Universitat Autònoma de Barcelona

Departament de Medicina

Efectes metabòlics de la cirurgia bariàtrica: comparació del Bypass Gàstric en Y de Roux Laparoscòpic i la Gastrectomia Tubular Laparoscòpica

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Tesis Doctoral

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Als meus amics, per fer-me millor persona.

Als meus germans, als meus cunyats i a David, l'alegria de la família.

A Laia, la meva millor amiga i l'amor de la meva vida.

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Índex

1. INTRODUCCIÓ

1.1.Definició i epidemiologia de l'obesitat

L'obesitat és una malaltia crònica que es defineix per l'excés de pes a causa de l'acumulació de greix, respecte al que correspondria per la talla, edat i sexe.

Els canvis d'estil de vida i d'alimentació estan causant un augment de l'obesitat tant en països industrialitzats com en aquells en vies de desenvolupament. Actualment a nivell mundial un 13,8% de les dones i un 9,8% dels homes presenten criteris d'obesitat, el que representa el doble de fa 25 anys (1). Això juntament amb un augment preocupant de l'obesitat infantil ha provocat que actualment es consideri la principal epidèmia del segle XXI (2). A Espanya s'estima que un 39,4% de la població presenta sobrepès, un 22,9% té un IMC >30Kg/m^2 i que un 1,2% compleixen criteris d'obesitat greu (IMC >40Kg/m) (2, 3). La prevalença d'obesitat augmenta progressivament amb l'edat, de forma que a Espanya la presenten un 35% de les persones majors de 65 anys. És també més freqüent en homes, excepte en els grups d'edat més avançada en que predomina en dones. En els països en vies de desenvolupament és més prevalent en entorns urbans i en classes socials altes, en canvi en països en desenvolupats és més freqüent en àrees rurals, en classes socials baixes i enpersones amb un menor nivells d'estudis (2, 3).

A més a més dels problemes estètics i socials que condiciona, l'obesitat greu s'associa a una major prevalença de factors de risc cardiovascular com la hipertensió arterial, la diabetis mellitus tipus 2 (DM2) o la dislipèmia (4). Però a més a més, cada cop hi ha més evidències sobre l'associació amb altres malalties com la síndrome d'apnees obstructives de la són o certs càncers com el de còlon o els ginecològics (5). Això condiciona un major risc de desenvolupar malalties cardiovasculars (4) i una major mortalitat principalment d'origen cardiovascular (6).

És important remarcar els costos associats a l'obesitat. Comparats amb aquells amb un pes normal, els subjectes amb obesitat consumeixen més fàrmacs, requereixen més dies d'hospitalització i visites ambulatòries, i se'ls adjudica amb més freqüència una invalidesa (7). S'ha estimat que els costos anuals en persones amb un IMC >35Kg/m^2 poden ser un 44% superiors a aquells subjectes amb un IMC normal (8).

1.2. La cirurgia bariàtrica com a tractament de l'obesitat

La cirurgia bariàtrica és un dels tractaments d'elecció de l'obesitat greu. Això es veu reflectit en un augment progressiu del número d'intervencions. En aquest sentit, a Catalunya es va passar de 51 intervencions l'any 1996 a 544 l'any 2003 (9). El tractament convencional de l'obesitat, consistent en canvis de l'estil de vida, té una eficàcia limitada. Produeix un màxim de pèrdua de pes de entre el 3 i el 6% als 12 mesos, amb una posterior recuperació ponderal progressiva (10). En canvi la cirurgia bariàtrica s'ha establert com una opció terapèutica eficaç com a tractament de l'obesitat greu. Així, després d'un bypass gàstric en Y de Roux laparoscòpic (BGYRL) s'aconsegueixen pèrdues de pes màximes als 12 mesos al voltant del 30%. Posteriorment s'observa una lleu recuperació de pes, mantenint-se eficaç a llarg termini (11).

Tot i això, els beneficis de la cirurgia bariàtrica van més enllà de la pèrdua de pes. Múltiples estudis han demostrat que és capaç de millorar les comorbiditats associades a la obesitat, fins al punt de que aquestes entrin en remissió (entès com a normalització dels paràmetres que defineixen la comorbiditat, sense necessitat de medicació específica) (12). Això condiciona que a més a més, la cirurgia bariàtrica s’associï a una disminució de la mortalitat del 29% a 10 anys (11).

1.3.Tècniques de cirurgia bariàtrica

Les tècniques de cirurgia bariàtrica es classifiquen segons el mecanisme per perdre pes en restrictives, malabsortives o mixtes. Les tècniques restrictives com la banda gàstrica ajustable laparoscòpica o la gastroplastia vertical anellada, disminueixen la capacitat de l'estómac amb la conseqüent reducció de la ingesta alimentària. Les tècniques malabsortives com la derivació biliopancreàtica escurcen la longitud de l'intestí, disminuint l'absorció de nutrients. El bypass gàstric en Y de Roux laparoscòpic (BGYRL) és una tècnica mixta que combina la restricció gàstrica mitjançant una gastroplàstia i la malabsorció mitjançant el bypass del duodè i la part proximal de jejú.

L’eficàcia sobre el pes i les comorbiditats, a més a més del risc operatori, varia entre les tècniques com es desprèn del metanàlisis de Buchwald *et al* (12). Aquest va analitzar l’any 2004 les dades publicades de 136 estudis amb un total de 22094 pacients inclosos.

	Banda gàstrica ajustable	Gastroplas-tia vertical en anell	Bypass gàstric en Y de Roux	Derivació biliopancreà-tica
Percentatge de pèrdua de l'excés de pes	48	68	62	72
Remissió de la diabetis mellitus tipus 2 (%)	48	72	84	98
Remissió de la hipertensió arterial (%)	28	73	75	81
Milloria de la dislipèmia (%)	71	81	94	100
Mortalitat operatòria (%)	0,1	0,1	0,5	1,1

Resultats del metanálisis de Buchwald et al (12).

Les tècniques malabsortives són les que produeixen majors pèrdues ponderals i més mantingudes, però amb una major mortalitat perioperatòria i un major risc de dèficits nutricionals (11, 13). En canvi el BGYRL és la tècnica que ofereix un millor equilibri entre eficàcia i efectes adversos, per la qual cosa s'ha convertit en la tècnica de referència i la més utilitzada (14). Existeix una relació directa entre el grau de malabsorció que produeix la tècnica quirúrgica i la pèrdua de pes postoperatòria. A més a més, aquesta disminució ponderal és proporcional a la taxa de resolució de les comorbiditats com la hipertensió arterial (12). En canvi la resolució de la DM2 després de les tècniques malabsortives o mixtes es produeix de forma molt més marcada que en les altres comorbiditats i a més a més ho fa quan encara no s'han aconseguit pèrdues ponderals significatives (15). Això fa pensar que existeixen mecanismes hormonals intestinals implicats en la milloria del metabolisme hidrocarbonat. S’han generat dues hipòtesis hormonals: la de l'intestí distal i la de l'intestí proximal. A la primera, un estímul precoç de la part distal de l'intestí provocaria la secreció d’hormones amb efecte incretina per tant sensibilitzadores de la insulina (16). A la segona, l'exclusió de l'intestí proximal provocaria que no es secretin hormones amb efecte antiincretina produint el mateix efecte (17, 18).

1.4. La Gastrectomia tubular laparoscòpica

La gastrectomia tubular laparoscòpica (GTL) o sleeve gatrectomy és una tècnica restrictiva que es va començar a utilitzar l’any 1999 com un primer pas per disminuir pes abans de realitzar una tècnica purament malabsortiva en pacients que patien una obesitat extrema (Índex de Massa Corporal (IMC) > 60 Kg/m^2) (19). La tècnica consisteix en la creació d'un tub estret d'estómac a través de la resecció de la major part de l'estómac. Els bons resultats en termes d’eficàcia i la baixa taxa de complicacions (20, 21) ha provocat que actualment es consideri com una tècnica de primera elecció. No existeixen uns criteris clars a l’hora d’elegir la GTL respecte a altes tècniques, peròs’ha proposat que sigui d’elecció en pacients amb un alt risc quirúrgic, en edats extremes (adolescència i edats avançades), en IMC entre 35 i 40 Kg/m^2, en subjectes amb antecedents de malaltia de Crohn o en ètnies amb risc augmentat de càncer d'estómac (22).

Els últims anys s'han publicat diversos articles sobre la GTL que suggereixen que la pèrdua de pes i la milloria de la DM2 és superior a la d'altres tècniques malabsortives i similar a la del BGYRL (23-25).En aquest sentit, Abbatini *et al* va observar en 60 subjectes amb DM2, una taxa de remissió de la DM2 12 mesos després de GTL del 80,9%, la qual va ser superior a la banda gàstrica ajustable (60,8%) i similar al BGYRL (81,2%) (25). Al tractar-se d'una tècnica relativament nova actualment existeixen poques evidències sobre els efectes en altres aspectes metabòlics com el risc cardiovascular, el metabolisme dels lípids o la resistència a la insulina.

1.5. Efectes de la cirurgia bariàtrica sobre el risc cardiovascular estimat

Els subjectes amb obesitat tenen un risc més elevat de patir una malaltia per obstrucció dels vasos arterials, principalment en territoris coronaris, cerebrals o d'extremitats inferiors; donant lloc a cardiopatia isquèmica, accidents vasculars cerebrals i vasculopatia arterial perifèrica. El risc de patir algun d'aquest esdeveniments en el temps és el que és coneix com a risc cardiovascular. En aquest sentit, l'anàlisi del Prospective Studies Collaboration va mostra una forta associació entre mortalitat i obesitat. En IMCs entre 25 i 50Kg/m^2, cada augment de 5 Kg/m^2 del IMC es va relacionar amb un augment del 39% en mortalitat per un infart agut de miocardi o per accident vascular cerebral (26). Per altra banda al Nurses' Health Study el risc relatiu de malaltia cardiovascular per a IMC >29 Kg/m^2 va ser de 3,56 respecte a aquelles dones amb IMC <21 Kg/m^2 (27).

Aquest augment del risc cardiovascular en pacients obesos es deu principalment a un augment dels factors de risc cardiovascular. Així, Nguyen *et al* ha descrit que els subjectes amb un IMC ≥35 Kg/m^2 presenten respecte als subjectes amb un IMC <25 Kg/m^2 una major prevalença d'hipercolesterolèmia (48% vs 40%), de colesterol HDL baix (18% vs 31%), d'hipertensió arterial (54% vs 24%) i de DM2 (7 vs 26%) (4).Tot i això, aquest excés de risc cardiovascular no es pot atribuir exclusivament a l'augment de les comorbiditats, ja que alguns estudis ha han mostrat que l'obesitat es un factor independent de risc cardiovascular (27, 28).

Per tal de poder estimar el risc de patir esdeveniments cardiovasculars en persones aparentment sanes s'han desenvolupat múltiples models de risc multivariat. El model més conegut i mes utilitzat i avui en dia és l'obtingut a partir del Framingham Heart Study. Aquest és un estudi longitudinal de base poblacional a llarg termini realitzat amb els residents de la població de Framingham als Estats Units d'Amèrica. Es va iniciar l'any 1948 i estudia els factors que es relacionen amb el desenvolupament de malaltia cardiovascular (29). A partir d'aquest estudi es va desenvolupar el Framingham Risk Score, una equació que permet estimar el risc de desenvolupar un esdeveniment cardiovascular a 10 anys, en funció de les següents variables: edat, sexe, tabaquisme, diagnòstic de DM2, colesterol total, colesterol HDL i pressions arterials sistòlica i diastòlica (30).

El risc de desenvolupar un esdeveniment cardiovascular varia en funció de l'ètnia, l'estil de vida i la dieta (31). En aquest sentit és ben conegut que la població mediterrània té un risc cardiovascular menor que la nord-americana o la del nord d'Europa (32). Això s'ha definit com la paradoxa mediterrània. En conseqüència s'han realitzat calibratges de l'equació de Framingham, sent la puntuació de REGICOR (Registre Gironí del Cor) l'adaptada per la nostra població (33).

Estudis en població nord-americana han observat una disminució del risc cardiovascular estimat per l'equació de Framingham després de BGYRL (33-37). Tot i això, no hi ha evidències sobre l'efecte d'altres tècniques de cirurgia bariàtrica com la GTL, ni tampoc sobre els canvis en el risc cardiovascular estimat en població mediterrània.

1.6. Efectes de la cirurgia bariàtrica sobre el perfil lipídic

La dislipèmia és una alteració en la concentració de lípids que s'associa a un efecte aterogènic sobre les parets vasculars i conseqüentment amb un augment del risc cardiovascular (38). La dislipèmia pot estar causada per un augment del lipoproteïnes de baixa densitat (colesterol LDL), per un descens de lipoproteïnes d'alta densitat (colesterol HDL), per un augment dels triglicèrids o per una combinació d'aquestes.

