic, laboratory, and clinical) at the baseline and follow-ups in the two cohort studies (i.e., TLGS and TOTS), which followed a somewhat similar process, have been precisely described [18, 19].
Definitions of terms

Type 2 diabetes mellitus was defined based on the American Diabetes Association's criteria as having either fasting plasma glucose (FPG) levels ≥ 126 mg/dL, 2-h plasma glucose (2-hPG) ≥ 200 mg/dL, or HbA1c > 6.5% or being under treatment with hypoglycemic drugs [20]. HbA1c was not available for the participants of TLGS, hence FPG and 2-hPG levels were utilized; for the surgical group selected from TOTS, laboratory FPG and HbA1c data were available, which we used to diagnose T2DM. Regarding HTN, the subjects who had systolic BP levels higher than 140 mmHg or diastolic BP levels of 90 mmHg or consumed antihypertensive medications were considered hypertensive [21]. Dyslipidemia was defined as either TC > 240 mg/dL, HDL < 40 mg/dL, TG > 200 mg/dL, or LDL > 160 mg/dL or being under treatment with lipid-lowering drugs [22].

Statistical procedures

All normally-distributed continuous variables were expressed as mean ± standard deviation (SD). Otherwise, skewed continuous variables were reported as the median and interquartile range (IQR) 25–75%. Baseline categorical variables were expressed using frequency (percentage). Differences in various characteristics between the control and surgery groups were tested using the independent sample t-test, Mann–Whitney U test, and chi-square test for normal, skewed, and categorical variables, respectively. To assess possible differences between the study groups, binary logistic regression was applied. Possible confounders (age, sex, BMI, and a family history of T2DM at the baseline) were included in the model. All statistical analyses were performed using STATA version 12 (STATA, College Station, TX, USA); the significance level was set at P < 0.05 (two-tailed).

Results

Participants with severe obesity were enrolled from two cohort studies (i.e., TOTS that was the source for the surgery group's participants and TLGS that provided the participants of the control group). Baseline characteristics of participants in the surgery and control groups have been demonstrated in Table 1. Female participants constituted 503 (82.2%) in the surgery group and 468 (78.9%) in the control group. Anthropometric parameters, including weight, BMI, and waist, and hip circumferences, were significantly higher in the surgery group. Baseline characteristics of participants in the surgery and control groups based on the absence of T2DM or HTN or dyslipidemia at baseline have been demonstrated in Additional file 1: Table S1.

The median durations of the follow-up in the surgery and control groups were 3.63 (2.82–5.08) and 3.21 (2.93–3.69) years, respectively. Anthropometric measures showed significant variations between the groups at the follow-up (P < 0.001). In the surgery group, weight and BMI reached from 119.8 (20.1) kg and 45.0 (6.0) kg/m² to 81.9 (14.2) kg and 30.8 (4.6) kg/m², respectively, whereas in the control group, they reached from 96.5 (15.6) kg and 38.5 (3.5) kg/m² to 95.9 (17.0) kg and 38.0 (4.7) kg/m², respectively. New-onset comorbidities in the participants of the two groups during the follow-up have been shown in Fig. 2. During the follow-up, T2DM developed in 8/272 (2.9%) participants of the surgery group (3 patients with consuming medications and 5 patients with impaired HbA1C and FPG) and 66/440 (15.0%) participants of the control group (35 patients with consuming medications and 9 patients with impaired 2-hPG and FPG and 22 patients with impaired 2-hPG or FPG). (New-onset HTN and dyslipidemia were significantly lower in the surgery group vs. the control group (4/224 (1.8%) vs. 70/343 (20.4%) and 33/230 (14.3%) vs. 93/295 (31.5%), respectively). There was no significant difference between the three types of surgical methods regarding the incidence of new-onset comorbidities.

