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Original Article

Efficacy of Intragastric Balloons in the Markers of Metabolic Dysfunction-associated Fatty Liver Disease: Results from Meta-analyses

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Abstract

Background and Aims: Nonalcoholic fatty liver disease, now renamed metabolic dysfunction-associated fatty liver disease (MAFLD), is common in obese patients. Intragastric balloon (IGB), an obesity management tool with low complication risk, might be used in MAFLD treatment but there is still unexplained heterogeneity in results across studies. ***Methods:*** We conducted a systematic search of 152 citations published up to September 2020. Meta-analyses, stratified analyses, and meta-regression were performed to evaluate the efficacy of IGB on homeostasis model assessment of insulin resistance (HOMA-IR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT), and to identify patients most appropriate for IGB therapy. ***Results:*** Thirteen observational studies and one randomized controlled trial met the inclusion criteria (624 participants in total). In the overall estimate, IGB therapy significantly improved the serum markers change from baseline to follow-up [HOMA-IR: 1.56, 95% confidence interval (CI)=1.16–1.95; ALT: 11.53 U/L, 95% CI=7.10–15.96; AST: 6.79 U/L, 95% CI=1.69–11.90; GGT: 10.54 U/L, 95% CI=6.32–14.75]. In the stratified analysis, there were trends among participants with advanced age having less change in HOMA-IR (1.07 *vs.* 1.82). The improvement of insulin resistance and liver biochemistries with swallowable IGB therapy was no worse than that with endoscopic IGB. Multivariate meta-regression analyses showed that greater HOMA-IR loss was predicted by younger age (p=0.0107). Furthermore, effectiveness on ALT and GGT was predicted by basal ALT (p=0.0004) and GGT (p=0.0026), respectively. ***Conclusions:*** IGB is effective among the serum markers of MAFLD. Younger patients had a greater decrease of HOMA-IR after IGB therapy.

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Introduction

As the prevalence of obesity and insulin resistance continues to rise, nonalcoholic fatty liver disease (NAFLD), now rebranded as metabolic dysfunction-associated fatty liver disease (MAFLD), has emerged as the most prevalent parenchymal liver disease worldwide and explains 9% of deaths from liver cirrhosis.[1–3] Currently, there are no approved pharmacotherapies for fatty liver disease.[4] Bariatric surgery for fatty liver disease has enjoyed a high profile due to its remarkable capacity for improving liver enzyme, NAFLD activity score, and fibrosis.[5,6] However, unexpected rates of liver fibrosis progression in patients who undergo bariatric surgery and excessive risks of postoperative complications limit the acceptance of bariatric surgery.[7,8] Additionally, lifestyle modification strategies are difficult to address the disadvantage regarding treatment compliance.[9,10] As a result, novel therapeutic applications, which take all efficacy, safety, and treatment compliance into account, are urgently needed for all MAFLD patients.

Recently, the potential role of endoscopic bariatric and metabolic therapies (EBMT) in the management of fatty liver disease has been highlighted.[11,12] EBMT are developed to avoid the invasive nature of laparoscopic or open bariatric surgery, in contrast, reproducing similar gastrointestinal physiological alterations and therapeutic effects.[13] Among these interventions, intragastric balloon (IGB), as a space-occupying EBMT device with proven efficacy in inducing weight loss, has been used in diminishing liver volume to reduce the risks of subsequent bariatric surgery and has met with success.[14,15] Prior study has demonstrated that the change in liver volume was positively correlated with the change in intrahepatic fat,[16] which suggested the potential therapeutic effect of using IGB in fatty liver disease. In terms of current evidence, a randomized controlled

Keywords: Intragastric balloon; Nonalcoholic fatty liver disease; Insulin resistance; Age groups; Treatment outcome.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; EBMT, endoscopic bariatric and metabolic therapies; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment of insulin resistance; IGB, intragastric balloon; I^2, inconsistency index; MD, mean difference; NAFLD, nonalcoholic fatty liver disease; NOS, Newcastle-Ottawa scale; MAFLD, metabolic dysfunction-associated fatty liver disease; RCT, randomized controlled trial.

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trial (RCT) evaluated changes in histological scores after 6-month IGB therapy and showed a beneficial effect on the severity of fatty liver disease.[17] However, due to the limited sample size of this trial, we still need to combine the existing RCT findings with observational longitudinal studies to present the effectiveness of IGB in larger sample size, before it is widely recommended for the treatment of MAFLD. Therefore, we performed a systematic review with meta-analyses to evaluate the therapeutic effect of IGB on the markers of MAFLD, such as homeostasis model assessment of insulin resistance (HOMA-IR) index, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT). Furthermore, to identify patients most appropriate for IGB therapy, stratified analyses and meta-regression were both implemented.

Methods

Data sources and search strategy

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analysis statement (see Table S1).[18] The protocol for this review is registered in PROSPERO (no. CRD42020214315).

To collect all full-text articles describing the effect of IGB on the markers of MAFLD, we performed a search of the Medline, Cochrane Library, and Web Of Science with English-language restriction and up to September 2020 using the following strategy: ("Intragastric balloon" OR "Gastric balloon") AND ("Alanine aminotransferase" OR "Alanine transaminase" OR "ALT" OR "Liver" OR "Nonalcoholic fatty liver disease" OR "Non-alcoholic fatty liver disease" OR "NASH" OR "NAFLD" OR "HOMA-IR" OR "Homeostasis model assessment" OR "Insulin resistance"). The detailed search strategy is summarized in Table S2. Furthermore, the reference lists of each article were manually searched to prevent the omission of any pertinent study.