La causa inicial de les alteracions del perfil lipídic dels subjectes amb obesitat són l'acumulació de greix en localització visceral i la conseqüent resistència a la insulina (39). Aquests dos factors produeixen una sèrie d'alteracions patofisiològiques que causen el característic perfil lipídic de les persones amb obesitat amb un augment dels triglicèrids i una disminució del colesterol HDL (40). Aquestes alteracions patofisiològiques són: un augment del flux d'àcids grassos lliures de l'adipòcit cap al fetge, una disminució de la captació perifèrica d'àcids grassos lliures, una sobreproducció hepàtica de colesterol de molt baixa densitat (VLDL) i una disminució de la lipòlisis de triglicèrids circulants (41). Tot i que alguns subjectes amb obesitat poden presentar elevacions del colesterol LDL, aquesta no és característica de l'obesitat i està determinada principalment per factors genètics. Tot i això, les partícules de LDL en les persones obeses són més aterogèniques al tornar-se més petites i denses (41).

L'estudi Program on the Surgical Control of the Hyperlipidaemia (POSCH) publicat a la dècada dels 90 està considerat com un dels inicis de la cirurgia bariàtrica. El POSCH no va estudiar els efectes d'una cirurgia intestinal sobre el pes, sinó sobre el perfil lipídic i la morbiditat cardiovascular. Es tractava d'un estudi multincèntric i randomitzat que va incloure 838 pacients en prevenció cardiovascular secundària. La realització d'un bypass ileal parcial es va associar a un descens mantingut del colesterol LDL del 37,7% i a una reducció de esdeveniments cardiovasculars (42).

La pèrdua de pes amb el tractament convencional de l'obesitat (la dieta i l'exercici), s'associa a una reducció en la concentració de triglicèrids i una elevació del colesterol HDL, però en canvi no té efecte sobre el colesterol LDL (43, 44). En referència a la cirurgia bariàtrica, aquesta produeix una important milloria en la concentració de lípids (45-47). Així, el BGYRL produeix milloria de la dislipèmia en un 94% dels subjectes (12). Pocs estudis han estudiat l'efecte sobre el perfil lipídic del BGYRL en comparació amb tècniques restrictives, amb resultats contradictoris (48-50) , i cap ho ha fet específicament amb la GTL. A més a més són poc coneguts els factors que s'associen amb els canvis en la concentració de lípids després de la cirurgia bariàtrica.

1.7. Efectes de la cirurgia bariàtrica sobre la resistència a la insulina

El terme resistència a la insulina connota resistència dels efectes de la insulina sobre la captació, metabolisme i emmagatzemament de la glucosa. A més a més de les alteracions del perfil lipídic que han estat esmentades anteriorment, la resistència a la insulina juga un paper fonamental en la fisiopatologia de la DM2. La presència de resistència a la insulina obliga a les cèl·lules beta pancreàtiques a secretar de forma compensatòria més insulina per poder mantenir la glicèmia dintre de la normalitat. Aquesta hiperinsulinèmia mantinguda produeix al cap dels anys un esgotament progressiu de la funció de la cèl·lula beta fins al moment que és incapaç de compensar la resistència a la insulina i apareix la hiperglucèmia i per tant la DM2 (51).

El teixit greixos, sobretot en localització visceral, no actua únicament com un dipòsit energètic, sinó que funciona com un òrgan endocrinològic secretant àcids grassos, mediadors inflamatoris i adipoquines (52). Aquestes substàncies actuen tant a nivell de la cèl·lula beta pancreàtica com a altres teixits com el fetge o el múscul esquelètic produint un augment de la resistència a la insulina (53). Això explica la íntima relació fisiopatològica que existeix entre l'obesitat i la DM2 (54, 55). Les pèrdues de pes intencionades mitjançant dieta o exercici produeixen una milloria en els mediadors inflamatoris sistèmics i de la resistència a la insulina (56, 57).

Existeixen diferents mètodes per avaluar la resistència a la insulina. El mètode de referència és el clamp hiperinsulinèmic (58). Aquest consisteix en la infusió endovenosa d'insulina per mantenir una insulinèmia permanentment elevada. Simultàniament es van realitzant determinacions de glucosa cada 2-5 minuts per infondre glucosa a un ritme que permeti mantenir la glicèmia al voltant de 90 mg/dl. El ritme d'infusió de la glucosa és inversament proporcional a la resistència a la insulina. A causa als inconvenients tècnics i d'interpretació s'han desenvolupat mètodes més senzills. El Homeostatic Model Assesment (HOMA) és un model matemàtic basat en mesures basals de glicèmia i insulinèmia que permet valorar la resistència a la insulina (HOMA-IR) i la funció beta pancreàtica (HOMA-B). Els seus principals avantatges són la bona correlació amb mètodes més complexos com el clamp hiperinsulinèmic (59) i que s'ha usat de forma estesa des de fa més de 20 anys, fet que permet fer comparacions entre estudis (60). El HOMA presenta importants variacions ètniques i demogràfiques, i per tant cada població ha de definir el seu punt de tall diagnòstic de resistència a la insulina (61, 62). Cap estudi ha definit la taxa de remissió de resistència a la insulina després de la cirurgia bariàtrica establint un punt de tall de HOMA-IR específic per la població de referència.

Per altra banda existeix una gran heterogeneïtat a la hora de definir remissió de diabetis tipus 2. Un comitè d'experts de l'American Diabetes Association (ADA) l'any 2009 va definir uns criteris de remissió parcial i total que són més estrictes que els utilitzats prèviament (63). Fins al moment, pocs estudis han avaluat la taxa de remissió de la DM2 amb els nous criteris de la ADA, obtenint taxes de remissió inferiors a les reportades anteriorment (64).

Remissió parcial	Glicèmia plasmàtica <125 mg/dl HbA1c <6,5% Sense necessitat de tractament i mantingut almenys durant un any
Remissió completa	Glicèmia plasmàtica <100 mg/dl HbA1c <6,5% Sense necessitat de tractament i mantingut almenys durant un any
Remissió perllongada	Remissió completa durant almenys 5 anys

Criteris de remissió de la diabetis mellitus proposada comitè d'experts de l'ADA l'any 2009 (63)

2. OBJECTIUS

Hipòtesis de treball

- El BGYRL és superior a les tècniques restrictives en termes de pèrdua de pes i milloria de comorbiditats associades a l'obesitat.
- La GTL, tot i ser una tècnica restrictiva, produeix pèrdues de pes i una taxa de remissió de DM2 similars a BGYRL.
- La GTL pot ser igual d'eficaç que BGYRL en altres aspectes del metabolisme com el risc cardiovascular estimat, la remissió de la hipertensió arterial i la dislipèmia, la concentració de les lipoproteïnes i la resistència a la insulina.

Objectiu general

- Comparar els efectes metabòlics de la GTL i el BGYRL.

Objectius secundaris

- Estudiar l'efecte de la cirurgia bariàtrica sobre les escales de risc cardiovascular generals i les adaptades a població mediterrània.
- Comparar els efectes de dues tècniques de cirurgia bariàtrica (BGYRL i GTL) sobre:
    - El risc cardiovascular estimat amb les equacions de Framingham i REGICOR.
    - La taxa de remissió i de milloria de la dislipèmia i la hipertensió arterial.
    - El perfil lipídic, i estudiar els factors predictors de milloria de la concentració de lípids.
    - La taxa de remissió de la resistència a la insulina.

- La taxa de remissió total de DM2 amb els nous criteris de la ADA, i estudiar els factors associats amb aquesta remissió.

3. PUBLICACIONS

3.1.Laparoscopic sleeve gastrectomy and laparoscopic gastric bypass are equally effective for reduction of cardiovascular risk in severely obese patients at one year of follow-up.

David Benaiges, Albert Goday, José Manuel Ramón, Elisa Hernández, Manuel Pera, Juan Francisco Cano.

Laparoscopic Sleeve Gastrectomy and Laparoscopic Gastric Bypass are equally effective for reduction of cardiovascular risk in severely obese patients at 1 year follow-up.

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Original article

Laparoscopic sleeve gastrectomy and laparoscopic gastric bypass are equally effective for reduction of cardiovascular risk in severely obese patients at one year of follow-up

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Abstract

Background: Very few studies have compared laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) outcomes or analyzed improvement in cardiovascular risk (CVR) after bariatric surgery. None of the studies considered the Mediterranean population. Our primary objective was to compare the 10-year estimated CVR reduction achieved by LRYGB and LSG in Spanish subjects with severe obesity. The secondary objectives were to compare the techniques in terms of weight loss and co-morbidity improvement. The study was performed at a university hospital in Barcelona, Spain.

Methods: A 12-month prospective cohort study of 140 consecutive patients (95 LRYGB and 45 LSG) compared the 2 surgical intervention groups to study the percentage of excess weight loss, resolution and improvement/resolution of co-morbidities, and effect on CVR using both the Framingham risk score (FRS) and the Registre Gironí del Cor (REGICOR) model.

Results: At 12 months, the overall CVR decreased from 6.6% to 3.4% using the FRS and from 3.7% to 1.9% using the REGICOR score. Neither model found a difference between the 2 surgical intervention groups in decreased postoperative CVR risk, with a FRS of 3.4% ± 2.2% for LRYGB versus 3.3% ± 2.1% for LSG (P = .872) and a REGICOR score of 1.9% ± 1.5% versus 1.8% ± 1.6%, respectively (P = .813). No differences were observed in the percentage of excess weight loss or the resolution of type 2 diabetes mellitus and hypertension. The hypercholesterolemia improvement/resolution rate was lower in the LSG group than in the LRYGB group.

Conclusion: Bariatric surgery reduces the estimated CVR by one half at 1 year after surgery. Except for the less-improved cholesterol metabolism, LSG, a restrictive technique, proved to be equally as effective at 1 year of follow-up as LRYGB. (Surg Obes Relat Dis 2011;7:575–580.)

Keywords: Laparoscopic sleeve gastrectomy; Laparoscopic Roux-en-Y gastric bypass; Cardiovascular risk; Co-morbidities

In Spain, the incidence of obesity has increased alarmingly in recent years and is now estimated to have reached 14.5% [1]. Severe obesity is associated with a greater prevalence of co-morbidities (e.g., hypertension, type 2 diabetes mellitus [DM2], and dyslipidemia [2]). This leads to increased cardiovascular risk (CVR) [3] and greater mortality [4].

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Table 2
Comparison of demographic and preoperative clinical characteristics

Characteristic	LRYGB (n = 95)	LSG (n = 45)	P value
Age (yr)	46.1 ± 8.2	44.1 ± 9.8	.294
Women (%)	88.5	78.6	.133
Weight (kg)	121.1 ± 16.7	119.1 ± 18.8	.535
BMI (kg/m²)	46.2 ± 4.8	44.6 ± 5.5	.078
Hypertension	43 (45.3)	14 (31.1)	.111
1 antihypertensive agent (% hypertensive patients)*	20 (46.5)	9 (64.3)	.249
>1 antihypertensive agent (% hypertensive patients)	17 (39.5)	4 (29.6)	.460
Impaired fasting glucose	38 (40)	18 (44.4)	.853
Diabetes mellitus type 2	25 (26.3%)	7 (15.6%)	.159
Oral hypoglycemic agents†	11 (44.0%)	4 (57.1%)	.538
Insulin†	1 (4.0%)	1 (14%)	.320
HbA1c (%)	6.4 ± .8	6.0 ± .8	.291
Hypercholesterolemia	22 (23.2%)	12 (26.7%)	.400
Lipid-lowering agent‡	15 (68.2%)	9 (75.0%)	.665
Current smoking	23 (24.2%)	10 (22.2%)	.796

LRYGB = laparoscopic Roux-en-Y gastric bypass; LSG = laparoscopic sleeve gastrectomy; BMI = body mass index; HbA1c = hemoglobin A1c.

Data presented as mean ± standard deviation or numbers, with percentages in parentheses.

Significance at $P < .05$ was determined using Student's t test for continuous variables and chi-square for categorical variables.

* Data in parentheses are percentages of all patients with hypertension.

† Data in parentheses are percentages of all patients with diabetes.

‡ Data in parentheses are percentages of all patients with hypercholesterolemia.

The diagnostic, resolution, and improvement criteria for each co-morbidity are summarized in Table 1 [10,17–19].

The 10-year risk of cardiovascular disease was estimated using 2 models: the 1998 Framingham equation [10] and the REGICOR adaptation of the FRS for the Mediterranean population [11]. The risk factors included in the calculation were age, gender, total cholesterol level, high-density lipoprotein cholesterol level, diastolic and systolic blood pressure, DM2, and smoking. According to their total risk factor scores, the subjects were classified into 3 categories of estimated 10-year risk: low (<10%), intermediate (10–20%), and high (>20%).

The sample size was calculated, accepting an alpha risk of .05 and a beta risk of .20 in a 2-sided Student's t test. Thus, 48 subjects were required in the first group and 96 in the second to detect a statistically significant difference ≥ .5. The standard deviation was assumed to be 1.

