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Article

Long-term iron and vitamin B12 deficiency are present after bariatric surgery, despite the widespread use of supplements.

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Abstract: Long-term nutritional studies in subjects undergoing bariatric surgery that have assessed weight regain and nutritional deficiencies are few. In this study, we report data 8 years after surgery on weight loss, use of dietary supplements and deficit of micronutrients in a cohort of patients from five centres in central and northern Italy. The study group consisted of 52 subjects (age: 38.1±10.6 yrs, 42 females): 16 patients had Roux-en-Y gastric bypass (RYGB), 25 patients sleeve gastrectomy (LSG) and 11 subjects adjustable gastric banding (AGB). All three bariatric procedures led to sustained weight loss: average percentage excess weight loss, defined as weight loss divided by excess weight based on ideal body weight was 60.6%±32.3. 80.7% of subjects (72.7%, AGB; 76%, SG; 93.7%, RYGB) reported at least one nutritional deficiency: iron (F 64.3% vs. M 30%), vitamin B12 (F 16.6% vs. M 10%), calcium (F 33.3% vs. M 0%) and vitamin D (F 38.1% vs. M 60%). Average weight loss was constant in RYGB and SG subjects from the third year after surgery. Long-term nutritional deficiencies were greater than the general population among men for iron and among women for vitamin B12.

Keywords: Iron; Vitamin D; Vitamin B12; Roux-en-Y gastric bypass; Sleeve gastrectomy; Adjustable gastric banding; nutritional deficiency; bariatric surgery

1. Introduction

Bariatric surgery is the most effective form of treatment for severe obesity (BMI ≥ 35). Laparoscopic Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and laparoscopic sleeve gastrectomy (LSG) are the most frequently performed procedures. LSG and AGB are restrictive surgical procedures performed to reduce the quantity of food a person can eat. RYGB is a restrictive/malabsorptive operation, which bypasses about 95% of the stomach, the entire duodenum, and 40-150 cm of the jejunum. The risks of nutritional deficiencies are higher in patients undergoing RYGB [1], but in our previous study, we showed that despite the widespread use of supplements, nutritional deficiencies are frequent in patients 5 years after LSG [2].

In bariatric patients, recent long-term studies provide evidence of durable 10-year weight loss and improvement in comorbidities and quality of life [3] and a reduced risk of developing new health-related comorbidities [4], together with decreased health care utilisation and a drop in direct health care costs [5]. However, many essential long-term health risks of bariatric surgery are still poorly understood. Weight regain (WR) is unluckily a frequent phenomenon linked to all bariatric procedures [6]. Nutritional requirements in patients who have undergone bariatric surgery are frequently not met despite the widespread use of vitamin-mineral supplements [7]. A recent systematic review revealed that long-term data are needed for RYGB and LSG [8].

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In this study, we report data 8 years after surgery on weight loss, use of dietary supplements and deficit of some micronutrients in an unselected cohort of patients from five centres in central and northern Italy. We also reviewed data on the prevalence of the same nutritional deficiencies in Italy and Europe for comparison with the study sample.

2. Materials and Methods

This was a non-randomised prospective study. Sixty severely obese subjects undergoing a clinical evaluation before bariatric surgery between 2011 and 2012 were initially included in the present study. Eight patients were excluded from the study because they never answered our communications. Included patients underwent LAGB, LSG or RYGB. The final data were obtained from 52 patients.

All of the subjects were evaluated preoperatively at five different centres in central and northern Italy. All procedures were standardised at the different centres. The evaluation consisted of a selected counselling specialties (nutrition, psychiatry, surgery and anaesthesiology) and gastrointestinal endoscopy as described before [9]. Anthropometric data (weight, height, BMI) were collected at baseline and at each follow-up visit. Following overnight fasting, weight and height were measured while the subjects were wearing only underwear. Outcome measures included absolute (EWL) and percent excess weight loss (%EWL) %EWL = [(Initial Weight) – (Postop Weight)] / [(Initial Weight) – (Ideal Weight)] in which ideal weight is defined by the weight corresponding to a BMI of 25 kg/m2. Informed consent was obtained from all individual participants included in the study. The exclusion criteria were as follows: age <18 years or >65 years, alcoholism, chronic kidney disease (CKD), or taking glucocorticoids, oestrogens or anti-convulsant therapies. All surgical procedures were performed laparoscopically as described elsewhere [2].