Study eligibility and selection criteria

Only observational longitudinal studies and RCTs were included. Inclusion criteria of the articles were as follows: (a) population: all patients who are obese or in need of obesity treatment; (b) intervention: liquid-filled IGB procedure; (c) comparator: the participants at baseline before IGB placement; and (d) outcome: the decrease of ALT, AST, GGT, or HOMA-IR index in all the participants treated with IGB. Moreover, the studies which recruited only pediatric patients or utilized the gas-filled IGB as an intervention were excluded to prevent bias.

Data extraction and quality assessment

Data extraction was performed independently by two investigators (ZYZ, JZ). The information and characteristics extracted from the included study were first author, year of publication, study design, country, study size of participants with IGB therapy, IGB type, dwelling time of IGB, filling of IGB, method of IGB implantation, additional nutrition and exercise prescription, description of liver disease in exclusion criteria, percentage of male individuals, prevalence of diabetes, participants' age and body mass index (BMI) at baseline, and participants' ALT, AST, GGT and HOMA-IR before and after IGB therapy. When standard deviation was unavailable, it was replaced with a quarter of the range.[19] The risk of bias of the selected studies was evaluated using the modified Newcastle-Ottawa scale (NOS) for observational longitudinal studies[20] and Cochrane Collaboration's tool for RCT.[21]

Data analysis

Using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), meta-analyses (quantitative synthesis) were performed to evaluate the pooled mean difference (MD) in HOMA-IR, ALT, AST and GGT from baseline to end of IGB therapy using the inverse variance method and random-effect model, with 95% confidence interval (CI) and p-value. A p-value <0.05 was considered statistically significant. Publication bias was evaluated by Egger's test and funnel plot.[22,23] Heterogeneity was evaluated with inconsistency index (I^2), classified as a low (I^2≥25%), substantial (I^2≥50%), or considerable (I^2≥75%).[24] Stratified analyses were conducted to investigate sources of heterogeneity based on the following characteristics: method of IGB implantation; mean basal level of serum markers (HOMA-IR, ALT, AST, or GGT); age and BMI of the participants; study region; and NOS score. When meta-regression analysis was performed, univariate and multivariate linear regression models were utilized to evaluate the slope coefficient between the reduced value of serum marker (HOMA-IR, ALT, AST, or GGT) after IGB therapy and the following covariates: mean basal level of serum marker; percentage of male individuals; and age and BMI of the participants. To summarize the results, the scatter plots were mapped to materialize the linear relationship between the changed value after IGB therapy and covariates which had statistical significance with both univariate and multivariate meta-regression analysis (p<0.05). Each study was represented by a circle of size proportional to the inverse of the variance of MD.

Results

Literature search results

Figure 1 summarizes the flow diagram of the selection process performed to identify eligible studies in this systematic review. Out of 152 references, a total of 14 studies[25–38] comprising 624 participants met the predefined inclusion criteria. All studies were published prior to September 13, 2020.

Improvement of insulin resistance after IGB on therapy

Summary of study characteristics: Eight studies[25–27,29,33,35,36,38] with a total of 352 individuals were included in this meta-analysis of HOMA-IR level, and their characteristics are summarized in Table 1. All included studies were published after 2007. Of these, one[38] was a two-arm RCT, and the rest[25–27,29,33,35,36] were observational longitudinal studies, meaning that a total of nine intervention arms were included in this analysis. The participants came from three countries (Brazil, Italy, Japan). Seven intervention arms[25–27,29,33,38] applied the Orbera IGB system, one arm[36] used the Orbera/Spatz IGB system, and the single remaining arm[35] reported results with the Elipse IGB system. Furthermore, the range of average baseline HOMA-IR was from 2.36 to 12.30. The results of the quality assessment using