Absolute risk (AR) and relative risk (RR) for new-onset comorbidities have been reported in Table 2. The participants undergoing surgery compared to the control group had a lower overall risk for new-onset T2DM (AR = 2.9% vs. 15.0%; absolute risk reduction (ARR) = 12.0% [95% CI: 8.1–15.9%]; adjusted-RR = 0.06 [95% CI: 0.02–0.17]), HTN (AR = 1.7% vs. 20.4%; ARR = 18.6% [95% CI: 14.2–23.2%]; adjusted-RR = 0.07 [95% CI: 0.02–0.22]), and dyslipidemia (AR = 14.3% vs. 31.5%; ARR = 17.1% [95%CI: 10.2–24.1%]; RR = 0.45 [95%CI: 0.26–0.78]). According to ARR, the “number need to treat” (NNT) for T2DM, was estimated at 8 (95% CI, 6–12), indicating that by surgery of 8 cases, 1 case of T2DM would be treated; also NNT for HTN, and dyslipidemia was estimated at 5 (95% CI, 4–7) and 5 (95% CI, 4–9), respectively.

Discussion

In this prospective study on the severe obese individuals taking part in two population-based cohorts (i.e., TLGS and TOTS), the participants who underwent bariatric surgery had significantly lower probability to develop T2DM, HTN, and dyslipidemia compared to the control (receiving no intervention) subjects over a mid-term follow-up period. According to the NNT in our study, bariatric surgery, compared to non-surgical interventions, resulted in the treatment of one out of eight patients with T2DM, five patients with HTN, and five patients with dyslipidemia. The relative risk reductions associated with
bariatric surgery were 94, 93, and 55% for the development of T2DM, HTN, and dyslipidemia, respectively.

The metabolic health status in the people living in the MENA region is unsatisfactory due to physical inactivity and unhealthy diets; more than one in every three women are obese in most countries of the region [16]. The MENA region harbored the highest global prevalence of T2DM (12.2%) in 2019 [23]. Over the past three decades, unlike European high-income countries where T2DM rates have been stable, the incidence of this condition has almost doubled in the MENA region, even in its high-income countries [16, 24]. The prevalence of HTN in this region was also higher than the rest of the world between 1975 and 2015 [25]. Accordingly, in recent years, metabolic status and morbid obesity have shown deteriorating and soaring trends among Iranian aging men and women [4]. According to the WHO, only 38% of disease preventive programs in the MENA region have been successfully implemented [13], demanding immediate attention to health sectors in the region to effectively implement preventive strategies and maintain optimal metabolic health.

Bariatric surgery provides a sustainable and beneficial treatment for weight loss and improving obesity-related diseases, especially in regions with the highest burden of metabolic risk factors [8, 12]. In our study, the incidence

| Characteristic                        | Surgery group  | Control group | P value |
|---------------------------------------|----------------|---------------|---------|
| N = 612                                | 503 (82.2)     | 468 (78.9)    | 0.152   |
| Age (year)                            | 39.2 ± 10.9    | 490 ± 13.3    | <0.001  |
| Weight (kg)                           | 119.8 ± 20.1   | 96.5 ± 15.5   | <0.001  |
| BMI (kg/m²)                           | 45.0 ± 6.0     | 38.5 ± 3.5    | <0.001  |
| BMI < 40, n (%)                       | 106 (17.3)     | 434 (73.2)    | <0.001  |
| BMI 40–50, n (%)                      | 407 (66.5)     | 155 (26.1)    |         |
| BMI > 50, n (%)                       | 99 (16.2)      | 4 (0.7)       |         |
| Waist circumference (cm)              | 123.4 ± 13.9   | 113.4 ± 10.2  | <0.001  |
| Hip circumference (cm)                | 135.8 ± 12.6   | 116.3 ± 8.3   | <0.001  |
| FPG (mg/dl)                           | 106.5 ± 32.5   | 101.5 ± 18.3  | 0.001   |
| HbA1c %                               | 5.6 ± 1.0      | NA            | NA      |
| 2-hPG (mg/dl)                         | NA             | 123.1 ± 38.5  | NA      |
| Impaired fasting glucose n (%)        | 223 (48.6)     | 217 (43.4)    | 0.108   |
| T2DM n (%)                            | 123 (21.4)     | 84 (14.7)     | <0.001  |
| Systolic BP (mm Hg)                   | 123.9 ± 13.9   | 125.3 ± 18.3  | 0.123   |
| Diastolic BP (mm Hg)                  | 79.5 ± 8.8     | 82.1 ± 10.6   | <0.001  |
| HTN, n (%)                            | 169 (29.1)     | 245 (41.5)    | <0.001  |
| Total cholesterol (mg/dl)             | 190.1 ± 36.4   | 198.8 ± 38.1  | <0.001  |
| Triglycerides (mg/dl)                 | 138.0 (102.0–181.2) | 148.0 (112.0–192.5) | 0.006 |
| HDL cholesterol (mg/dl)               | 49.4 ± 12.4    | 48.3 ± 11.4   | 0.112   |
| LDL cholesterol (mg/dl)               | 109.9 ± 32.3   | 118.0 ± 33.1  | <0.001  |
| Dyslipidemia n (%)                    | 274 (47.4)     | 295 (49.8)    | 0.406   |
| Never smoking n (%)                   | 483 (83.7)     | 525 (89.3)    | 0.003   |
| Family history of T2DM n (%)          | 218 (47.7)     | 69 (11.8)     | <0.001  |