Follow-up visits

Food habits, caloric intake through food research, level of physical activity and lifestyle; anthropometric data, routine and specific biochemical examinations and vitamin status were assessed. Nutritional follow-up visits provided proper food choices and portion sizes using a visual guide, while also providing education on proper eating behaviour to avoid dumping syndrome, meal patterns and monitoring supplements. An adequate physical activity programme with low intensity aerobic features (at least 150 minutes/week walking) was also provided.

Laboratory data and diagnostic criteria

Vitamins and minerals assessments were performed before and after 8 years postoperatively. The blood plasma samples were taken in the morning (between 7:00 AM and 9:00 AM). Serum iron was measured by the colorimetric method and the immunoturbidimetric system, respectively. Serum 25- hydroxyvitamin D (25OHD) concentrations were determined using an immunoradiometric assay (DiaSorin, Stillwater, MN). Serum vitamin B12 was measured by using immunoenzymatic method. Measurement of plasma calcium was performed via blood testing with ion-selective electrodes. All of these measurements were performed twice, and the interassay and intraassay coefficients of variation ranged from 1.8-9.2%. The deficit limits of serum micronutrients are: iron less than 200 pg/mL, vitamin B12 less than 200 pg/mL, 25OHD less than 25 nmol/L and calcium less than 9 mg/dL.

Nutritional supplements

Patients were considered adherent if they reported use of nutritional supplements at least 5 days per week. The following categories of supplements were considered: multivitamin/mineral with a specific formula for the type of bariatric surgery, a multivitamin/mineral for bariatric surgery, general multivitamin/mineral supplements, 25OHD (with or without calcium) containing at least 400 U vitamin D3, iron containing at least 65 mg iron sulphate or a B complex multivitamin.

Data on prevalence of nutritional deficiencies

We searched PubMed, using the following keywords as title/abstract fields: ('deficiency' AND 'prevalence') AND ('vitamin D' OR 'vitamin B12' OR 'iron' OR 'calcium') AND ('Italy' OR 'Europe').

We obtained data on the prevalence of iron [10-12], 25OHD [13-14] and vitamin B12 [15-16] deficiency. We could not find recent epidemiological data on calcium deficiencies. Deficiency of 25OHD was mostly similar in males and females in European adults. Vitamin B12 deficiency in the UK occurs in about 6% of people under the age of 60.

Statistical analysis

Statistical analysis was performed using Sofa Statistics 1.5.4 software. The means ± SD (interquartile range) were used as descriptive statistics for normally distributed or skewed continuous variables, respectively. All quantitative variables were tested for normal distribution using the Kolmogorov-Smirnov test. Differences in continuous variables were

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assessed with a Student t-test for paired data. For all of these analyses, a p-value <0.05, based on a two-sided test, was considered statistically significant.

3. Results

The study group consisted of 52 subjects (age: 38.1±10.6 yrs, 42 females). RYGB was performed in 16 patients, 25 patients had SG and 11 subjects had AGB. All procedures were laparoscopic, there was no operative mortality and revisional bariatric surgery was not performed in any patient. Table 1 shows the main characteristics of subjects before the surgery.

Table 1. Clinical Characteristics of the Subjects before the surgery

(n)	AGB (11)	SG (25)	RYGB (16)	Total (52)
Age	37.9	37.7	38.8	38.1±10.6
Gender	M2-F9	M8-F17	M0-F16	M10-F42
BW	130.6	136.6	137.6	135.7±29.6
BMI	45	47.2	49.8	47.5±8.5
BMI 30-34.9 (%)	1 (9)	0	0	1 (1.9)
BMI 35-40 (%)	3 (27.3)	5 (20)	1 (6.2)	9 (17.3)
BMI 40.1-50 (%)	4 (36.4)	12 (48)	9 (56.2)	25 (48.1)
BMI 50.1-60 (%)	3 (27.3)	6 (24)	4 (25)	13 (25)
BMI >60.1 (%)	0	2 (8)	2 (12.6)	4 (7.7)