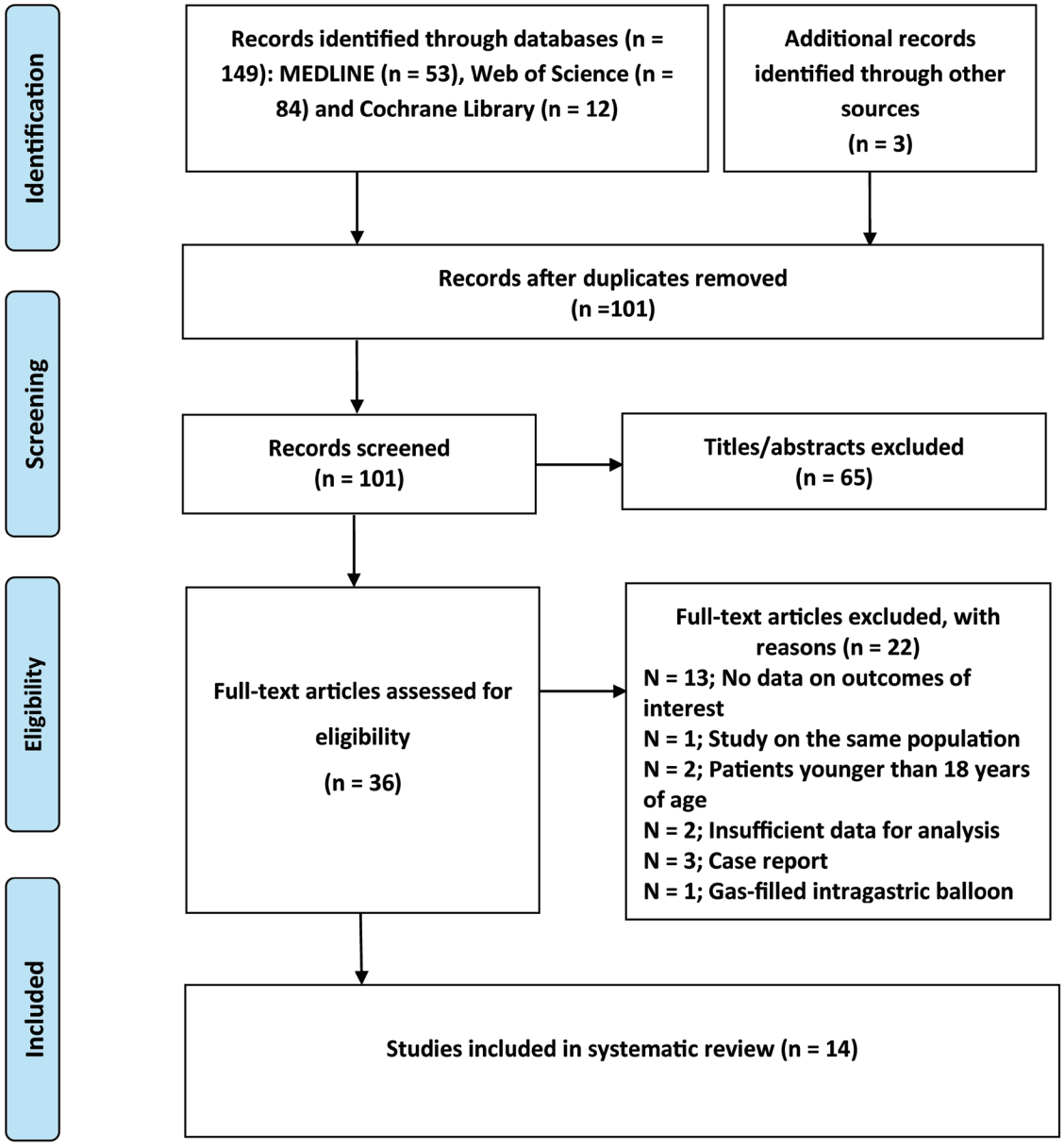

Fig. 1. Flow diagram of the study selection process.

the modified NOS and Cochrane Collaboration's tool can be found in Table S3 and Figure S1.

Quantitative synthesis and stratified analyses: Nine intervention arms[25–27,29,33,35,36,38] of 352 participants evaluated the effect of IGB on HOMA-IR. The pooled mean decrease in HOMA-IR levels with IGB therapy was 1.56 (95% CI=1.16–1.95, I^2=61.1; Fig. 2A). According to the Egger's test and funnel plot, no significant publication bias was present (p=0.2665; Fig. S2A). Table 2 presents the results of the stratified analyses. Both endoscopic IGB (MD=1.68, 95% CI=1.24–2.11) and swallowable IGB (MD=0.90, 95% CI=0.26–1.54) were effective in inducing HOMA-IR loss. There were trends showing the advanced age group had less change in HOMA-IR (MD=1.07, 95% CI=0.57–1.56) compared to those ≤40 years (MD=1.82, 95% CI=1.25–2.40), but the findings were not statistically significant (p=0.0502). Higher baseline HOMA-IR (>5) was associated with more significant reductions in HOMA-IR [MD=3.48 (95% CI=2.46–4.50) vs. MD=1.40 (95% CI=1.25–1.54), p<0.0001)]. Consequently, intra-subgroup heterogeneity was significantly diminished and almost absent with different basal HOMA-IR (basal HOMA-IR ≤5: I^2=0.0; basal HOMA-IR >5: I^2=0.0).

Meta-regression: Table 3 presents the meta-regression findings of HOMA-IR. In univariate meta-regression, basal HOMA-IR of the participants (slope coefficient=0.3966, 95% CI=0.1119–0.6814, p=0.0063) and percentage of male individuals (slope coefficient=0.0433, 95% CI=0.0183 to 0.0684, p=0.0007) seemed to be factors significantly associated with reductions in HOMA-IR. Subsequently, using a multivariate meta-regression approach, our final model consisted of four covariates: basal HOMA-IR, percentage of male individuals, age and BMI of the participants. Greater HOMA-IR loss was predicted by younger age (slope coeffi-

Table 1. Characteristics of the included studies

Author	IGB group, *n*	Type of study; Country; Prevalence of diabetes	Nutrition and exercise prescription	IGB type; IGB duration; Filling; Implantation of IGB	Liver disease excluded
Bazerbachi *et al*.[37]	21	Observational study; USA; 52%	Low-calorie diet + lifestyle therapy	Orbera; 6 months; Liquid-filled; Endoscopically	Other primary causes of liver disease
Maekawa *et al*.[38]	18	RCT; Japan; Not described	Low-carbohydrate diet	Orbera; 6 months; Liquid-filled; Endoscopically	Not described
Maekawa *et al*.[38]	13	RCT; Japan; Not described	Low-calorie diet	Orbera; 6 months; Liquid-filled; Endoscopically	Not described
Guedes *et al*.[36]	42	Observational study; Brazil; Not described	Low-calorie diet	Orbera/Spatz; 6 months; Liquid-filled; Endoscopically	Not described
Genco *et al*.[35]	38	Observational study; Italy; Not described	Low-calorie diet + exercise counseling	Elipse; 4 months; Liquid-filled; Swallowable	Not described
Raftopoulos *et al*.[34]	12	Observational study; Greece; Not described	Diet and exercise counseling	Elipse; 4 months; Liquid-filled; Swallowable	No history of alcohol
Folini *et al*.[32]	13	Observational study; Italy; Not described	Low-calorie diet + exercise counseling	Orbera; 6 months; Liquid-filled; Endoscopically	Alcohol consumption, presence of any predisposing disorders for liver diseases, pregnancy, and lactation
Takihata *et al*.[33]	8	Observational study; Japan; Not described	Low-calorie diet	Orbera; 6 months; Liquid-filled; Endoscopically	Not described
Tai *et al*.[31]	28	Observational study; China (Taiwan); Not described	Low-calorie diet	Orbera; Median 200 days; Liquid-filled; Endoscopically	Alcoholism or drug addiction
Nikolic *et al*.[28]	33	Observational study; Croatia; Not described	Low-calorie diet	Orbera; 6 months; Liquid-filled; Endoscopically	Not described
Sekino *et al*.[29]	8	Observational study; Japan; Not described	Not described	Orbera; 6 months; Liquid-filled; Endoscopically	Not described
Stimac *et al*.[30]	165	Observational study; Croatia; Not described	Not described	Orbera; 6 months; Liquid-filled; Endoscopically	Present alcohol or drug abuse
Forlano *et al*.[27]	120	Observational study; Italy; 13.3%	Low-calorie diet	Orbera; 6 months; Liquid-filled; Endoscopically	Use of drugs reported to cause liver damage, alcohol intake of 30 g/day or more, and viral hepatitis
Donadio *et al*.[26]	40	Observational study; Italy; Not described	Not described	Orbera; 6 months; Liquid-filled; Endoscopically	Alcoholism
Ricci *et al*.[25]	65	Observational study; Italy; Not described	Low-calorie diet	Orbera; 6 months; Liquid-filled; Endoscopically	Positivity for hepatitis B virus or hepatitis C virus, previous or current alcohol consumption >30 g/day, use of medications with reported hepatosteatogenic effect (amiodarone, tamoxifen, estrogens), and type 1 diabetes