The data are expressed as the average ± standard deviation for continuous variables and as percentages and frequencies for categorical variables. Significance at $P < .05$ was determined using the Student t test for continuous variables and the chi-square test for categorical variables. All statistical analysis used the Statistical Package for Social Sciences, for Windows, version 14.0 (SPSS, Chicago, IL).

Results

Of the 140 BS procedures performed during the study period, 95 (67.9%) were LRYGB and 45 (32.1%) were LSG. All patients were white, 82% were women, the average age was 45.4 ± 6.4 years, and the initial BMI was 45.7 ± 4.9 kg/m². DM2 was present in 25.5%, impaired fasting glucose in 46.1%, hypertension in 43.1%, and hypercholesterolemia in 35.7%.

At baseline, no differences were found between the 2 groups in age, gender, co-morbidity distribution and treatment, or the hemoglobin A1c of those with DM2 (Table 2). After surgery, both techniques significantly improved all the biochemical parameters studied, except for total and low-density lipoprotein cholesterol in the LSG group (Table 3). The follow-up rate was 100% of the cohort at 12 months.

Table 3
Baseline and 12-month clinical and laboratory measures

Variable	LRYGB (n = 95)			LSG (n = 45)			P value†
	Baseline	Follow-up	P value*	Baseline	Follow-up	P value*	
BMI (kg/m²)	46.2 ± 4.8	29.5 ± 4.1	<.001	44.6 ± 5.5	28.9 ± 3.6	<.001	.078
Venous blood glucose (mg/dL)	112.6 ± 29.7	88.5 ± 11.1	<.001	111.6 ± 37.4	88.7 ± 9.3	<.001	.749
HbA1c (%)	5.2 ± .7	4.6 ± .5	<.001	5.2 ± .8	4.9 ± .7	<.001	.497
Total cholesterol (mg/dL)	201.1 ± 35.6	176.5 ± 31.2	<.001	193.7 ± 33.9	200.6 ± 37.7	.142	.358
LDL cholesterol (mg/dL)	123 ± 29.5	102.0 ± 25.8	<.001	119.6 ± 33.0	117.4 ± 35.0	.708	.521
HDL cholesterol (mg/dL)	50.7 ± 12.5	59.5 ± 14.3	<.001	48.6 ± 9.0	63.1 ± 12.7	<.001	.328
Triglycerides (mg/dL)	134.0 ± 82.2	80.2 ± 27.9	<.001	132.6 ± 73.4	86.1 ± 35.1	<.001	.920
Systolic blood pressure (mm Hg)	131.9 ± 12.2	118.6 ± 16.7	.004	128.5 ± 12.9	113.4 ± 13.1	<.001	.163
Diastolic blood pressure (mm/Hg)	82.7 ± 12.4	74.4 ± 9.9	<.001	81.8. ± 9.5	71.9 ± 8.0	.001	.702

LDL = low-density lipoprotein; HDL = high-density lipoprotein; other abbreviations as in Table 2.

Significance at $P < .05$ determined using Student's t test.

* Within-technique comparison between baseline value and 1-year follow-up value.

† Comparison of 2 techniques at baseline.

Table 4
Baseline and 12-month cardiovascular estimated risk

Variable	LRYGB	LSG	P value
FRS (1998)			
Baseline (%)	6.9 ± 4.8	5.6 ± 5.0	.132
1-yr Follow-up (%)	3.3 ± 2.1	3.4 ± 2.2	.878
Absolute risk reduction (%)	3.6	2.2	
Relative risk reduction (%)	52.1	39.2	
REGICOR			
Baseline (%)	3.9 ± 2.6	3.2 ± 2.7	.139
1-yr Follow-up (%)	1.9 ± 1.5	1.8 ± 1.6	.813
Absolute risk reduction (%)	2	1.3	
Relative risk reduction (%)	51.2	40.6	

FRS = Framingham risk score; REGICOR = Registre Gironí del cor; other abbreviations as in Table 2.
Cardiovascular risk estimated using 2 risk scores: FRS and REGICOR scores.
Significance at $P < .05$ determined using Student's t test.

At 3 months of follow-up, the percentage of excess weight loss was significantly greater in the LSG group (50.6% ± 11.9% for LRYGB versus 58.3% ± 14.2% for LSG, $P = .017$). During the remaining follow-up period, the percentage of excess weight loss continued to increase, with no between-group differences at 6 months (68.5% ± 13.9% for LRYGB versus 72.0% ± 16.9% for LSG, $P = .602$) or 12 months (80.9% ± 16.7% for LRYGB versus 82.7% ± 18% for LSG, $P = .632$).

Before surgery, the 10-year CVR estimated by FRS was 6.55% ± 4.89%, significantly greater than the REGICOR score (3.75% ± 2.6%, $P < .001$). At 1 year after surgery, the risk assessment using the FRS showed a decrease to 3.34% ± 2.13%, an absolute CVR decline of 3.21% and a 49% decrease in relative risk. The corresponding REGICOR results were 1.92% ± 1.51%, 1.83%, and 48%. The number of patients presenting with low CVR was greater when estimated using REGICOR (80% with FRS versus 97.1% with REGICOR, $P < .001$), and FRS produced a greater number of intermediate-risk estimates (18% with FRS versus 2.9% with REGICOR, $P < .001$). REGICOR found no high-risk individuals and FRS identified only 2 (1.4%). At 12 months, the FRS equation found no patient presenting with high CVR and only 4 patients with intermediate risk; REGICOR identified 2 patients with intermediate risk. At 12 months, the CVR risk estimated by both formulas was comparable for both BS techniques (Table 4).

Hypertension resolved in 74.4% of the LRYGB patients and 64.3% of the LSG group ($P = .463$) and improved/resolved in 90.7% versus 78.6% ($P = .229$), respectively. The hypercholesterolemia improvement/resolution rate was 100% for LRYGB versus 75% for LSG ($P = .014$). Resolution itself was also greater with LRYGB, but the difference was not significant (86.4% versus 66.7%, $P = .174$). Impaired fasting glucose resolved in 97.3% of the LRYGB patients and 95.0% of the LSG group ($P = .589$). DM2 resolved in 96% and 85.7% of the LRYGB and LSG group, respectively ($P = .536$), and all patients with unresolved DM2 showed improvement. At 1 year after surgery, the prevalence of smokers had decreased to 17.1% (15.6% in the LSG group versus 18.3% in the LRYGB group, $P = .442$). The resolution of co-morbidities was gradual but was achieved in most cases at 3 months of follow-up (Fig. 1).

No difference was found in the perioperative complications rate between the 2 study groups (8.9% for LSG versus 16.8% for LRYGB, $P = .209$) nor in the readmission rate (2.2% for LSG versus 1.1% for LRYGB, $P = .586$). No mortality occurred in either group.

Discussion

At 12 months after surgery, LSG and LRYGB were equally effective in diminishing the estimated CVR, reducing weight, and resolving or improving the co-morbidities associated with obesity. Only hypercholesterolemia was significantly more improved by LRYGB than by LSG.

Various studies have analyzed the influence of BS on CVR and reported a preoperative FRS of 6–7% [12–14], very similar to the 6.6% in our series. These similar findings were probably because our cohort is representative of a normal BS cohort, with a female predominance, an average age of 45–50 years, and a DM2 prevalence of 35–50%.

CVR varies as a function of diet, lifestyle, and ethnic origin [20]. The Mediterranean region has lower CVR than northern Europe or the United States [21]. This has led to regional recalibrations of the FRS, such as the REGICOR model [11]. If we assume the REGICOR model is the best adapted model, the preoperative FRS would overestimate the CVR by 2.8% and the BS benefit would be lower, because although the CVR decreased by

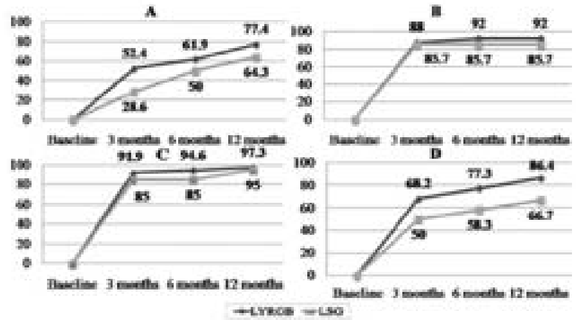

Fig. 1. Resolution of co-morbidities at 3, 6, and 12 months of follow-up in LSG and LRYGB groups. Data presented as percentage of patients achieving resolution criteria. (A) Resolution of hypertension during follow-up: LSG (n = 43 at baseline) and LRYGB (n = 41 at baseline). (B) Resolution of DM2 during follow-up: LSG (n = 7 at baseline) and LRYGB (n = 25 at baseline). (C) Resolution of impaired fasting glucose during follow-up: LSG (n = 12 at baseline) and LRYGB (n = 38 at baseline). (D) Resolution of hypercholesterolemia during follow-up: LSG (n = 12 at baseline) and LRYGB (n = 22 at baseline).

one half with both formulas, the estimated number of patients needed to treat to avoid a cardiovascular event at 10 years would be greater using the more accurate REGICOR model (54 versus 31).

Gastric bypass achieves an earlier [22] and a greater improvement in glucose metabolism than restrictive techniques. This is thought to be due to changes in intestinal hormones [23]. The LSG technique has been used as a first-step therapy when a malabsorptive technique is indicated in patients with super severe obesity [24]. Compared with LRYGB, it is a simpler and quicker technique [25]. Some studies have not found differences in the rate of postoperative complications [8,25,26], although a recent study by Birkmeyer et al. [27], including >15,000 BS subjects found that the rate of complications was lower in the LSG group. LSG has been shown to be more effective than other restrictive techniques in resolving DM2 [28] and that improved carbohydrate metabolism occurs early, just as it does with LRYGB [8,29]. The stomach resection done in LSG, in contrast to other restrictive techniques, could explain the greater decrease in ghrelin, a hormone with a diabetogenic effect, primarily secreted in the stomach [30].

At 1 year of follow-up, the only difference between the 2 techniques studied was no decline in total or low-density lipoprotein cholesterol after LSG, along with lower values than LYRGB for the resolution/improvement of hypercholesterolemia. Previous studies have reported contradictory findings [8,26]; therefore, additional studies are needed to clarify the effect of LSG on the cholesterol metabolism.

The present study had limitations. At 12 months of follow-up, the long-term progress is unknown. The patients were assigned to a surgical technique on the basis of clinical criteria, not randomly; nonetheless, both groups had comparable preoperative characteristics. In general, the diabetes cases were minor, with one half of patients receiving dietary treatment and only 2 requiring insulin therapy, and a mean hemoglobin A1c <6.5%, all of which could contribute to the nearly 100% resolution rate.

Conclusion

Our study has shown that LSG, a restrictive technique, achieves 12-month results comparable to LRYGB with respect to weight loss, CVR reduction, and improved comorbidity. Long-term studies are needed to confirm our results and to determine the actual decline in CVR after various bariatric surgical procedures in populations with a low risk of cardiovascular events. The large decrease in CVR contributes to the benefits of BS, outweighing the risk of the surgical procedure.

Disclosures

All authors declare no conflict of interest.

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3.2.Impact of restrictive (sleeve gastrectomy) vs hybrid bariatric surgery (Roux-en-Y gastric bypass) on lipid profile

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CLINICAL RESEARCH

Impact of Restrictive (Sleeve Gastrectomy) vs Hybrid Bariatric Surgery (Roux-en-Y Gastric Bypass) on Lipid Profile

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Abstract

Background Few studies have evaluated the impact of hybrid versus purely restrictive bariatric surgery on lipid profile, with the results being contradictory. The effect of laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) on lipid profile was compared.

Methods A nonrandomized prospective cohort study was conducted on severely obese patients undergoing bariatric surgery. Indication for the type of surgical procedure was based on clinical criteria. Patients on lipid-lowering drugs and those that could not be matched for age, sex, and body mass index were excluded. Finally, 51 patients who underwent LSG and 51 undergoing LRYGB completed this study.

Results During the first year post-surgery, no differences in percentage of excess weight loss and triglyceride reduction were found between groups. After LRYGR, low-density lipoprotein (LDL) cholesterol concentrations fell significantly (125.9±29.3 to 100.3±26.4 mg/dl, $p<0.001$), whereas no significant changes were observed in the LSG group (118.6±30.7 to 114.6±33.5 mg/dl, $p=0.220$). High-density lipoprotein (HDL) cholesterol increase was significantly greater after LSG (15.4±13.1 mg/dl) compared with LRYGB (9.4±14.0 mg/dl, $p=0.032$). Factors independently associated with LDL cholesterol reduction were higher baseline total cholesterol and undergoing LRYGB. A greater increase in HDL cholesterol was associated with LSG, older age, and baseline HDL cholesterol.

Conclusions LRYGB produces an overall improvement in lipid profile, with a clear benefit in all lipid fractions. Although LSG does not alter LDL cholesterol levels, its effect on HDL cholesterol is comparable to or greater than that obtained with malabsorptive techniques.