AGB: laparoscopic adjustable gastric banding. SG: sleeve gastrectomy. RYGB: Roux-en-Y gastric bypass. BW: body weight (kg). Data as mean ± SD or proportions (%)

The mean BMI was 47.5 kg/m2. 17.3% were severely obese (BMI 35-40 kg/m2), 48.1% were morbidly obese (BMI 40.1-50 kg/m2), 25% were super-obese (BMI 50.1-60 kg/m2), and 7.7% were super-super obese (BMI over 60.1 kg/m2). There were no statistically significant differences in most of the baseline features between the different bariatric surgery types (Table 2).

Table 2 . Postoperative changes (96 months) in body weight, BMI, and % excess body weight loss

	T0	(95% CI)	T96	(95% CI)	p*	Δ		
	AGB (11)							
BW	130.6±25.2	115.7 -145.8	113.0±17.9	102.5 -125.5	0.03	17.6±22.5 §		
BMI	45.0±8.5	39.3 - 50.6	38.9±5.9	34.9 - 42.9	0.02	6.0±7.1 #		
EBW	57.7±24.3	41.4 - 74	40.1±16.8	28.8 - 51.4	0.03			
%EWL			22.9±32.3	1.1 - 44.6				
	SG (25)							
BW	136.6±33.8	123.4 – 149.9	91.1±15.3	85.1 - 97.1	<0.001	45.6±27.8 §		

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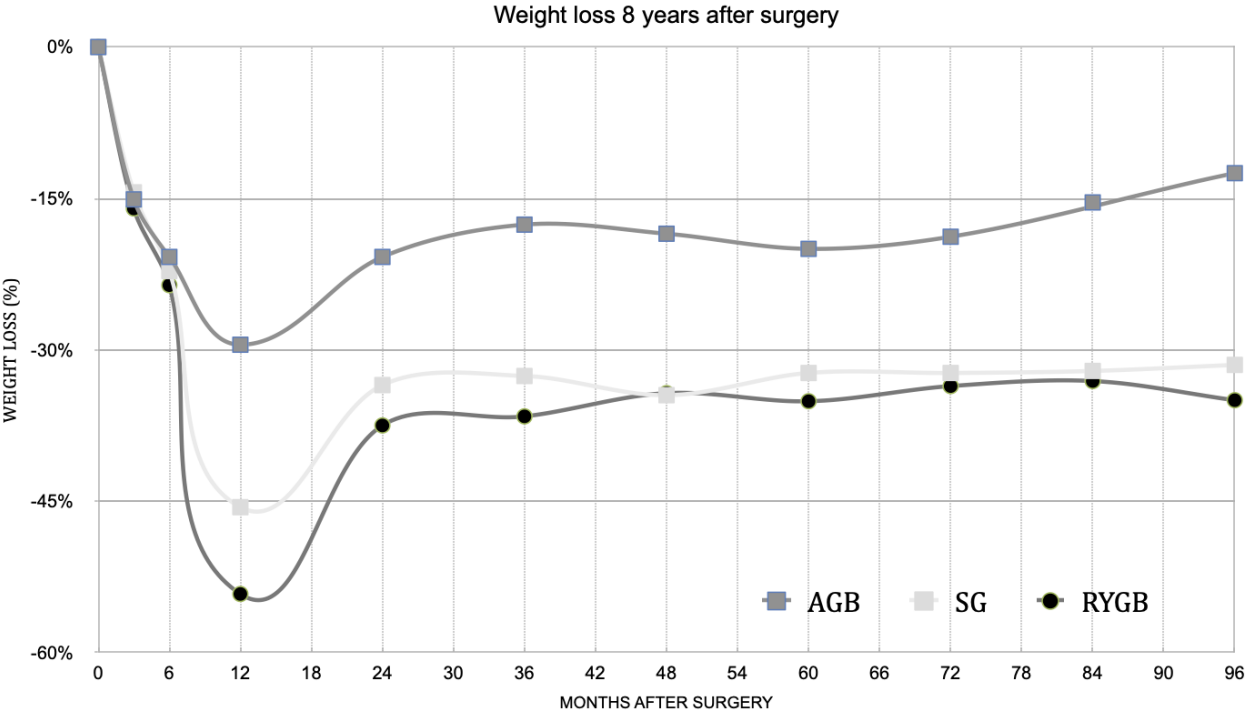
BMI	47.2±9.2	43.6 - 50.8	31.6±4.9	29.7 – 33.6	<0.001	15.6±8.6 #		
EBW	64.5±30.3	52.0 - 77.1	19.0±14.1	13.1 - 24.8	<0.001			
%EWL			70.0±21.9	60.9 - 79.0				
	RYGB (16)							
BW	137.6±26.3	124.7 -150.5	87.3±16.0	79.5 - 95.1	<0.001	50.3±28.8 §		
BMI	49.8±7.1	46.4 -53.3	32.0±6.5	28.8 - 35.2	<0.001	17.9±9.1 #		
EBW	68.9±22.9	57.7 - 80.1	18.6±17.4	10.0 - 27.1	<0.001			
%EWL			71.7±27.4	57.1 - 86.3				
	ALL SUBJECTS							
BW	135.7±29.6	127.4 -143.9	94.6±18.5	89.4 - 99.7	<0.001	41.1±29.3		
BMI	47.5±8.5	45.2 - 49.9	33.3±6.3	31.5 - 35.0	<0.001	14.3±9.4		
EBW	64.4±26.8	57.0 - 71.9	23.3±17.7	18.3 - 28.3	<0.001	41.1±29.3		
%EWL			60.6±32.3	51.6 - 69.5				