BMI: body mass index, FPG: fasting plasma glucose, 2-hPG: 2-h plasma glucose, T2DM: type 2 diabetes mellitus, BP: blood pressure, HTN: hypertension
Data are presented as mean ± SD or n (%) except triglycerides which are presented as median (IQ 25–75)
Table 2  Absolute and relative risks for new-onset comorbidities

|                        | % (95% CI) | Absolute risks surgery group | Absolute risks control group | Absolute risk reduction | Unadjusted relative Risk | Adjusteda relative Risk | Number need to treat |
|------------------------|------------|------------------------------|-----------------------------|-------------------------|--------------------------|------------------------|----------------------|
| New-DM n (%)           | 2.9 (0.9–4.9) | 2.9 (0.9–4.9)                | 15.0 (11.6–18.3)            | 12.0 (8.1–15.9)         | 0.17 (0.08–0.36)          | 0.06 (0.02–0.17)       | 8 (12–6)             |
| New-HTN n (%)          | 1.7 (0.5–3.5)   | 1.7 (0.5–3.5)                | 20.4 (16.1–24.6)            | 18.6 (14.2–23.2)        | 0.07 (0.02–0.20)          | 0.07 (0.02–0.23)       | 5 (7–4)              |
| New-Dyslipidemia n (%) | 14.3 (9.8–18.8) | 14.3 (9.8–18.8)              | 31.5 (26.2–368)             | 17.1 (10.2–24.1)        | 0.36 (0.23–0.57)          | 0.45 (0.26–0.78)       | 5 (9–4)              |

T2DM type 2 diabetes mellitus, HTN hypertension, CI confidence interval

* The analyses were adjusted for sex, age, and body mass index at baseline
rates of new-onset T2DM, HTN, and dyslipidemia in the participants undergoing bariatric surgery were 2.9%, 1.8%, and 14.3%, respectively. The incidence of new-onset T2DM after bariatric surgery in previous studies has been reported between 0.4 and 9.7%, which was consistent with our findings [26–28]. In Swedish Obese Subjects, T2DM developed in 392 participants in the control group and in 110 in the bariatric-surgery group, corresponding to incidence rates of 28.4 cases per 1000 person-years and 6.8 cases per 1000 person-years, respectively [29, 30]. Studies on the incidence of new-onset HTN and dyslipidemia after bariatric surgeries are infrequent, reporting ranges from 3.1 to 5.6% and from 2.1 to 6.8%, respectively [22, 26–31]. In this investigation, the incidence of new-onset comorbidities after bariatric surgery was not significantly different between the types of surgical procedures. On the other hand, the incidence rates of T2DM, HTN, and dyslipidemia in the non-surgical group were 15.0%, 20.4%, and 31.5%, respectively, ringing the alarm bell. These incidence rates of obesity-related diseases observed here in people with severe obesity receiving no therapeutic intervention were clearly higher than those reported in previous studies [22, 26–28, 31, 32], which is a reminder of the unfavorable metabolic status of populations in the MENA region.