Keywords Laparoscopic sleeve gastrectomy · Laparoscopic Roux-en-Y gastric bypass · Lipid profile · Cholesterol · Triglyceride

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Introduction

Severe obesity is associated with an increased mortality rate, particularly of cardiovascular origin, due to the close association between obesity and cardiovascular risk factors such as type 2 diabetes, hypertension, and dyslipidaemia. In this respect, low high-density lipoprotein (HDL) cholesterol, hypertriglyceridaemia, and desirable to mildly increased low-density lipoprotein (LDL) cholesterol levels are frequently seen in obese patients [1].

Laparoscopic Roux-en-Y gastric bypass (LRYGB) is a hybrid technique that combines gastric restriction with gastrectomy and malabsorption by bypassing the duodenum and proximal jejunum. Given its higher efficacy compared to purely restrictive techniques and the fact that it offers a good balance between benefits and adverse event rate, it has become the gold standard and the most widely used [2, 3]. Laparoscopic sleeve gastrectomy (LSG) is a restrictive technique used as a first step for patients with extreme obesity (body mass index (BMI) >50 Kg/m^2) before they undergo a malabsorptive technique [4]. Owing to its technical simplicity [5], low complication rate [6], and greater efficiency compared with other purely restrictive techniques [7], the use of this procedure as a definitive technique is becoming more widespread [3, 8].

Both bariatric surgery procedures have yielded similar results in terms of weight loss, improved glucose metabolism, and cardiovascular risk reduction [9–13]. Although weight loss surgery results in significant improvements in serum lipid concentrations [14–16], few studies have compared the effect of hybrid versus purely restrictive procedures on lipid profile and, moreover, show contradictory results [17–20]. Thus, the aims of the present study were to compare the effect of two bariatric surgery techniques, LSG and LRYGB, on lipid profile during the first year of follow-up and analyze predictive factors for dyslipidemia improvement.

Materials and Methods

Study Protocol

A nonrandomized prospective cohort study was conducted on severely obese patients undergoing bariatric surgery at the Hospital del Mar, Barcelona. Patients were aged between 18 and 55 years and met the 1991 bariatric surgery criteria of the National Institutes of Health [21]. Indication for the type of surgical procedure (LSG or LRYGB) was based on clinical criteria and the consensus of the Bariatric Surgery Unit. Patients receiving lipid-lowering drugs and those who could not be matched for age (±2 years), sex, and BMI (±2 Kg/m^2) were excluded.

Sample size was calculated accepting an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided Student's *t* test; 45 subjects were required in each group to detect a difference ≥20 mg/dl in LDL cholesterol concentration as statistically significant. We assumed a standard deviation of 30 mg/dl and a loss rate of 20 % in the matching process and follow-up.

In accordance with the study protocol approved by the hospital ethics committee, all patients were evaluated preoperatively and at 3, 6, and 12 months post-surgery. Protocol appointments included measurements of weight, waist, and hip circumferences; blood pressure and laboratory testing for glucose; insulin; glycated hemoglobin (HbA_{1c}); total cholesterol; HDL cholesterol; and triglyceride levels. All patients signed their informed consent for the procedure and for the study.

Of the Caucasian patients, 167 were operated on between 2005 and 2009; of these, 61 underwent LSG and 106 LRYGB. Twenty-one patients (six of the LSG group and 15 of the LRYGB group) receiving lipid-lowering drugs and 44 patients (four of the LSG group and 40 of the LRYGB group) who could not be matched for age, sex, and BMI were excluded. Thus, the final analysis included 51 patients undergoing LSG and 51 LRYGB (Fig. 1).

Anthropometric and Biochemical Measurements

BMI was calculated as weight in kilograms divided by height in square meters. Type 2 diabetes was defined as two fasting plasma glucose values >125 mg/dl or treatment with oral hypoglycaemic agents or insulin [22]. The criteria for hypertension diagnosis were systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or current treatment with antihypertensive agents [23].

Total cholesterol and triglycerides were determined using enzymatic methods in a Cobas Mira automatic analyzer (Baxter Diagnostics AG, Düdingen, Switzerland). HDL cholesterol was measured using separation by precipitation with phosphotungstic acid and magnesium chloride. Glucose was determined by the oxidase method. HbA_{1c} was quantified by chromatography (Biosystem, Barcelona, Spain). Insulin was measured by radioimmunoassay (Insulin kit, DPC, Los Angeles, CA, USA) and insulin resistance was estimated using the Homeostasis Model Assessment for Insulin Sensitivity (HOMA-IR) [24]. LDL cholesterol concentration was calculated by the Friedewald formula [25].

Surgical Techniques

The LRYGB technique involved a 150-cm antecolic Roux limb with 25-mm circular pouch–jejunostomy and exclusion of 50 cm of the proximal jejunum. In LSG, the longitudinal resection of the stomach from the angle of His to approximately 5 cm proximal to the pylorus was performed using a 35 French bougie inserted along the lesser curvature. All operations were performed by the same team of surgeons.

Statistical Analysis

Data were expressed as mean±standard deviation for continuous variables and as percentages and frequencies for categorical variables. Student's *t* test was performed to assess differences between two means. Chi-square or Fisher's exact tests were used to evaluate the degree of association of categorical variables. Pearson's correlation coefficient was applied to establish correlations among quantitative variables. Multivariate linear regression analysis was used to assess the effects of multiple factors on lipid concentration variation. A p value<0.05 was considered statistically

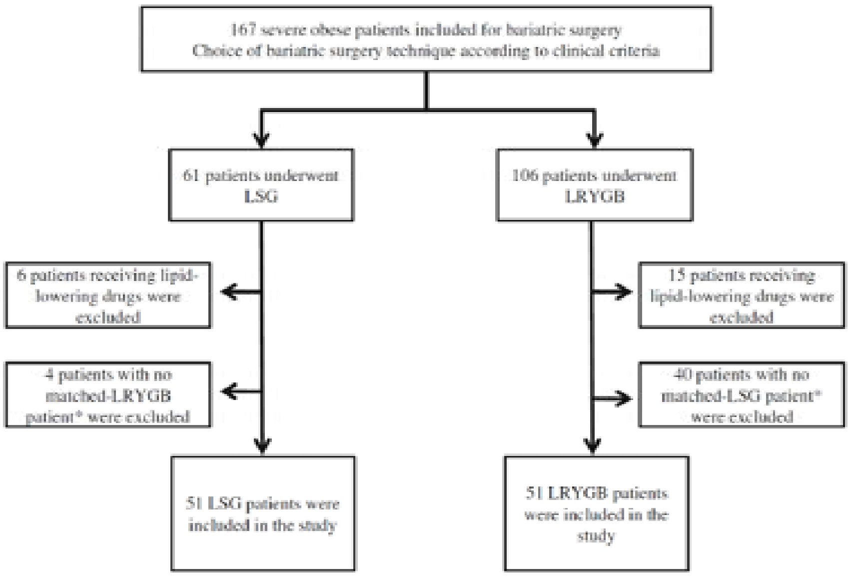

Fig. 1 Study flow diagram. *Asterisks* matched for age, sex and body mass index. *LSG* laparoscopic sleeve gastrectomy, *LRYGB* laparoscopic Roux-en-Y gastric bypass. No fatal cases or drop-outs were observed in this cohort

significant. The SPSS for Windows, version 14.0 was used for all statistical analyses.

Results

Baseline characteristics of LRYG or LSG patients are listed in Table 1. No differences were observed in the perioperative complication rate between surgical procedures (8.2 % LSG vs. 16.9 % LRYGB, $p=0.112$) or in the readmission rate (1.6 % LSG vs. 2.8 % LRYGB, $p=0.627$), with no fatal cases reported with either technique.

During the first year post-surgery, no differences in BMI and percentage of excess weight loss (EWL%) were found between groups (Table 2). Changes in lipid profile 1 year after surgery differed between the two study groups. After LRYGB, total and LDL cholesterol concentrations fell significantly whereas no significant changes were observed in the LSG group. Both techniques achieved a rise in HDL cholesterol levels; however, this increase was more marked after LSG. Triglyceride concentrations decreased similarly with both surgical procedures (Table 3). The effect of both techniques on cholesterol levels was apparent from the third month. At 6 months, the differences were maintained, except for HDL cholesterol (Fig. 2a–c). Changes in triglyceride concentrations during follow-up were comparable in both groups (Fig. 2d).

Factors independently associated with a greater decrease in total cholesterol concentration were younger age, higher baseline total cholesterol, and undergoing LRYGB. Predictive factors for LDL cholesterol lowering were the same as those for total cholesterol, except for age. However, a greater rise in HDL cholesterol was associated with older age and LSG, in addition to the HDL cholesterol concentration prior to surgery. Baseline triglyceride and HbA_{1c} levels were independently and positively associated with triglyceride lowering (Table 4).

Discussion

Dyslipidemia is a recognized cardiovascular risk factor that could explain, at least in part, the excessive mortality rate in severely obese patients [26]. The present study, the first to be prospectively designed to compare the effects of LRYGB and LSG on the lipid profile, shows that LRYGB improves overall lipid profile compared to LSG, since the latter was not associated with an improvement in LDL cholesterol levels.

The effect of bariatric surgery on total cholesterol concentrations obviously reflects the impact on their lipid fractions. In this respect, the 26 mg/dl mean decrease in total cholesterol after LGYGB concurs with previous studies [16–19] and is caused by a similar reduction in LDL cholesterol. However, no differences in total cholesterol levels have been reported previously after restrictive techniques [18, 27–29]. The slight increase in total cholesterol observed post-LSG in the present study could be explained by the significant increase in HDL cholesterol and the fact that LDL cholesterol levels remained stable.

The two surgical procedures differ mainly in their effect on LDL cholesterol. LSG does not alter LDL cholesterol concentration as has been described with other restrictive techniques [18, 26–28]. These data suggest that the decrease in LDL cholesterol observed for LRYGB could be related to

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Table 1 Baseline characteristics of patients undergoing LRYGB or LSG

	LRYGB (n=51)	LSG (n=51)	p value
Age (years)	44.7±8.6	44.5±8.8	0.892
Female/male	42/9	42/9	0.602
Weight (Kg)	121.2±19.9	119.6±18.6	0.686
Body mass index (Kg/m^2)	45.7±5.4	44.6±5.3	0.298
Waist circumference (cm)	131.9±11.8	126.9±14.5	0.227
Hip circumference (cm)	139.7±11.2	137.0±14.6	0.521
Waist-to-hip ratio	0.94±0.09	0.93±0.08	0.641
Systolic blood pressure (mmHg)	139.1±22.3	132.0±20.0	0.095
Diastolic blood pressure (mmHg)	87.1±13.3	83.5±10.7	0.139
Fasting glucose (mg/dl)	110.7±27.1	110.1±35.6	0.913
Insulin (mU/ml)	15.8±12.6	16.6±11.8	0.776
HOMA-IR	4.4±3.6	4.6±3.6	0.748
HbA_{1c} (%)	5.2±0.8	5.2±1.0	0.923
Total cholesterol (mg/dl)	201.2±36.4	191.6±36.0	0.184
HDL cholesterol (mg/dl)	50.3±12.0	48.3±10.1	0.394
LDL cholesterol (mg/dl)	125.9±29.3	118.6±30.7	0.233
Triglycerides (mg/dl)	125.3±64.8	120.0±56.7	0.674
Type 2 diabetes (%)	19.6	16.0	0.416
Hypertension (%)	47.1	30.0	0.060
Patients with total cholesterol >200 mg/dl (%)	49.0	37.3	0.159
Patients with LDL cholesterol >130 mg/dl (%)	41.2	29.4	0.150
Patients with HDL cholesterol <40 mg/dl for men and <50 mg/dl for women (%)	45.1	52.9	0.276
Patients with TG >150 mg/dl (%)	19.6	27.5	0.242

Data presented as mean±standard deviation or percentages. Significance at $p<0.05$ was determined using Student's t test for continuous variables and chi-square for categorical variables

HbA_{1c} glycated hemoglobin, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *TC* total cholesterol, *TG* triglycerides, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy

the malabsorptive effect produced by this technique. Several data support this hypothesis. First, Pihlajamaki et al [18] found, as expected based on observed weight loss, decreased serum levels of cholesterol synthesis markers after LRYGB or gastric banding; however, a reduction in cholesterol absorption markers was observed only after LRYGB, an effect not reported following a restrictive technique (gastric banding). Second, a relationship exists between the extent of intestinal bypass, which in turn relates to a reduced intestinal absorption area, and the effects on LDL cholesterol. This fact could explain the greater reduction (50 %) in LDL cholesterol levels seen after purely malabsorptive techniques such as biliopancreatic diversion [2, 28] compared to the 17–20 % described for LRYGB [16–18], a technique with a lower degree of malabsorption. Finally, it is noteworthy that the LDL cholesterol reduction after LRYGB was comparable to that obtained when ezetimibe, a selective inhibitor of intestinal cholesterol absorption, was administered [30]. On the other hand, secondary prevention patients of the Program on the Surgical Control of the Hyperlipidaemia study allocated to partial ileal bypass surgery showed an LDL cholesterol decrease of 37.7 %, along with improvement in cardiovascular endpoints [31, 32].