AGB: laparoscopic adjustable gastric banding SG: sleeve gastrectomy. RYGB: Roux-en-Y gastric bypass. BW: body weight. EBW: excess body weight to the ideal body weight (BMI=25 kg/m2) %EWL: % weight loss achieved to the ideal body weight. Data as mean ± SD and 95% CI. *t-test .# p=0.002 § p=0.008

All three bariatric procedures led to sustained weight loss (Figure 1). The mean BMI decreased from a baseline of 47.5 kg/m2 to 33.3 kg/m2 and average weight loss was 41.1±29.3 kg after 96 months. Average percentage excess weight loss, defined as weight loss divided by excess weight based on ideal body weight at BMI 25kg/m2, was 60.6%±32.3 from baseline to 8 years after surgery. RYGB patients had the greatest weight loss of 50.3±28.8 kg (%EWL = 71.7±27.4%) at the end of follow-up period, although not dissimilar to what observed in SG patients 45.6±27.8 kg (%EWL = 70.0±21.9%), whereas weight loss in AGB patients was lower (17.6±22.5 kg; %EWL = 22.9±32.3%).

Figure 1. Weight loss (%) in patients undergoing AGB, SG and RYGB procedures 8 years after surgery



At 8 years after surgery, a total of 80.7% of subjects (72.7%, AGB; 76%, SG; 93.7%, RYGB) reported at least one nutritional deficiency; 23.1% of the subjects had three or more

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nutritional deficiencies (Table 3).

Table 3 . Patients' nutritional deficiencies (%)

%		After 8 years				Prevalence in adult population	References
		AGB (11)	SG (25)	RYGB (16)	Total (52)		
Iron	F	66.7	58.8	68.8	64.3	8.2 – 32.9	[10-12]
	M	0	37.5	/	30	3	
	Total	54.6	52	68.8	57.7	?	
Vitamin D	F	33.3	41.2	37.5	38.1	28 – 76	[13-14]
	M	50	75	/	60		
	Total	36.3	48	37.5	42.3		
Vitamin B12	F	22.2	17.6	12.5	16.6	6	[15-16]
	M	0	12.5	/	10	6	
	Total	18.2	16	12.5	15.4	6 – 20	
Calcium	F	22.2	29.4	43.8	33.3	Data not available	
	M	0	0	/	0		
	Total	18.2	28	43.8	30.8		
No deficiency		27.3	24	6.3	19.2		
1 deficiency		36.4	16	50	30.8		
2 deficiencies		9.1	36	25	26.9		
3 or more deficiencies		27.3	24	18.7	23.1		
TOTAL°		72.7	76	93.7	80.7		