IGB, intragastric balloon; RCT, randomized controlled trial.

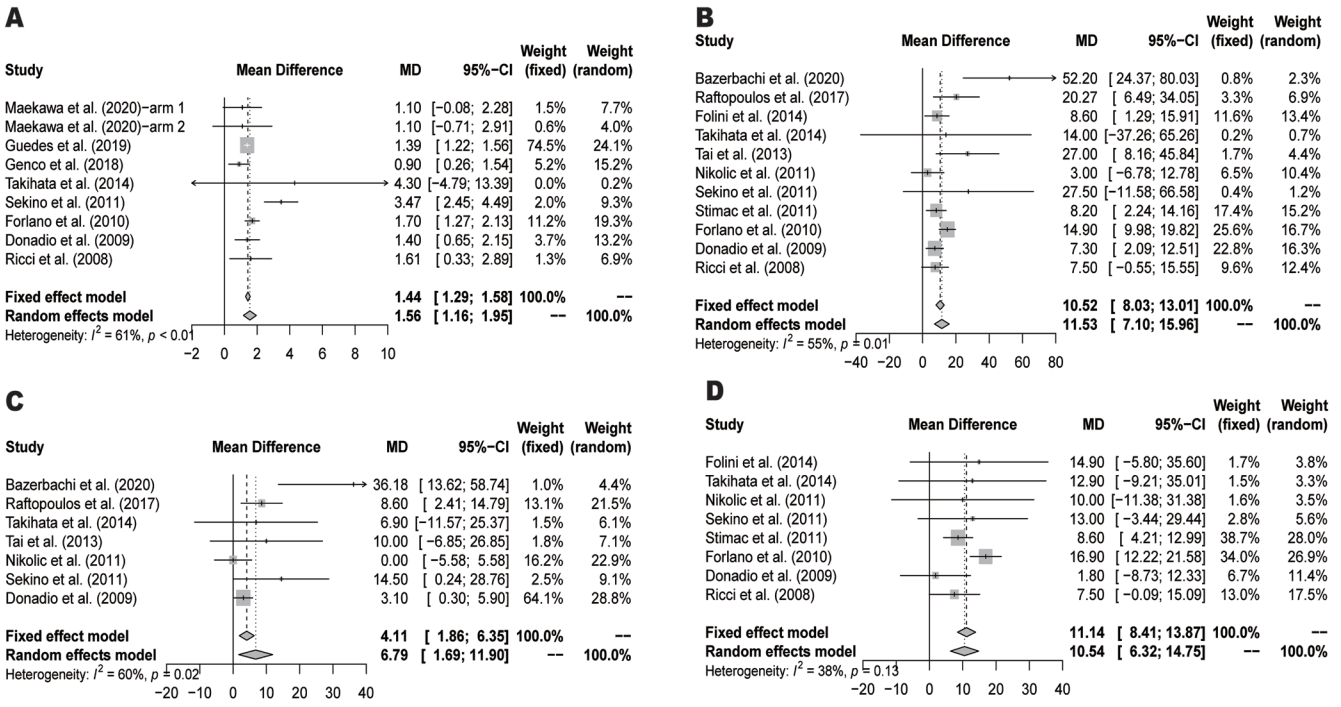

Fig. 2. Forest plots. HOMA-IR (A), ALT (B), AST (C), and GGT (D) decreased after IGB treatment and removal. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment of insulin resistance; IGB, intragastric balloon.

cient=−0.0932, 95% CI=−0.1647 to −0.0216, p=0.0107).

Decrease in ALT after IGB therapy

Summary of study characteristics: Eleven observational longitudinal studies[25–34,37] with a total of 513 individuals were included in this meta-analysis of ALT level, and their characteristics are summarized in Table 1. All included studies were published after 2007. The participants included in the meta-analysis of ALT level came from six countries (China, Croatia, Greece, Italy, Japan, USA). Ten studies[25–33,37] applied the Orbera IGB system, and one study[34] reported results with the Elipse IGB system. Furthermore, the range of average baseline ALT was from 26.0 to 91.6 U/L. The results of the quality assessment using the modified NOS can be found in Table S3.