Most studies show an increase in HDL cholesterol after LRYGB [16–19, 33]. However, data from studies on restrictive techniques show contradictory results with respect to HDL

Table 2 Changes in body mass index and percentage of excess weight loss in severely obese patients after bariatric surgery

Months	BMI (Kg/m^2)			BWL (Kg)		
	LRYGB	LSG	p value	LRYGB	LSG	p value
3	35.0±4.1	33.5±4.1	0.080	30.0±11.3	29.4±10.6	0.799
6	31.6±4.1	30.7±4.4	0.324	39.0±12.8	38.1±12.0	0.730
12	29.1±4.1	28.5±4.4	0.504	45.0±14.3	43.6±13.0	0.601

Data presented as mean±standard deviation or percentages. Significance at $p<0.05$ was determined using Student's t test

BMI body mass index, *BWL* body weight loss

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Table 3 Changes in lipoprotein profile in severe obese patients after bariatric surgery

		Presurgery	12 Months	p Value[a]	Δ 12 Months (mg/dl)	p Value[b]	Δ 12 Monthss (%)	p Value[b]
Total cholesterol (mg/dl)	LRYGB	201.2±36.4	175.0±31.0	<0.001	−26.2±37.6	<0.001	−11.3±16.8	<0.001
	LSG	191.6±36.0	196.4±38.5	0.231	4.7±28.2		3.3±15.3	
LDL cholesterol (mg/dl)	LRYGB	125.9±29.3	100.3±26.4	<0.001	−26.5±31.6	0.001	−18.5±22.3	0.002
	LSG	118.6±30.7	114.6±33.5	0.220	−5.2±28.7		−2.1±27.7	
HDL cholesterol (mg/dl)	LRYGB	50.3±12.0	59.8±14.5	<0.001	9.4±14.0	0.032	22.2±29.5	0.030
	LSG	48.3±10.1	64.3±13.0	<0.001	15.4±13.1		36.7±35.6	
Triglycerides (mg/dl)	LRYGB	125.3±64.8	78.2±27.4	<0.001	−47.6±53.9	0.256	−28.9±31.3	0.293
	LSG	120.0±56.7	84.3±35.2	<0.001	−35.9±49.0		−22.4±31.1	

LDL low-density lipoproteins, *HDL* high-density lipoproteins, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy

[a] p Values for comparisons within study group

[b] p Values for comparisons between study groups

cholesterol changes [2, 16, 18, 32]. These discrepancies can be partly explained by the impact of the genetic polymorphism of HDL on the response after bariatric surgery [34]. Few studies have compared the effects of LSG and LRYGB on HDL cholesterol, with LSG showing similar efficacy to LRYGB in increasing HDL cholesterol [19]. In the present study, HDL cholesterol increased after both surgical procedures; however, surprisingly, this increase was more marked after LSG. In LSG, unlike other restrictive techniques, resection of the gastric fundus is performed, after which a reduction in ghrelin has been

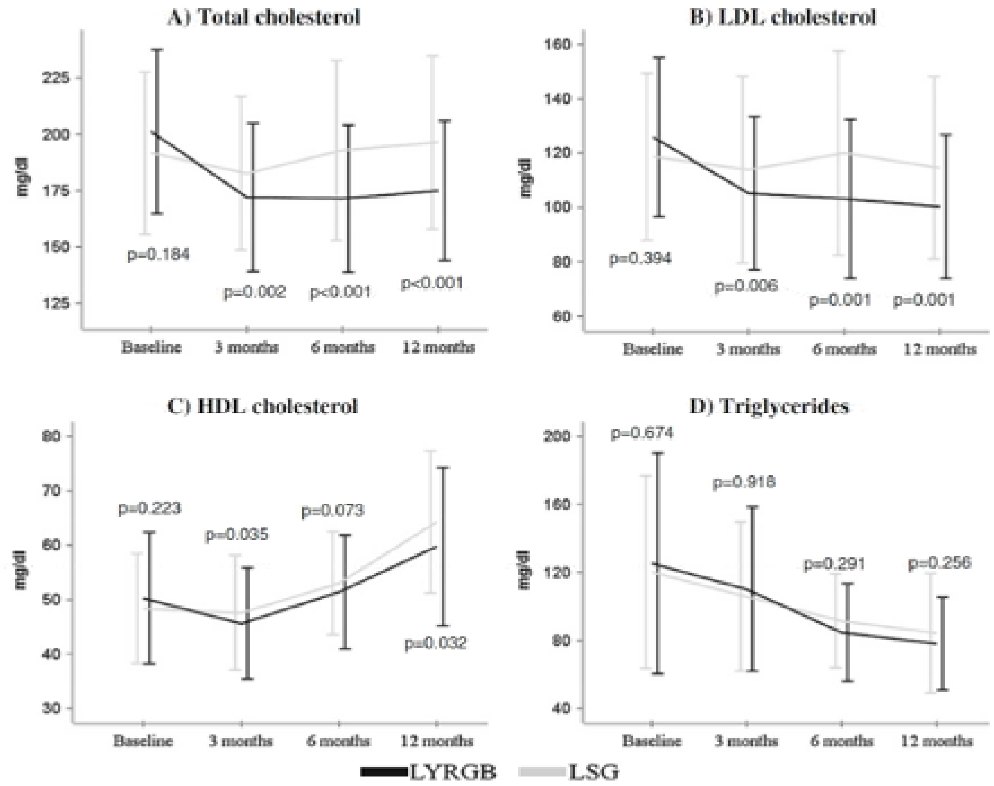

Fig. 2 Changes in lipoprotein concentrations (milligrams per deciliter) during 12 months follow-up after the bariatric surgical procedure. *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *LRYGB* laparoscopic Roux-en-Y gastric bypass, and *LSG* laparoscopic sleeve gastrectomy. Data are expressed as means (standard deviation). p values are for the differences respect baseline values between groups 3, 6, and 12 months. Significance at $p<0.05$ was determined using Student's t test

Table 4 Predictive factors for changes in lipid profile 12 months after surgery

Dependent variable	Independent variables	β (95 % CI)	*p* value	R^2
Δ Total cholesterol	Constant	−73.1 (−123.3 to −22.9)	0.005	0.425
	Baseline total cholesterol	0.5 (0.3 to 0.6)	<0.001	
	Surgical procedure (LRYGB)	25.6 (14.3 to 36.8)	0.004	
	BWL at 12 months	0.3 (−0.2 to 0.7)	0.276	
	Gender	−2.4 (−18.7 to 13.8)	0.764	
	Age	−0.8 (−1.4 to −0.1)	0.033	
Δ LDL cholesterol	Constant	−47.5 (−92.3 to −2.7)	0.038	0.359
	Baseline LDL cholesterol	0.5 (0.3 to 0.7)	<0.001	
	Surgical procedure (LRYGB)	15.9 (5.3 to 26.4)	0.004	
	BWL at 12 months	0.2 (−0.2 to 0.7)	0.320	
	Gender	2.8 (−12.4 to 18.0)	0.712	
	Age	−0.4 (−1.0 to 0.2)	0.190	
Δ HDL cholesterol	Constant	26.3 (10.5 to 42.2)	0.001	0.256
	Baseline HDL cholesterol	−0.6 (−0.7 to −0.3)	<0.001	
	Surgical procedure (LRYGB)	−5.0 (−9.9 to −0.1)	0.046	
	Gender	1.1 (−5.7 to 8.0)	0.738	
	Age	0.3 (0.1 to 0.6)	0.021	
Δ Triglycerides	Constant	−72.4 (−127.0 to −17.6)	0.010	0.767
	Baseline triglycerides	0.6 (−0.5 to 0.7)	<0.001	
	Surgical procedure (LRYGB)	9.2 (−1.3 to 19.8)	0.085	
	Type 2 diabetes	−17.3 (−38.2 to −3.6)	0.103	
	Baseline HbA_{1c}	12.7 (3.0 to 21.7)	0.010	
	Gender	−12.5 (−27.3 to −2.3)	0.097	
	Age	−0.5 (−1.1 to 0.1)	0.132	

Multivariate linear regression analysis to assess the effects of multiple factors on changes in lipid profile 12 months after surgery

BWL body weight loss, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *HbA_{1c}* glycated hemoglobin

described [9]. Some evidence points to a relationship between ghrelin and HDL metabolism, since the presence of certain single nucleotide polymorphisms in ghrelin may affect HDL cholesterol concentrations [35–37]. This fact, together with the effects of this hormone on satiety, glucose metabolism, and gastric filling [38], may explain the results obtained with LSG in this and other studies in terms of weight loss, diabetes remission, and HDL metabolism [9–11]. On the other hand, we want to emphasize that, regardless of the surgical procedure, the benefits on HDL cholesterol of bariatric surgery are equal to or even greater than those obtained with the available pharmacological strategies. Bariatric surgery results in a 30–40 % decrease in triglyceride concentration, regardless of the technique, as previously described [9, 16–19].

In the present study, after establishing the differing impact of both bariatric techniques on lipid profile, we went a step further by analyzing factors that may predict lipid response. The only factor associated with a reduction in LDL cholesterol was the type of surgical technique used, probably because malabsorption appears to play a basic role, and this can be achieved with LRYGB, but not with LSG. The correlation between older age and HDL cholesterol improvement concurs with the study of Dixon et al [26].

The main predictor of triglyceride reduction is HbA_{1c} level, regardless of diabetes status, insulin resistance, and baseline triglyceride concentrations. Bariatric surgery results in normalization of HOMA-IR and HbA_{1c} in most diabetic patients as well as in nondiabetic subjects [2]. These results suggest that patients with higher HbA_{1c} (although not meeting criteria for diabetes) and therefore with a lower beta cell response to insulin resistance, could achieve a greater reduction in triglyceride concentrations.

Although weight loss and calorie restriction may be important factors in dyslipidaemia improvement, the magnitude of BWL was not a predictor of lipid changes in the present study. Dixon et al [26] reported similar results and Brolin et al [39] found no differences in lipid profile between patients who maintained weight loss 5 years after surgery and those who regained weight.

Limitations of the present study are mainly related to the nonrandomized design, since patients were assigned to either technique according to clinical criteria. The low percentage of male patients in this study may have influenced the results. However, the sex distribution was similar to that reported in most studies [2, 26, 27]. Data on physical activity, dietary habits, alcohol consumption, or smoking cessation that could have beneficial effects on HDL cholesterol were not collected. We have minimized these limitations by matching both groups for age, sex, and BMI.

In conclusion, LRYGB, probably due to its malabsorptive effect, produces an overall improvement in lipid profile, with a clear benefit in all lipid fractions. Although LSG does not alter LDL cholesterol levels, its effect on HDL cholesterol, as occurs with weight loss and type 2 diabetes, is comparable to or greater than that obtained with malabsorptive techniques. These findings on the different effects of the surgical techniques on lipid profile could be useful in the decision process of the optimal surgical procedure in individual cases. Thus, from a lipid point of view, the presence of hypercholesterolaemia due to increased LDL cholesterol should be a criterion to take into account when considering LRYGB. In cases of atherogenic dyslipidaemia, LSG could be considered the first option.

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3.3. Sleeve gastrectomy and roux-en-Y gastric bypass are equally effective in correcting insulin resistance

David Benaiges,Juana Antonia Flores Le-Roux, Juan Pedro-Botet, Juan José Chillarón, Marine Renard, Alejandra Parri, Jose Manuel Ramón, Manuel Pera, Albert Goday.

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Original research

Sleeve gastrectomy and Roux-en-Y gastric bypass are equally effective in correcting insulin resistance

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ABSTRACT

Background: Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are associated with glucose metabolism improvement although data on insulin resistance remission rates after these procedures are lacking.
Aims: Primary aim was to compare insulin resistance remission rates achieved after LRYGB and LSG, using population-specific HOMA-IR cut-off points. Secondary objectives were to analyze factors associated with type 2 diabetes mellitus (T2DM) complete remission according to the new American Diabetes Association criteria and to examine changes in HOMA-B during follow-up.
Methods: Non-randomized, prospective cohort study of patients undergoing LRYGB or LSG with a minimal follow-up of 24 months. Patients on insulin therapy were excluded.
Results: At baseline, 56 (48.7%) of the 115 LRYGB group and 48 (61.5%) of the 78 LSG group had insulin resistance, and 29 (25.2%) and 20 (25.6%) T2DM, respectively. No differences were detected in insulin resistance remission rate (92.9% LRYGB and 87.5% LSG, $p = 0.355$) nor in T2DM complete remission at 2 years (62.1 vs 60% respectively, $p = 0.992$). Factors independently associated with T2DM complete remission were diabetes treatment and a greater decrease in 3-month HOMA-IR index. The HOMA-B index showed a progressive decline during follow-up.
Conclusion: Both surgical techniques are equally effective in achieving insulin resistance normalization in the majority of severely obese patients. Three-month HOMA-IR reduction after surgery was the main predictor of T2DM complete remission.