AGB: laparoscopic adjustable gastric banding. SG: sleeve gastrectomy. RYGB: Roux-en-Y gastric bypass. Nutritional deficiency limits: iron less than 200 pg/mL, vitamin B12 less than 200 pg/mL, 1,25-dihydroxyvitamin D less than 25 nmol/L , calcium less than 9 mg/dL. ° Subjects with at least one nutritional deficiency

The prevalence of some nutritional deficiencies was higher in females for iron (F 64.3% vs. M 30%), vitamin B12 (F 16.6% vs. M 10%) and calcium (F 33.3% vs. M 0%). Deficiency in 25OHD was more prevalent in males (F 38.1% vs. M 60%).

The rate of dietary supplement use was similar between SG (88%) and RYGB (93.8%), while this was 72.8% in AGB patients (Table 4). 3.8% of patients with nutritional deficiencies did not use supplements (9.1%, AGB; 4%, SG; 0% RYGB).

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Table 4 . Patients' supplement use (%)

	8 years post-operation			
%	AGB (11)	SG (25)	RYGB (16)	Total (52)
Bariatric supplements	9.1	40	31.2	30.8
Bariatric procedure specific supplements	27.3	24	18.8	23.1
Multivitamin supplements	18.2	12	12.5	13.5
Vitamin D 3 + calcium	27.3	20	43.8	28.8
Generic vitamin B supplements	0	8	12.5	7.7
Iron	27.3	12	25	19.2
Total patients that take at least one supplement	72.8	88	93.8	86.5
Patients with deficiencies that do not take supplements	9.1	4	0	3.8

For oral supplements, patients were considered to take the specified supplement if they reported taking that supplement at least 5 days per week. AGB: laparoscopic adjustable gastric banding, SG: sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass.

4. Discussion

Our data confirm that the different bariatric surgery options offer the possibility of weight loss that, although with a different WR, is lasting after a period of eight years.

There are several studies in the literature that have evaluated the long-term effects of bariatric surgery on WR, nutritional deficiencies and supplement use. Our data on weight loss (%EWL; AGB: 22.9±32.3%, SG: 70.0±21.9%, RYGB: 71.7±27.4%) turns out to be similar to those present in the literature. Another paper showed that in AGB patients percentage of weight loss was 14.9% at year 7 and mean year 3 to 7 regain was 1.4% of baseline weight [17], For SG patients, a recent review showed in long-term studies (8+years of follow-up) a %EWL between 54 and 62.5% [18]. In a 2016 review and meta-analysis on the midterm results of RYGB, the %EWL was 70% in 10 years [19]. In RYGB subjects, a recent trial revealed that a mean percentage of weight loss after 7 years was 28.4% and between years 3 and 7, there was a mean regain of 3.9% [17]. A total of 405 of 564 patients undergoing RYGB (71.8%) had more than 20% estimated weight loss by 10 years [20].

Our data revealed that the maximal weight loss occurred after 12-24 months in the majority of patients. From the second year onwards, the weight lost remained stable and there was no further WR. On the contrary, the weight of LAGB patients, as expected, continued to rise. It has been demonstrated that SG generates 30% sustained WL, although a portion of patients had WR in the long term [21] The mechanism of postoperative WR is barely known because of the deficiency of long-term data. The easiest explanation may be related to the enlargement of the gastric pouch, which would increase the amount of food eaten per meal. A decrease in ghrelin, a fast-acting hormone that plays a role in meal initiation, may be related to weight loss after bariatric surgery [22], but long term variations in ghrelin levels do not appear to correlate with WR after the RYGB nadir weight has been achieved [23]. WR may be related to a decrease in the resting metabolic after long-term follow-up in bariatric patients [24].