Bariatric surgery seems to be effective in preventing obesity-related diseases, including T2DM, HTN, and dyslipidemia. Also, the relative risk reductions associated with bariatric surgery were 94, 93, and 55% for the development of T2DM, HTN, and dyslipidemia, respectively. Similarly, a study in Norway compared the preventive effects of bariatric surgery and pharmaceutical treatments against obesity-related comorbidities, reporting the relative risk reductions of 93, 60, and 70% for T2DM, HTN, and dyslipidemia, respectively [14]. In a recent meta-analysis, the risk reduction rates of T2DM, HTN, and dyslipidemia were reported 61, 64, and 77%, respectively [15]. The preventive effect of bariatric surgery against obesity-associated comorbidities was more pronounced in our study compared to previous studies. This difference can be attributed to the fact that the control group’s participants in our study did not receive any treatment while control subjects in similar studies had been medically managed. As well, various surgical procedures, variable follow-up durations, and the low access of people with severe obesity to health facilities in developing countries compared to developed countries can explain this difference. Based on these findings, bariatric surgery seems to be effective in reducing obesity-related comorbidities and long-term all-cause mortality [15]. Regarding the unsatisfactory metabolic status of severely obese people receiving no therapeutic interventions in our population, it is advisable to implement informative programs for severely obese patients at risk of associated comorbidities for considering bariatric surgeries. It should be noted that recent studies have revealed that some pharmacological treatments, in addition to having a significant influence on weight loss, also have a positive effect on improving glycemic status [33, 34]. In developing countries with limited access to bariatric surgery, clinical studies can be conducted to assess the efficacy of these medications in morbidly obese individuals at high risk of developing T2DM.

Mechanisms for preventing T2DM after bariatric surgery are probably similar to those behind T2DM remission and can be summarized in four pathways. The first is to alter the secretion of hormones such as glucagon-like peptide 1, gastric inhibitory peptide, ghrelin, and glucagon [35, 36]. The second mechanism is related to the histological and anatomical changes caused by hepatic and pancreatic lipid content changes [37, 38]. Changes at cellular and molecular levels, such as inflammatory markers and gene expression, can be regarded as the third mechanism [39]. Finally, gut microbiome changes can be associated with decreased lipopolysaccharide and lipopolysaccharide-binding protein levels and altered glucose metabolic rate [40]. The remission and prevention of HTN after bariatric surgery can be attributed to weight control and modulation of hormonal mechanisms [41]. The elevation of serum nitric oxide and improvement of endothelial vasomotor function and aortic elasticity are some other explanations noted in previous studies [42–44].

Our study has several strengths and limitations. To the best of our knowledge, our retrospective study on two population-based cohorts with a mid-term follow-up was the first report concerning the preventive effects of bariatric surgery against obesity-related diseases in a developing country in the MENA region. The current study has fourth noteworthy limitations. First, the small number of patients with new-onset comorbidities at the end of the follow-up may reduce the accuracy of the calculated risks. Second, no data was available on the participants’ nutritional and social status and physical activities for the surgery group. Third, lack of treatment control group, which would be considered that the people participating in the TLGS are more conscious of their health status than the overall population. Fourth, T2DM was defined differently in the two groups (in TOTS with HbA1c or FPG or medication; TLGS with 2-hPG or FPG or medication), which was likely to affect the different incidence of T2DM in both groups.
Conclusion
Among participants with severe obesity, bariatric surgery was associated with a clinically meaningful reduction in the risk of new-onset T2DM, HTN, and dyslipidemia compared to a control group. The key role of bariatric surgery in reducing the risk of obesity-related comorbidities should be considered in the decision-making process for public health in Iran and other countries in the MENA region. Due to the undesirable metabolic status of the people living in this region and the preventive role of bariatric surgery in developing obesity-related diseases, it is suggested that clinical trials be designed to evaluate the affordability and cost–benefit of bariatric surgery for patients with BMI less than 35 kg/m² in the countries of MENA region.

Supplementary Information
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Author contributions
Study conception and design: AE, MB, MV, AK, DE. Drafting and revising the article: AE, BA. Analysis and interpretation of data: MM, FH. Final approval: AE, MB, MV, BA, MM, FH, AK, DE. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Declarations
Ethical approval and consent to participate
The Ethics Committee of Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran approved all procedures concerning human participants (IR.SBMU.ENDOCRINE.REC. 1400.050). This study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its later amendments or comparable ethical guidelines. Written informed consent was obtained from all the participants included in the study. Informed consent was obtained from the participant included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no financial or non-financial competing interests.

Author details
1Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 2Tehran Obesity Treatment Center, Department of Surgery, Faculty of Medicine, Shahed University, Tehran, Iran. 3Department of Surgery, Faculty of Medicine, Shiraz University, Shiraz, Iran.

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