1. Introduction

In addition to weight loss, some bariatric procedures appear to have independent metabolic benefits associated with incretin effects and possibly other hormonal and neural mechanisms.[1] In this respect, laparoscopic sleeve gastrectomy (LSG) has yielded better results than other restrictive techniques in terms of weight loss and improved glucose metabolism[2] but similar or slightly inferior outcomes when compared with hybrid techniques such as laparoscopic Roux-en-Y gastric bypass (LRYGB).[3–5] Although the beneficial effects of bariatric surgery on glucose metabolism are known, data on insulin resistance remission rates after surgery are lacking. In clinical practice, insulin resistance and beta-cell function have been assessed over the last 20 years by the homeostatic model assessment (HOMA-IR and HOMA-B, respectively).[6] Despite a good correlation with the euglycemic hyperinsulinemic clamp method,[7] the HOMA-IR index varies widely among populations.[8,9] Therefore, specific cut-off points to define insulin resistance in each population should be established.

Given the terminological problems of "remission" versus "cure" and the great heterogeneity among studies in defining remission criteria for type 2 diabetes mellitus (T2DM), the American Diabetes Association (ADA) in 2009 defined and agreed the criteria for partial and complete remission that are stricter than those previously used.[10] Given the short time elapsed, scant studies have evaluated

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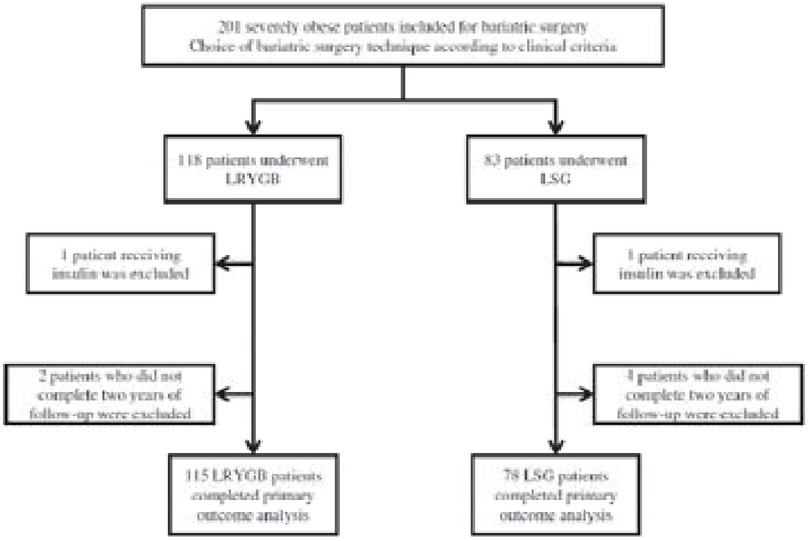

Fig. 1. Study flow diagram. LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass. No fatal cases were observed.

the remission rate of T2DM after bariatric surgery in obese diabetic patients with these new criteria.[5]

The primary aim of the present study was to compare insulin resistance remission rates achieved after LRYGB and LSG, using population-specific HOMA-IR cut-off points. Secondary objectives were to examine T2DM complete remission rates after both techniques according to the new ADA criteria and possible associated factors and to study changes in HOMA-B during follow-up.

2. Material and methods

2.1. Study protocol

A non-randomized, prospective cohort study was conducted on severely obese patients undergoing bariatric surgery at the Hospital del Mar, Barcelona. Patients were aged between 18 and 55 years and met the 1991 bariatric surgery criteria of the National Institutes of Health.[11] Indication for the type of surgical procedure (LRYGB or LSG) was based on clinical criteria and the consensus of the Hospital del Mar Bariatric Surgery Unit. In this respect, LSG was preferred in younger patients, in those with a BMI of 35–40, as a first-step treatment in cases with BMI>50 (although given the positive LSG outcomes none of these patients had to further undergo LRYGB), and when drug malabsorption was to be avoided. Patients who did not complete a minimum of 2 year-follow-up were excluded. Because insulinemia is included in the equation for HOMA index calculation, T2DM patients on insulin treatment were also excluded.

Table 1
Baseline characteristics of severely obese patients undergoing LRYGB or LSG with a minimum of two years of follow-up.

	LRYGB (n = 115)	LSG (n = 78)	p Value
Age (years)	45.0 ± 8.6	45.6 ± 8.7	0.640
Gender (% female)	87.8	76.9	0.037
Weight (Kg)	119.8 ± 15.8	119.3 ± 17.9	0.853
Body mass index (Kg/m^2)	45.8 ± 4.3	43.9 ± 5.0	0.006
Waist circumference (cm)	127.6 ± 11.0	125.0 ± 13.5	0.394
Fasting glucose (mg/dl)	110.2 ± 26.7	111.8 ± 27.2	0.691
Insulin (μU/ml)	14.7 ± 8.7	17.8 ± 14.1	0.066
HOMA-IR	4.1 ± 2.8	5.0 ± 4.1	0.075
HOMA-B	140.4 ± 133.1	153.5 ± 128.1	0.506
HbA_{1c} (%)	5.6 ± 0.8	5.7 ± 0.8	0.391
Insulin resistance (%)	56 (48.7)	48 (61.5)	0.054
Type 2 diabetes mellitus (%)	29 (25.2)	20 (25.6)	0.539

LRYG, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; HOMA, Homeostatic Model Assessment.
Data presented as mean ± standard deviation or percentages. Significance at $p < 0.05$ was determined using Student's t-test for continuous variables and chi-square for categorical variables.

Sample size was calculated accepting an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided Student's *t*-test; 65 subjects were required in each group to detect a difference ≥1 in the HOMA-IR index as statistically significant. A 3% patient loss rate during follow-up was expected and a 2 standard deviation was assumed.

In accordance with the study protocol approved by the hospital Ethics Committee, all patients were evaluated preoperatively and at 3, 6 and 12 months post-surgery and annually thereafter. Protocol appointments included measurements of weight, waist and hip circumferences, and laboratory tests including glucose, insulin and glycosylated hemoglobin (HbA_{1c}) determinations. T2DM pharmacological treatment was recorded at each visit. All patients signed their informed consent for the procedure and for the study.

Two hundred and one patients were operated on between January 2006 and June 2010; of these, 118 underwent LRYGB and 83 LSG. Two diabetic patients (1 of each group) receiving insulin, and 6 patients (2 of the LRYGB group and 4 of the LSG group) who did not complete a minimum of 2 years of follow-up were excluded. Thus, the final analysis included 115 patients undergoing LRYGB and 78 LSG (Fig. 1).

2.2. Anthropometric and biochemical measurements

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The percentage of excess weight loss (% EWL) was calculated based on the excess weight above ideal weight (weight corresponding to BMI of 25 kg/m^2). T2DM diagnosis was defined as two fasting plasma glucose concentrations above 125 mg/dl or HbA_{1c} ≥6.5% or treatment with oral hypoglycemic agents or insulin.[12]

Glucose was determined by the oxidase method. HbA_{1c} was quantified by chromatography (Biosystem, Barcelona, Spain). Insulin was measured by radioimmunoassay (Insulin kit, DPC, Los Angeles, USA). HOMA indexes were estimated using the following formulas[8]: HOMA-IR = insulin (μU/ml) × fasting glucose (mmol/l)/22.5 and HOMA-B = 20 × insulin (μU/ml)/(glucose (mmol/l) − 3.5).

In accordance with data from our population, the cut-off for the HOMA-IR index to define insulin resistance was a level ≥3.29.[5] Thus, HOMA <3.29 in patients not using insulin-sensitizing drugs (metformin or glitazones) was established as a criterion of insulin resistance normalization.

T2DM complete remission was defined based on the ADA consensus as a plasma glucose < 100 mg/dl with an HbA_{1c} < 6.0% without drug therapy maintained for at least one year.[10]

2.3. Surgical techniques

The LRYGB technique involved a 150-cm antecolic and antegastric Roux limb with 25-mm circular pouch-jejunostomy, with the exclusion of 50 cm of the proximal jejunum. In LSG, the longitudinal resection of the stomach from the angle of His to approximately 5 cm proximal to the pylorus was performed using a 36 French

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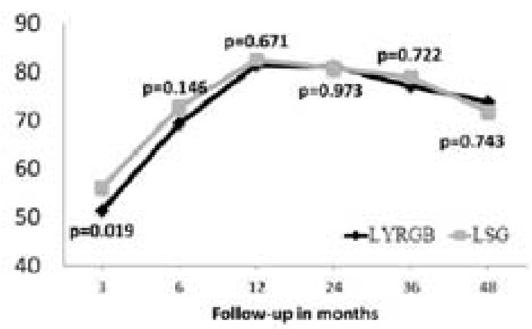

Fig. 2. Changes in percentage of excess weight loss during follow-up after the bariatric surgical procedure. LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy. Data are expressed as means. Significance at $p < 0.05$ was determined using Student's *t*-test.

bougie inserted along the lesser curvature. All operations were performed by the same team of surgeons.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables and as percentages and frequencies for categorical variables. Student's *t*-test was performed to assess differences between two means. Chi-square or Fisher exact tests were used to evaluate the degree of association of categorical variables. Logistic regression analysis was applied to assess the effects of multiple factors on the T2DM complete remission rate at two years post-bariatric surgery. A *p* value <0.05 was considered statistically significant. Statistical analysis was made with SPSS (version 14.0 for Windows; SPSS, Chicago, IL).

3. Results

All 193 patients of the study were Caucasian, with a mean age of 45.2 ± 8.7 years, baseline BMI of 45.0 ± 4.7 kg/m^2 and mean follow-up of 2.9 ± 0.9 years. Baseline characteristics of LRYGB and LSG patients are listed in Table 1. Patients in the LRYGB group differed from the LSG group in a higher proportion of women and BMI.

Progressive weight loss, more marked during the first 3 months in the LSG group, was observed in both groups during the first year of follow-up. Thereafter, weight loss remained stable and without differences between groups (Fig. 2).

At baseline, 56 (48.7%) patients of the LRYGB group and 48 (61.5%) of the LSG had insulin resistance. Three months after surgery, HOMA-IR had decreased dramatically in both groups (Fig. 3A), with a remission rate of 91.1% in the LRYGB patients and 91.7% in the LSG, $p = 0.914$. Insulin resistance remission rate achieved after 2 years of follow-up was 92.9% in LRYB group and 87.5% in LSG ($p = 0.355$). The HOMA-B index progressively decreased in both groups during follow-up; however, it was significantly higher in the LSG group at the second and third year post-bariatric surgery (Fig. 3B).

No differences were observed in baseline characteristics of T2DM patients between groups (Table 2). According to the applied bariatric surgery technique, no differences were found in the T2DM complete remission rate (62.1% for LRYGB and 60% for LSG, $p = 0.992$). Factors independently associated with T2DM complete remission were preoperative diabetes treatment with diet only, compared with oral drug treatment, and a greater decrease in HOMA-IR index values three months post-surgery (Table 3).

4. Discussion

The present study showed that two different bariatric surgery techniques, LRYGB and LSG, are equally effective in achieving insulin resistance normalization using a population-specific HOMA-IR cut-off.

Insulin resistance normalization was attained with both surgical techniques in almost all patients as early as 3 months after surgery. This finding suggests that weight loss was not the only factor responsible for the decline in HOMA-IR after bariatric surgery. Previous studies found that surgical techniques with a malabsorptive component like LRYGB produce a greater HOMA-IR reduction than that obtained after restrictive techniques such as vertical banded gastroplasty. Furthermore, this reduction occurred soon after the procedure, when significant weight loss had not yet been achieved.[1] These findings could be explained by changes in gut hormonal mechanisms, such as increased secretion of incretins that enhance insulin sensitivity.[13,14] In the present study, LSG, despite being a restrictive technique, produced an early improvement in insulin sensitivity of a similar magnitude to that achieved with LRYGB. A possible explanation for this finding could be related to the characteristics of the LSG technique. LSG includes a gastric fundus resection, unlike other restrictive techniques, that causes a decrease in ghrelin concentration, a hormone that produces insulin resistance.[15–17]

In the present study, all patients met the criteria for partial remission and approximately 60% for complete T2DM remission after a 2 year-follow-up. In other studies comparing LRYGB and LSG,

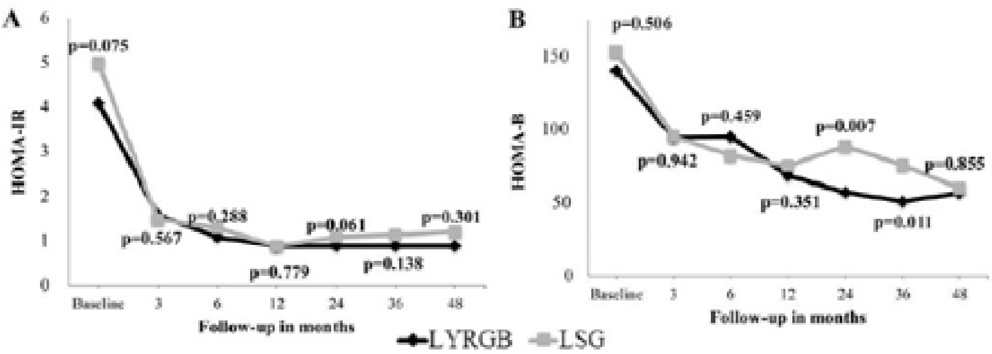

Fig. 3. Changes in HOMA during follow-up after the bariatric surgical procedure. A: Changes in HOMA-IR; B: Changes in HOMA-B. HOMA, homeostatic model assessment; HOMA-IR: Model to define insulin resistance, HOMA-B: Model to define beta-cell function; LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy. Data are expressed as means (standard deviation). Significance at $p < 0.05$ was determined using Student's *t*-test.