Quantitative synthesis and stratified analyses: Eleven studies[25–34,37] of 513 participants evaluated the effect of IGB on ALT. The pooled mean decrease of ALT with IGB therapy was 11.53 U/L (95% CI=7.10–15.96, I^2=55.4; Fig. 2B). According to the Egger's test and funnel plot, no significant publication bias was present (p=0.2422; Fig. S2B). Table 2 presents the results of the stratified analyses. Both endoscopic IGB (MD=10.85 U/L, 95% CI=6.31–15.39) and swallowable IGB (MD=20.27 U/L, 95% CI=6.49–34.05) were effective in inducing ALT loss. The advanced age group had similar change in ALT (MD =15.57 U/L, 95% CI=5.20–25.93) compared to those ≤40 years (MD =10.40 U/L, 95% CI=5.38–15.41). Higher baseline ALT (>40 U/L) was associated with more significant reductions in ALT [MD=32.43 U/L (95% CI=18.49–46.37) vs. MD=9.58 U/L (95% CI=6.18–12.98), p=0.0018]. Overall, intra-subgroup heterogeneity in different basal ALT diminished significantly and was classified as a low (basal ALT ≤40 U/L: I^2=38.7; basal ALT >40 U/L: I^2=0.0).

Meta-regression: Table 3 presented the meta-regression findings of ALT. In univariate meta-regression, basal ALT of the participants (slope coefficient=0.7314, 95% CI=0.3862–1.0767, p<0.0001) seemed to be a factor significantly associated with reductions in ALT. Subsequently, using a multivariate meta-regression approach, our final model consisted of four covariates: basal ALT; percentage of male individuals; age; and BMI. Effectiveness on ALT was predicted by basal ALT (slope coefficient=0.7135, 95% CI=0.3213–1.1057, p=0.0004). The scatter plot showed a linear trend towards increasing effectiveness of IGB therapy with increasing basal ALT of the participants (Fig. 3A).

Decrease in AST after IGB therapy

Summary of study characteristics: Seven observational longitudinal studies[26,28,29,31,33,34,37] with a total of 150 individuals were included in this meta-analysis of AST level, and their characteristics are summarized in Table 1. The participants included in the meta-analysis of AST level came from six countries (China, Croatia, Greece, Italy, Japan, USA). Six studies[26,28,29,31,33,37] applied the Orbera IGB system, and one study[34] reported results with the Elipse IGB system. Furthermore, the range of average baseline AST was from 21.7 to 67.5 U/L. The results of the quality assessment using the modified NOS can be found in Table S3.

Quantitative synthesis and stratified analyses: Seven studies of 150 participants evaluated the effect of IGB on AST. The pooled mean decrease of AST with IGB therapy was 6.79 U/L (95% CI=1.69–11.90, I^2=59.9; Fig. 2C). According to the Egger's test and funnel plot, no significant publication bias was present (p=0.3768; Fig. S2C). Table 2 presents the results of the stratified analyses. Both endoscopic IGB (MD=6.74 U/L, 95% CI=0.53–12.96) and swallowable IGB (MD=8.60 U/L, 95% CI=2.41–14.79) were effective in inducing AST loss. The advanced age group had a similar change in AST (MD =14.54 U/L, 95% CI=−0.04 to 29.12) compared

Table 2. Pooled change in HOMA-IR, ALT, AST, and GGT after IGB treatment and removal: Stratified analyses

	Intervention arm, n	MD (95% CI)	I^2
Pooled change in HOMA-IR after IGB treatment and removal			
Insertion of IGB (IGB type)			
Endoscopic (Orbera/Spatz)	8	1.68 (1.24–2.11)	60.3
Swallowable (Elipse)	1	0.90 (0.26–1.54)	–
Basal HOMA-IR			
≤5	7	1.40 (1.25–1.54)	0.0
>5	2	3.48 (2.46–4.50)	0.0
Mean age, years			
≤40	4	1.82 (1.25–2.40)	82.0
>40	5	1.07 (0.57–1.56)	0.0
Mean BMI, kg/m^2			
≤40	4	1.35 (1.19–1.51)	0.0
>40	5	2.01 (1.25–2.77)	66.4
Region			
Asia	4	1.35 (1.19–1.51)	72.4
Europe	4	1.41 (1.01–1.81)	29.1
South America	1	1.39 (1.22–1.56)	–
NOS scale			
High	3	1.37 (0.88–1.87)	52.0
Fair	4	2.16 (0.87–3.44)	81.2
Pooled change in ALT after IGB treatment and removal			
Insertion of IGB (IGB type)			
Endoscopic (Orbera)	10	10.85 (6.31–15.39)	55.9
Swallowable (Elipse)	1	20.27 (6.49–34.05)	–
Basal ALT, U/L			
≤40	7	9.58 (6.18–12.98)	38.7
>40	4	32.43 (18.49–46.37)	0.0
Mean age, years			
≤40	6	10.40 (5.38–15.41)	54.6
>40	5	15.57 (5.20–25.93)	64.6
Mean BMI, kg/m^2			
≤40	2	22.61 (11.49–33.74)	0.0
>40	9	9.98 (5.59–14.38)	53.7
Region			
Asia	3	25.80 (9.69–41.91)	0.0
Europe	7	9.58 (6.18–12.98)	38.7
North America	1	9.88 (7.33–12.44)	–
NOS scale			
High	4	12.71 (5.27–20.16)	78.0
Fair	7	10.59 (4.84–16.35)	29.4
Pooled change in AST after IGB treatment and removal			
Insertion of IGB (IGB type)			
Endoscopic (Orbera)	6	6.74 (0.53–12.96)	60.4

(continued)