The risks of long-term nutritional deficiencies have been known since the beginning of bariatric surgery [25]. In our sample, despite the widespread use of nutritional supplements, most patients have at least one nutritional deficiency. In comparison with healthy adults, our sample of bariatric patients demonstrated a higher deficiency of iron, 25OHD

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and vitamin B 12 (table n.3). Patient data reveal a higher prevalence of iron deficiency in RYGB patients than in SG and AGB patients. Our results are different of data from a systematic review suggesting that SG and RYGB are comparable with regard to the risk of postoperative anaemia and iron deficiency [26].
An important finding was the iron deficiency in males undergoing SG (unfortunately, in our study sample there were no males undergoing RYGB). Data from the literature show that obesity is significantly associated with iron deficiency [27] and long-term energy restriction does not affect iron status [28]. It is necessary therefore to pay attention to the risk of iron deficiency in male patients undergoing SG.
Although 25OHD supplementation (in the form of vitamin D3 or a multivitamin) was prescribed for the vast majority of patients, the nutritional deficiency of this vitamin was 42.3% in these subjects, particularly in patients undergoing SG. These data are however in line with the prevalence in the general population [13-14]. Another study showed that, in RYGB subjects, supplementation does not warrant the nutritional status of this vitamin, because after surgery 91% of women and 85% of men had 25OHD deficiency. The study also revealed no change in serum calcium before and after surgery [29]. It is interesting to note that adiposity loss should lead to a release of 25OHD into the bloodstream and increase circulating 25OHD levels with fat mass loss through lifestyle modifications without supplementation [30]. In recent years, several studies have shown that the current limits of blood 25OHD might have been wrongly estimated and that, therefore, widespread nutritional deficiencies in the population may be overestimated [31]. There is no clear evidence for a beneficial effect of 25OHD supplementation on cardio-metabolic parameters in obese individuals, and data on such parameters with weight loss are very scarce [32]. Interestingly, our data show that 25OHD deficiency is more prevalent among males than women; this aspect contradicts the lower 25OHD concentrations found in obese females than males, due to the higher fat mass[33].
Vitamin B12 deficiency was found to be higher, mainly in women, compared to the data from the general population, and showed no particular differences between procedures or between sexes. Because vitamin B12 deficiency can, if discovered late, lead to irreversible neurological damage, subjects of both sexes who have had bariatric surgery should be supplemented with 1 mg of oral vitamin B12 per day for life [34]. Supplements taken 8 years after surgery were generic multivitamin and minerals, bariatric surgery supplements, supplements specific for a surgery type or B complex supplements. The use of multivitamins, calcium, iron and 25OHD is lower when compared to another cohort of bariatric patients; however, the use of at least one supplement is higher [35].
There are many limitations to our study. There was a higher prevalence in the sample of women than men; in particular, there was no male patient who underwent RYGB. Many important nutritional blood tests, such as albumin, vitamin B1, folic acid and zinc were not performed. We do not have data on nutritional deficiencies before surgery, so we decided to compare our patients' data with epidemiological data in the literature.

5. Conclusions

From the third year after surgery, weight loss in patients undergoing RYGB and SG appears constant. Nutritional deficiencies, despite the use of new surgery-specific supplements in part of the sample, appear similar to other papers published a few years ago. In comparison with the general population, nutritional deficiencies in bariatric patients are greater among men for iron and among women for vitamin B12.

Author Contributions: A.F., G.R. and R.B.F. performed the literature search, participated in the data collection and analyses, and drafted the manuscript; M.D., V.G. performed the literature search and drafted the manuscript; A.B., E.P., M.C. and P.S. participated in the design of the study, data collection, and drafted the manuscript; M.L. was the principal investigator of the study, led its design, coordinated the steps of the data collection and data analyses, and drafted the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by Institutional Research Board (School of Sports and Exercise Science, University of Rome “Tor Vergata”, Faculty of Medicine and Surgery - protocol number ITPro2012-000108). All participants could choose if they wanted to participate in the study and could at any time withdraw their consent.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study
Conflicts of Interest: The authors declare no conflict of interest.

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