Table 2
Baseline characteristics of severely obese patients with type 2 diabetes mellitus undergoing LRYG or LSG with a minimum of two years of follow-up.

	LRYGB (n = 29)	LSG (n = 20)	p Value
Age (years)	49.2 ± 6.2	50.6 ± 7.4	0.488
Gender (% female)	79.3	75.0	0.492
Body mass index (Kg/m^2)	45.7 ± 4.6	45.6 ± 5.8	0.954
Treatment			
Diet alone (%)	16 (55.2)	7 (35)	0.164
Oral hypoglycemic drugs (%)	13 (44.8)	13 (65)	
Duration of diabetes (years)	1.3 ± 2.4	1.5 ± 2.5	0.746
Fasting glucose (mg/dl)	143.1 ± 31.0	150.0 ± 25.9	0.415
HbA_{1c} (%)	6.5 ± 0.8	6.9 ± 0.7	0.113
HOMA-IR	6.1 ± 3.3	7.6 ± 4.8	0.212
HOMA-B	123.0 ± 207.6	91.3 ± 81.9	0.553

HbA_{1c}, glycosylated hemoglobin; HOMA, Homeostatic Model Assesment.
Data presented as mean ± standard deviation or percentages. Significance at $p < 0.05$ was determined using Student's t test for continuous variables and Chi-square for categorical variables.

the overall remission rate of T2DM was above 80% with both techniques.[18–24] The lower T2DM remission rate found in the present study could be explained by at least two facts. First, in previous studies there was a wide heterogeneity in the criteria used for diabetes remission. In some studies, remission criteria were non-specified,[19,20,22] others only included diabetes medication withdrawal,[23,24] while others used HbA_{1c} <6.5% and fasting glucose <125 mg/dl once medication had been withdrawn.[18,21] And second, in addition to stricter biochemical criteria for T2DM remission (fasting glucose < 100 mg/dl and HbA_{1c} < 6.0%), the new ADA criteria require these biochemical parameters to be maintained for at least one year.[10]

In obese patients with short T2DM duration, such as those in our study population, insulin resistance predominates over beta-cell dysfunction.[25] Therefore, in these patients, enhancement of insulin sensitivity is a key factor for glucose metabolism improvement. This is consistent with the finding that HOMA-IR reduction 3 months post-surgery was a predictor of T2DM complete remission two years after the procedure. Moreover, the short duration of diabetes of the subjects included in this study may explain the lack of association of diabetes remision with other factors previously described such as waist circumference and T2DM duration.[26,27]

The HOMA-B index is a marker of pancreatic beta-cell function. In a healthy subject with a normal BMI and no family history of diabetes mellitus, the HOMA-B index is expected to be close to 100, indicating optimal beta-cell function (100%). Subjects in the present study had a mean baseline level above 100 that progressively decreased during follow-up. These results suggest that, preoperatively, beta cells in these patients had a compensatory hyperfunction and, after bariatric surgery, insulin resistance remission caused a decline in this compensatory insulin secretion, reflected in a reduction in the HOMA-B index. On the other hand, surgical techniques with a malabsorptive component cause an increase in hormones with an incretin effect. These hormones raise insulin secretion, but only in the postprandial period. Therefore, the HOMA-B index, which estimates beta-cell function in the fasting state, would not be the optimal method of evaluating postprandial insulin secretion improvement in these patients.[28]

The present study was not without limitations. First, patients were not randomly assigned to either of the bariatric surgery techniques and therefore the baseline characteristics of patients included in each group were not comparable. Second, diabetic patients included in the present study had a short disease duration, the majority did not require pharmacological treatment and those on insulin therapy were excluded. Therefore, the results found cannot be generalized to the whole diabetic population. Finally, insulin resistance was assessed using the HOMA-IR index; however, a more accurate method for quantifying insulin resistance, the euglycemic hyperinsulinemic clamp, was not used since it is invasive and time-consuming.

Table 3
Factors related to complete remission of type 2 diabetes mellitus two years after surgery. Odds ratio (OR) obtained by logistic regression analysis.

	OR	95% confidence interval	p Value
Age	0.91	0.78–1.06	0.217
Diet therapy alone	9.69	1.36–69.10	0.023
LRYGB	0.71	0.11–4.77	0.722
Decrease in HOMA-IR units at 3 months	1.31	1.01–1.70	0.045
% EWL at 3 months	1.07	0.99–1.14	0.60

LRYGB, laparoscopic Roux-en-Y gastric bypass; HOMA, Homeostatic Model Assessment; % EWL, percentage excess weight loss.

5. Conclusion

In conclusion, LRYGB and LSG are equally effective in achieving insulin resistance normalization in almost all patients. Furthermore, both techniques achieved similar T2DM complete remission rates and HOMA-IR reduction at 3 months after surgery was the main predictor. The HOMA-B index should be carefully interpreted in these patients.

Ethical approval

Study protocol was approved by the hospital del mar (Barcelona) Ethics Committee.

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None.

Author contribution

BD contributed for the study design, data collection, data analysis and writing.

FLRJA contributed for the study design and writing.

PBJ contributed for the data analysis and writing.

CJJ contributed for the data analysis and writing.

RM contributed for the data collection.

PA contributed for the data collection.

RJM contributed for the study design.

PM contributed for the study design.

GA contributed for the study design, data analysis and writing.

Conflict of interest

The authors declare no potential conflicts of interest relevant to this article.

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4. DISCUSSIÓ

La realització i finalització d'aquest projecte d'investigació ha permès conèixer alguns dels efectes metabòlics de la GTL, mitjançant la comparació amb l'actual tècnica de referència, el BGYRL. Ambdues tècniques produeixen una similar pèrdua de pes, disminució del risc cardiovascular estimat i de la concentració de triglicèrids, i remissió de la DM 2, la hipertensió arterial i la resistència a la insulina. En canvi, s'han detectat diferències en la evolució postoperatòria de la concentració dels colesterols total, LDL i HDL. A més a més, s'han obtingut resultats sobre quina és la taxa de remissió total de la DM2 amb els nous criteris de la ADA. Per últim s'ha avaluat quins factors es relacionen amb la remissió de la DM2 i amb els canvis del perfil lipídic.

Com s'ha exposat anteriorment la superioritat del BGYRL a les tècniques restrictives clàssiques com la gastroplastia vertical anellada, es deu en part a mecanismes hormonals intestinals (16-18). El fet que una tècnica restrictiva és mostri igual d'eficaç que el BGYRL, fa pensar que amb la realització d'una GTL també està implicat algun mecanisme hormonal. L'explicació sembla trobar-se en diferències tècniques entre les cirurgies restrictives. La restricció gàstrica amb altres tècniques restrictives com la gastropastia vertical anellada es realitza mitjançant unes sutures sobre l'estómac sense realitzar cap resecció. En canvi amb la GTL es realitza una resecció principalment de l'antre gàstric. En aquesta localització és on es produeix la ghrelina, una hormona amb efecte diabetògen i que augmenta l'apetit (65). Recentment varis autors, incloent el nostre grup, han descrit un descens d'aquesta hormona després de la GTL (24, 66) donant suport a aquesta hipòtesis.

En el primer dels treballs publicats, s'ha observat un important descens en el risc cardiovascular estimat un any després de la cirurgia bariàtrica. Aquest descens s'explica per la milloria de varies variables incloses en la fórmula. Així, s'ha produït un descens en el colesterol total, i les pressions arterials, un augment del colesterol HDL i una resolució de la malaltia en pràcticament tots els subjectes amb DM2.

Existeixen unes remarcables diferències segons la fórmula utilitzada per estimar el risc cardiovascular. Així, abans de la cirurgia el risc cardiovascular estimat amb la fórmula de Framingham és del 6,55%, similar al d'altres estudis amb població americana (34-37). En canvi amb el model REGICOR és del 3,75%. Per tant, si assumim que el model REGICOR és el més adequat per a la nostra població, el risc cardiovascular estaria sobreestimat un 2,8% amb la fórmula de Framingham. Per altra banda, tot i que amb els 2 models es produeix un descens relatiu al voltant del 50%, el descens absolut és major amb el model Framingham (3,2% vs 1,8%). Per tant, els beneficis de la cirurgia bariàtrica són menors usant el model REGICOR, ja que el nombre de pacients a tractar per evitar un esdeveniment cardiovascular a 10 anys són majors (54 vs 31).

Aquest millor perfil cardiovascular en població mediterrània es pot explicar en part per la dieta mediterrània. Aquesta és una dieta rica en vegetals, fruites, fruits secs, peix, carn blanca i oli d'oliva. Recentment l'estudi PREDIMED ha mostrat una reducció en el desenvolupament d'esdeveniments cardiovasculars amb la dieta mediterrània en comparació amb una dieta baixa en greixos (67).

No s’han detectat diferències entre les tècniques en la evolució del risc cardiovascular. Totes 2 tècniques presenten un any després de la cirurgia un risc cardiovascular al voltant del 3,5% amb la fórmula de Framingham i del 2% amb el model REGICOR. Tot i això cal destacar que el descens del risc cardiovascular és major amb el BGYRL encara que les diferències no han estat significatives. Una possible explicació a aquest fet és el major descens dels colesterols total i LDL i la major taxa de milloria de la dislipèmia amb el BGYRL.

L’estudi publicat posteriorment a la revista *Obesity Surgery* ha permès conèixer amb més profunditat els canvis en el perfil lipídic durant l’any posterior a la realització de les 2 tècniques de cirurgia bariàtrica.

No s’han detectat diferències en el descens dels triglicèrids durant l’any posterior a la cirurgia al comparar les dues tècniques. La seva concentració ha disminuït progressivament i de forma similar a altres estudis, assolint als 12 mesos un descens entre el 30 i el 40% (45-49). El descens en la concentració dels triglicèrids durant el seguiment s’ha associat amb un major valor inicial de la HbA1c, independentment del diagnòstic de diabetis i de la resistència a la insulina. Són ben coneguts per una banda la estreta relació entre el metabolisme de la glucosa i el dels triglicèrids, i per altra banda que després de la cirurgia bariàtrica la A1c baixa a pràcticament tots els subjectes independentment de si tenen o no diabetis (12). Tenint en compte aquests dos factors, els resultats obtinguts suggereixen que aquells subjectes amb una major A1c, i per tant amb una menor resposta de la cèl·lula beta a la resistència a la insulina, poden tenir un major potencial per disminuir la concentració de triglicèrids.

La principal diferència en la resposta del lípids entre les dues tècniques ha estat l'evolució en el colesterol LDL. Per una banda, la seva concentració ha baixat de forma important després del BGYRL i en canvi per altra banda s'ha mantingut estable després de la GTL. El fet que la concentració del colesterol LDL no variï després de GTL al igual que després d'altres tècniques restrictives (48-50, 69, 69), fa pensar que la malabsorció produïda per la tècnica quirúrgica és un factor determinant, i que en canvi els factors hormonals intestinals no hi juguen un paper important. Hi ha diversos arguments que suporten aquesta hipòtesi. En primer lloc, s'ha observat que com major és la malabsorció de la tècnica quirúrgica major és el descens del colesterol LDL. D'aquesta manera, el descens del 50% en el colesterol LDL després d'una tècnica amb un gran component malabsortiu com la derivació biliopancreàtica (12, 70) és molt superior al 17-20% observat després de BGYRL (45-47). En segon lloc, Pihlajamaki *et al* va descriure que després d'un BGYRL disminueixen els marcador sèrics d'absorció de colesterol, a diferència del que passa després d'una banda gàstrica (50). Per últim, cal destacar que el descens en el colesterol LDL és similar al que es produeix amb l'ezetimibe, un inhibidor selectiu de l'absorció intestinal de colesterol (71). A part de la tècnica quirúrgica, no s'ha detectat cap altre factor associat al descens del colesterol LDL durant el seguiment.