Table 2. *(continued)*

	Intervention arm, n	MD (95% CI)	I^2
Swallowable (Elipse)	1	8.60 (2.41–14.79)	–
Basal AST, U/L			
≤40	6	4.52 (1.05–7.99)	29.8
>40	1	36.18 (13.62–58.74)	0
Mean age, years			
≤40	4	3.30 (−0.66 to 7.26)	29.9
>40	3	14.54 (−0.04 to 29.12)	63.5
Mean BMI, kg/m^2			
≤40	2	8.77 (2.95–14.58)	0.0
>40	5	6.64 (−0.20 to 13.49)	66.8
Region			
Asia	3	11.15 (1.77–20.53)	0
Europe	3	3.59 (−0.34 to 7.52)	52.1
North America	1	36.18 (13.62–58.74)	–
NOS scale			
High	2	17.67 (−14.52 to 49.86)	87.7
Fair	5	6.17 (0.53–11.81)	38.2
Pooled change in GGT after IGB treatment and removal			
Insertion of IGB (IGB type)			
Endoscopic (Orbera)	8	9.45 (4.46–14.45)	53.0
Swallowable (Elipse)	0	–	–
Basal GGT, U/L			
≤40	6	8.74 (2.89–14.59)	66.2
>40	2	12.96 (−0.23 to 26.15)	0.0
Mean age, years			
≤40	5	8.75 (1.71–15.79)	71.3
>40	3	8.80 (2.02–15.58)	0.0
Mean BMI, kg/m^2			
≤40	8	9.45 (4.46–14.45)	53.0
>40	0	–	–
Region			
Asia	2	12.96 (−0.23 to 26.15)	0.0
Europe	6	8.74 (2.89–14.59)	66.2
NOS scale			
High	3	10.10 (2.49–17.72)	80.1
Fair	5	7.88 (1.86–13.89)	0.0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment of insulin resistance; IGB, intragastric balloon.

to those ≤40 years (MD=3.30 U/L, 95% CI=−0.66 to 7.26). Higher baseline AST (>40 U/L) was associated with more significant reductions in AST [MD=36.18 U/L (95% CI=13.62–58.74) vs. MD=4.52 U/L (95% CI=1.05-7.99, p=0.0065)]. Overall, intra-subgroup heterogeneity in different basal AST diminished significantly and was classified as a low (basal AST ≤40 U/L: I^2=29.8; basal AST >40 U/L: I^2=0.0).

Meta-regression: Table 3 presents the meta-regression findings of AST. In univariate meta-regression, basal AST of the participants (slope coefficient=0.7650, 95% CI=0.3319–1.1982, p=0.0005) and age of the participants (slope coefficient=1.4430, 95% CI=0.5644–2.3216, p=0.0013) seemed to be factors significantly associated with reductions in AST. Subsequently, using a multivariate meta-regression approach, our final model consisted of four covariates: basal AST; percentage of male individuals; age;

and BMI. Effectiveness on AST could not be predicted by all of the above covariates.

Decrease in GGT after IGB therapy

Summary of study characteristics: Eight observational longitudinal studies[25–30,32,33] with a total of 452 individuals were included in this meta-analysis of GGT level, and their characteristics are summarized in Table 1. The participants included in the meta-analysis of GGT level came from three countries (Croatia, Italy, Japan). All eight studies[25–30,32,33] applied the Orbera IGB system. Furthermore, the range of average baseline GGT was from 29.8 to 53.0 U/L. The results of the quality assessment using the modified NOS can be found in Table S3.

Quantitative synthesis and stratified analyses: Eight studies[25–30,32,33] of 452 participants evaluated the effect of IGB on GGT. The pooled mean decrease of GGT with IGB therapy was 10.54 U/L (95% CI=6.32–14.75, I^2=37.6; Fig. 2D). According to the Egger's test and funnel plot, no significant publication bias was present (p=0.8620; Fig. S2D). Table 2 presented the results of the stratified analyses. The advanced age group had a similar change in GGT (MD =8.80 U/L, 95% CI=2.02–15.58) compared to those ≤40 years (MD=8.75 U/L, 95% CI=1.71–15.79). There were trends showing that the higher basal GGT group had more change in GGT (MD=12.96, 95% CI=−0.23 to 26.15) compared to those ≤40 U/L (MD=8.74, 95% CI=2.89–14.59) but the findings were not statistically significant (p=0.6919). Overall, intra-subgroup heterogeneity diminished significantly in the higher basal GGT group (I^2=0.0).

Meta-regression: Table 3 presents the meta-regression findings of GGT. In univariate meta-regression, basal GGT of the participants (slope coefficient=0.7968, 95% CI=0.2032–1.3904, p=0.0085) seemed to be a factor significantly associated with reductions in GGT. Subsequently, using a multivariate meta-regression approach, our final model consisted of four covariates: basal GGT; percentage of male individuals; age; and BMI. Effectiveness on GGT was predicted by basal GGT (slope coefficient=1.3773, 95% CI=0.4793–2.2754, p=0.0026). The scatter plot showed a linear trend towards increasing effectiveness of IGB therapy with increasing basal GGT of the participants (Fig. 3B).

Discussion

Principal findings and relevant mechanisms

IGB is the most widely available EBMT with proven efficacy in inducing weight loss. According to the IGB type, an empty balloon is introduced into the stomach by an upper gastrointestinal endoscopy or by swallowing the balloon capsule directly. The liquid-filled IGB is inflated with saline and methylene blue to occupy the space in the stomach. After that, the IGB dwells in the stomach for 4 to 6 months until it ruptures or is removed.[14,39] Due to its moderate efficacy of weight loss and excellent safety profiles, the potential utility of IGB was mentioned by the Asian-Pacific clinical practice guideline on MAFLD.[40] IGB has also been employed for clinical research of fatty liver disease. However, there is still substantial heterogeneity in results across studies. One explanation is that patients with fatty liver disease can be subdivided into IGB responder and non-responder groups. In this systematic review with meta-analysis, we demonstrated that IGB could reverse the serum markers of MAFLD, including HOMA-IR, ALT, AST, and GGT levels. Furthermore, the change of ALT and GGT with IGB therapy had a positive linear relationship with the basal value. This means that even at higher levels of disease severity, abnormal liver enzymes can be controlled within the reported range of included studies (ALT: 26.0–91.6 U/L; GGT: 29.8–53.0 U/L).

Due to the dearth of eligible studies, the histological and radiological findings cannot be quantitatively pooled through meta-analyses and can only be described in the discussion. In terms of histological variables, a small RCT,[17] with 18 patients who completed the study, reported that NAFLD activity score at post-therapy was significantly lower among the IGB-treated compared with the sham-treated arm. On the other hand, there seemed to be no difference between the IGB-treated arm and the sham-treated arm in improving fibrosis. Consistent with this finding, according to another observational study,[37] significant improvement of NAFLD activity score was reached in most NAFLD patients treated with IGB (p<0.001). Apart from these, some of the studies assessed non-invasive radiological parameters of NAFLD. A prospective single-arm study[27] showed that after 6 months of IGB therapy, the number of patients with severe hepatic steatosis confirmed by abdominal ultrasound decreased from 52% to 4%. Two other clinical studies,[32,37] respectively, demonstrated that hepatic fat fraction and fibrosis by magnetic resonance imaging could be significantly alleviated by IGB therapy. Taken together, these histological and radiological findings were consistent with the results of serum markers (HOMA-IR, ALT, AST, and GGT) in our meta-analyses.

To date, no study has looked at the impact of age on insulin resistance amelioration in patients receiving IGB therapy. In our meta-analysis, multivariate linear meta-regression and stratified analyses indicated that participants with advanced age had less change in HOMA-IR after IGB therapy. Several weight-dependent and non-weight-dependent hypotheses may explain this phenomenon. A previously published study reported that advanced age was significantly correlated with less excess weight loss in females after IGB intervention.[41] Given that clinically significant weight loss can alleviate insulin resistance,[42] age-related differences in insulin resistance outcomes might be partly attributed to the different weight loss during treatment. Additionally, both obesity and aging are linked to and engender insulin resistance.[43] Among elderly patients, the effect of aging is strongly amplified and cannot be eliminated by the obesity management tools. Taken together, age might be considered as a predictor of insulin resistance amelioration in patients undergoing IGB therapy.

Comparison with other studies or reviews

In terms of the impact of IGB on liver enzymes, a commendable meta-analysis published in 2016 showed that the use of IGB could decrease ALT (MD=10.02, 95% CI=6.8–13.2),[19] which was in line with our findings. When their meta-analysis was published, swallowable IGB had not been widely used and investigated.[14] To help clinicians and researchers keep up to date with current evidence, we performed this systematic review including more updated studies. Our stratified analysis revealed that the improvement of ALT, AST, and HOMA-IR with swallowable IGB therapy was no worse than that with endoscopic IGB. Future RCTs are needed to comprehensively compare the efficacy and safety between these two IGBs.

Limitations and strengths

Our systematic review does have some shortcomings. First,

Table 3. Univariate and multivariate meta-regression analyses on the mean deference of HOMA-IR, ALT, AST, and GGT after IGB treatment and removal

Moderators	Intervention arm, *n*	Univariable analysis		Multivariable analysis	
		Slope coefficient (95% CI)	***p***	**Slope coefficient (95% CI)**	***p***
Mean deference of HOMA-IR after IGB treatment and removal					
Basal HOMA-IR	9	**0.3966 (0.1119–0.6814)**	**0.0063**	0.2361 (−0.2764 to 0.7487)	0.3665
Mean age	9	−0.0753 (−0.1891 to 0.0386)	0.1950	**−0.0932 (−0.1647 to −0.0216)**	**0.0107**
Mean BMI	9	0.0975 (−0.0288 to 0.2238)	0.1302	−0.0473 (−0.1298 to 0.0351)	0.2607
Male	9	**0.0433 (0.0183–0.0684)**	**0.0007**	0.0381 (−0.0094 to 0.0856)	0.1159
Mean deference of ALT after IGB treatment and removal					
Basal ALT	11	**0.7314 (0.3862–1.0767)**	**<0.0001**	**0.7135 (0.3213–1.1057)**	**0.0004**
Mean age	11	0.8603 (−0.3376 to 2.0582)	0.1593	0.3408 (−0.5602 to 1.2417)	0.4585
Mean BMI	11	−1.1489 (−2.6746 to 0.3767)	0.1399	−0.5035 (−1.6750 to 0.6681)	0.3996
Male	11	0.0851 (−0.3480 to 0.5181)	0.7002	−0.0652 (−0.3742 to 0.2437)	0.6791
Mean deference of AST after IGB treatment and removal					
Basal AST	7	**0.7650 (0.3319–1.1982)**	**0.0005**	0.5438 (−0.0501 to 1.1378)	0.0727
Mean age	7	**1.4430 (0.5644–2.3216)**	**0.0013**	0.5348 (−0.8576 to 1.9272)	0.4516
Mean BMI	7	−0.1374 (−1.5495 to 1.2747)	0.8488	−0.1086 (−0.8199 to 0.6028)	0.7648
Male	7	0.1362 (−0.2020 to 0.4744)	0.4299	0.0699 (−0.2378 to 0.3777)	0.6562
Mean deference of GGT after IGB treatment and removal					
Basal GGT	8	**0.7968 (0.2032–1.3904)**	**0.0085**	**1.3773 (0.4793–2.2754)**	**0.0026**
Mean age	8	0.5022 (−2.0156 to 3.0201)	0.6958	0.3219 (−1.9139 to 2.5577)	0.7778
Mean BMI	8	−0.2371 (−4.2184 to 3.7441)	0.9071	−1.3277 (−4.6165 to 1.9612)	0.4288
Male	8	0.0996 (−0.3201 to 0.5193)	0.6418	−0.4310 (−0.9670 to 0.1051)	0.1151

Boldface font denotes statistical significance. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment of insulin resistance; IGB, intragastric balloon.