Un dels resultats més remarcables d'aquest treball ha estat la evolució del colesterol HDL després de la cirurgia bariàtrica. S'ha observatque el colesterol HDL augmenta després de les dues tècniques, però que ho fa de forma més important després de la GTL. L'augment del colesterol HDL després de BGYRL està ben documentat a la literatura (45-47). En canvi després de tècniques restrictives els resultats són contradictoris i, en general, es mostren menys eficaces que el BGYRL (48-50, 72). El fet que la GTL es mostri com a mínim igual d'eficaç que el BGYRL podria estar causat també pel descens de la ghrelina després de la cirurgia. En aquest sentit, s'ha descrit que alguns polimorfismes de nucleòtids simples de la ghrelina poden influenciar en el metabolisme del colesterol HDL (73, 74). A més a més de la tècnica quirúrgica, l'augment amb la concentració del colesterol HDL s'associa de forma directament proporcional amb la edat, dada que coincideix amb l'estudi de Dixon *et al* (69).

L'evolució del colesterol total s'explica pels canvis en les diferents fraccions, els colesterols LDL i HDL. Així, el descens després del BGYRL es deu principalment a l'important descens del colesterol LDL. En canvi, l'augment (tot i que no assoleix la significació) després de la GTL s'explica per fet que el colesterol HDL augmenta i en canvi el colesterol LDL es manté estable.

Tot i que altres treballs ja han estudiat els efectes de les dues tècniques sobre el metabolisme de la glucosa i la resistència a la insulina (45-48), aquest projecte d'investigació ha detectat resultats destacables i que aporten novetats en el coneixement d'aquesta àrea.

Aquest estudi ha estat el primer en determinar la taxa de remissió de la resistència a la insulina, establint el punt de tall del HOMA-IR que defineix resistència a la insulina per a la població de l'estudi. Totes dues tècniques produeixen un descens profund i precoç en el HOMA-IR, de forma que als 3 mesos pràcticament tots els subjectes presenten remissió de la resistència a la insulina. El descens del HOMA-IR després de tècniques restrictives diferents a la GTL es produeix de forma més gradual i en relació directa amb la pèrdua de pes (75). L'augment de la secreció d'hormones amb efecte incretina després del BGYRL (76, 77) i el descens de la ghrelina després de la GTL poden explicar aquest descens brusc en el índex HOMA-IR després de les dues cirurgies (66).

El HOMA-B és un marcador de la funció de les cèl·lules beta pancreàtiques. Així, un subjecte sa sense sobrepès ni antecedents familiars de diabetis ha de presentar un HOMA-B de 100, indicant que la funció de beta pancreàtica és del 100%. Els subjectes amb obesitat greu inclosos a l'estudi presenten abans de la cirurgia un índex HOMA-B superior a 100. Això suggereix que les cèl·lules beta estan hiperfuncionant per intentar compensar la resistència a la insulina que presenten les persones amb obesitat. La remissió en la resistència a la insulina després de la cirurgia, explicaria el descens del HOMA-B, ja que no seria necessària aquesta hipersecreció d'insulina. Tot i això, la secreció hormones amb efecte incretina després del BGYRL faria esperar un augment de la funció beta i per tant de l'índex HOMA-B. Tot i això el HOMA-B estima la funció beta pancreàtica en dejú i en canvi aquestes hormones milloren la secreció d'insulina al període postprandial (78).

Clàssicament ha existit una gran heterogeneïtat per definir remissió de DM2. Així, alguns autors no defineixen els criteris (79, 80), alguns ho defineixen únicament per la retirada de medicació (81, 82) i altres utilitzen diferents punts de tall d'HbA1c i glicèmia plasmàtica basal (64, 83). Per intentar solucionar aquest problema un grup d'experts de la ADA va definir l'any 2009 uns criteris de remissió total i parcial (63). Aquests criteris són més estrictes que els utilitzats en la majoria d'estudis ja que, per una banda, marquen uns punts de tall més baixos i, per altra banda, exigeixen que aquests objectius metabòlics es mantinguin com a mínim durant un any. La taxa de remissió de diabetis ha estat avaluada a dos dels treballs publicats utilitzant diferents criteris de remissió. Al primer, s'ha obtingut una taxa de remissió del 90%, definint remissió com una glicèmia <126 mg/dl i una HbA1c <6% sense necessitat de tractaments hipoglucemiants. En canvi a l'article publicat a la revista *International Journal of Obesity* utilitzant els criteris nous de la ADA la remissió total és destacadament inferior amb un valor d'aproximadament el 60%. Actualment s'accepta que la remissió de la DM2 després de la GTL i el BGYRL és superior al 80%, com es desprèn de la majoria d'estudis que comparen aquestes tècniques quirúrgiques (23, 25, 83). Tot i això, l'ús generalitzat dels criteris de la ADA en publicacions futures pot condicionar un descens en la taxa de remissió de DM2 acceptada fins a l'actualitat.

Alguns treballs han avaluat quins són els factors que s'associen a remissió de DM2 durant el seguiment (84, 85). En un dels estudis més destacats, Dixon *et al* (86), va descriure que la remissió de DM2 s'associa a un temps d'evolució de la DM2 menor a 4anys, un IMC major a 35Kg/m^2 i un pèptid C superior a 2,9ng/ml. Aquests resultats suggereixen que aquells subjectes amb una DM2 amb una major conservació de la funció secretora d'insulina, són els que es poden beneficiar més de la cirurgia bariàtrica. En canvi, al present estudi l'únic factor que s'ha associat amb la remissió de DM2 ha estat el descens del HOMA-IR tres mesos després de la cirurgia. Aquest resultat es pot explicar pel fet que els pacients amb DM2 de la nostra cohort presenten una evolució de la diabetis d'aproximadament 1 any i mig. En la fisiopatologia de la DM2, als pacients amb una curta evolució de la malaltia predomina la resistència a la insulina per sobre de la disfunció de la cèl·lula beta (87). I per tant, la milloria en la sensibilitat a la insulina ha de ser un factor clau en la milloria del metabolisme hidrocarbonat.

S'ha de reconèixer que el present projecte d'investigació no està exempt de limitacions. En primer lloc cal destacar que tot i ser un estudi prospectiu, l'assignació dels pacients no s'ha realitzat de forma aleatoritzada sinó que s'han utilitzat criteris clínics i consensuats per la unitat de cirurgia bariàtrica de l'hospital del Mar. Així, en l'elecció de la GTL s'ha seguit uns criteris similars als proposats per Tucker *et al* (22): subjectes joves, aquells amb IMC entre 35 i 40 Kg/m^2, com una cirurgia de primera fase en aquells amb un IMC >50kg/m^2 (tot i que donats els bon resultats obtinguts amb la GTL, cap subjecte ha requerit un posterior BGYRL) o quan ha existit la possibilitat de malabsorció de fàrmacs. Tot i això, cal destacar que no s'han detectat diferències significatives entre els grups al treball publicat a *Surgery for Obesity and Related Diseases* i que únicament hi ha hagut diferències en la distribució del sexe a l'estudi publicat a *International Journal of Surgery*. Coneixent la influència que poden tenir el sexe, la edat i el IMC en el metabolisme dels lípids, a l'estudi publicat a *Obesity Surgery* s'ha optat per aparellar els subjectes per aquestes tres característiques.

És remarcable també que el seguiment es limita als primers 12-24 mesos després de la cirurgia. Per tant es desconeix si la igualtat en la eficàcia de la GTL respecte a BGYRL en molts aspectes es manté a llarg termini.

No s'han recollit dades sobre activitat física, hàbits alimentaris, consum d'alcohol i abstinència en el consum de tabac. Aquests són factors poden influenciar en diferents aspectes del metabolisme de la glucosa i dels lípids.

Per a la determinació de la resistència a la insulina no s'han utilitzat mètodes altament precisos com el clam hiperinsulinèmic. S'ha optat per l'ús del HOMA-IR perquè és menys invasiu, consumeix menys temps, està validat per a la nostra població (62) i perquè, com que el seu ús està àmpliament estès, es poden comparar els resultats amb els obtinguts per altres estudis.

Per últim cal destacar que els pacients amb DM2 inclosos a l'anàlisi poden ser catalogats com amb "diabetis mellitus lleus", ja que presenten una curta evolució de la malaltia, presenten un bon control metabòlic i la majoria no requereixen tractament farmacològic. Per tant, els resultats obtinguts no es poden extrapolar a la resta de població amb DM2. En aquest sentit cal destacar que els subjectes han estat controlats per una unitat de cirurgia bariàtrica i no de cirurgia metabòlica. La cirurgia metabòlica és un concepte que ha emergit els últims anys arrel dels efectes més enllà de la pèrdua de pes que produeix la cirurgia bariàtrica. La indicació de la cirurgia es realitza amb l'objectiu de controlar les malalties metabòliques i no només per perdre pes (88, 89).

5. CONCLUSIONS

D'acord amb els objectius específics plantejats a l'inici d'aquest projecte d'investigació que compara els efectes de la GTL i el BGYRL 12-24 mesos després de la intervenció quirúrgica, les conclusions pertinents són les següents:

Després de 12 mesos de la cirurgia, la GTL i el BGYRL produeixen un descens comparable en el risc cardiovascular estimat tant amb la fórmula de Framingham com amb la de REGICOR. L'ús del model de Framingham en la nostra població pot sobreestimar els beneficis de la cirurgia bariàtrica sobre el risc cardiovascular. Per tant l'ús del model REGICOR podria resultar de major utilitat a la nostra població.

No es detecten diferències entre les dues tècniques en la taxa de remissió de la hipertensió arterial 12 mesos després de la cirurgia. La milloria o remissió de la dislipèmia és menor amb la GTL.

Un any després de la intervenció, el BGYRL produeix una milloria global en el perfil lipídic (descens del colesterol total, colesterol LDL i triglicèrids amb augment del colesterol HDL). En canvi, la GTL no altera les concentracions de colesterol LDL i s'associa a un major augment en el colesterol HDL que el BGYRL.

Els predictors en la milloria de les concentracions de lípids són la realització d'un BGYRL per al colesterol LDL; una major edat i la realització d'una GTL per al colesterol HDL; i els nivells inicials de HbA1c per als triglicèrids.

La remissió de la resistència a la insulina s'assoleix en la pràctica totalitat de subjectes intervinguts, tant amb BGYRL com amb GTL. La remissió s'aconsegueix de forma precoç als 3 mesos, i es manté 24 mesos després de la intervenció.

Aquest descens del HOMA-IR tres mesos després de la cirurgia s'associa amb la remissió de DM2, a la nostra cohort de subjectes amb curta evolució de la DM2. Les dues tècniques es mostren igual d'eficaces en assolir remissió total de la DM2 amb els nous criteris de la ADA als dos anys de seguiment.

Els resultats globals obtinguts al present projecte d'investigació han aportat una important informació que pot ser utilitzada en la pràctica clínica a l'hora d'elegir la tècnica de cirurgia bariàtrica. La milloria del colesterol LDL s'aconsegueix únicament amb el BGYRL. Per altra banda la GTL és una tècnica amb major simplicitat tècnica i menor taxa de complicacions postquirúrgiques (20, 21). Tenint en compte aquests dos fets, el BGYRL podria estar sobretot en aquells subjectes amb un major colesterol LDL i la GTL podria substituir el BGYRL com a tècnica de referència. Tot i això, són necessaris estudis que avaluïn la eficàcia de la GTL a llarg termini.

6. FUTURES INVESTIGACIONS

Futures investigacions

La principal investigació de futur serà determinar si els beneficis de la GTL es mantenen equiparables al BGYRL a llarg termini. Estudis recents semblen mostrar que a partir dels 18 mesos després de la GTL s'observa una lleugera recuperació de pes, però que aquesta és similar a la del BGYRL (90, 91). Falten estudis que constatin els efectes metabòlics de la GTL a llarg termini.

S'han detectat importants diferències en la reducció del risc cardiovascular entre els models Framingham i REGICOR. Per tal de poder determinar quin dels dos models prediu millor el desenvolupament de malaltia cardiovascular en subjectes mediterranis amb obesitat mòrbida sotmesos a cirurgia bariàtrica, seria necessari seguir aquests subjectes durant 10 anys per tal de determinar la incidència real de malaltia cardiovascular.

Un dels resultats destacables d'aquest projecte han estat les importants diferències observades segons el criteri utilitzat per definir remissió de DM2. Actualment s'està analitzant la taxa de remissió de DM2 després de la cirurgia bariàtrica, comparant el criteris més utilitzats els últims anys amb els criteris que ha proposat la ADA, el quals s'han d'imposar com els criteris a utilitzar en tots els estudis futurs.

Per últim, s'investigarà l'efecte de les diferents tècniques de cirurgia bariàtrica sobre un grup de subjectes amb obesitat definits com a obesos metabòlicament sans (92,93). Es tracta de subjectes amb obesitat, però que a diferència de la majoria de persones amb obesitat no presenten resistència a la insulina ni comorbiditats.

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