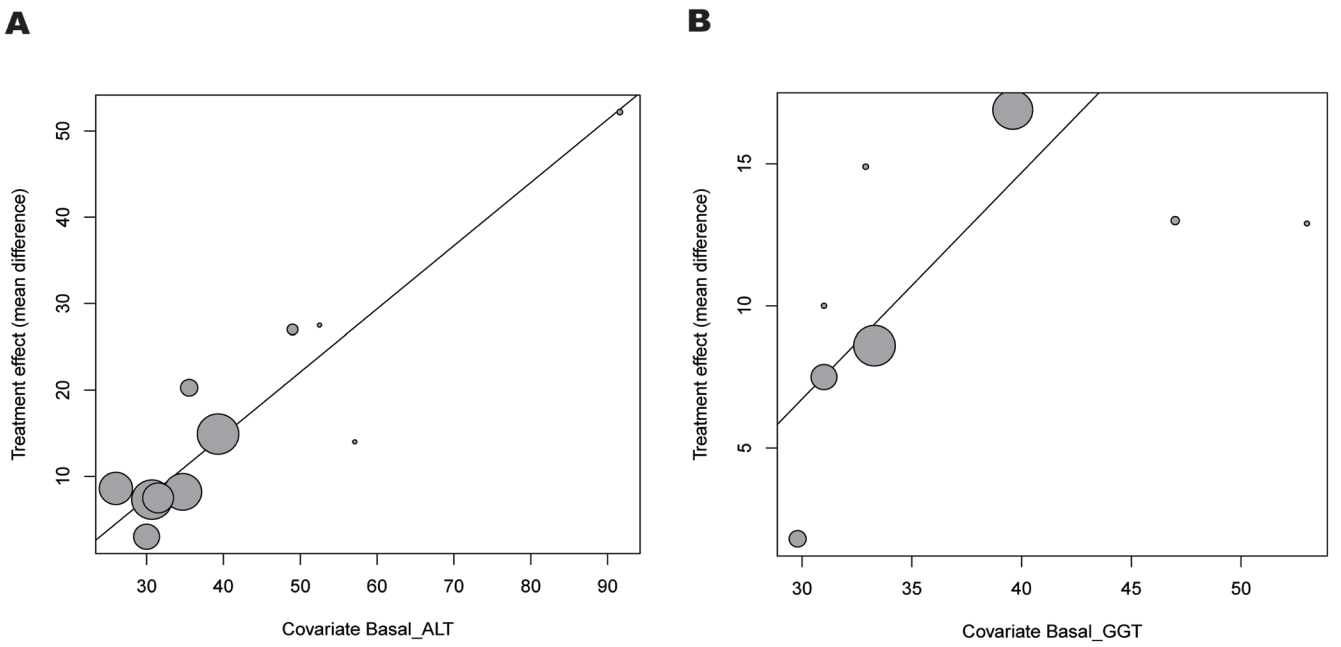

Fig. 3. Scatter plots. (A) Change in ALT is positively correlated with basal ALT. (B) Change in GGT is positively correlated with basal GGT. ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase.

although our review included studies of both endoscopic and swallowable IGB, there were still a number of IGB types (such as ReShape Duo Balloon and Obalon Gastric Balloon) not mentioned in the current review due to the lack of relevant clinical research.[14] Second, at the time of the preliminary search, we found that most of the clinical studies in this field were of longitudinal observational design. Thus, when formal screening of the search was performed, we defined the patient at baseline, but not the sham-treated group, as comparators. However, this approach ignored the potential for spontaneous remission of the disease.[44] Despite these limitations, our systematic review provides the most comprehensive evaluation of the effect of IGB on the serum markers of MAFLD, with low intra-subgroup heterogeneity in stratified analysis, suggesting that the evidence is highly credible. More impressively, our observations demonstrate for the first time that age has an adverse effect on IGB treatment of insulin resistance.

Conclusions and perspectives

IGB therapy has led to improvements in the serum markers of MAFLD, including HOMA-IR, ALT, AST, and GGT. Significant reductions in HOMA-IR and liver biochemical parameters were seen across different methods of balloon implantation and different age/BMI classes. The improvement of insulin resistance and liver biochemistries with swallowable IGB therapy was no worse than that with endoscopic IGB. Furthermore, greater insulin resistance amelioration with IGB therapy was predicted by younger age and the relevant mechanism needs further investigation. Although IGB has the potential to become a multidisciplinary management tool of MAFLD, it cannot be ignored that IGB is a temporary measure. If the patient cannot maintain an active lifestyle after the first balloon is removed, relapse of MAFLD is an expected result. In this regard, IGB combined with other pharmacotherapy or sequential IGB therapy could be a potential solution, and further RCT is warranted.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design (JGF), funding acquisition and supervision (JGF, TYR), collection and assembly of data (ZYZ, JZ), data analysis and interpretation (ZYZ), manuscript writing (ZYZ, JZ, TYR, YWS, RXY, JGF), final approval of manuscript (ZYZ, JZ, TYR, YWS, RXY, JGF).

Data sharing statement

No additional data are available.

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