Introduction
Obesity is a major problem affecting modern society. In the United Kingdom (UK), the prevalence of obesity has doubled in the last 25 years, with a similar pattern being observed in most Western countries. Currently, 26% of adults in the UK are obese. By 2050, it is estimated that 60% of adult men and 50% of adult women will be obese. Studies have shown that obesity is linked to ill health, with a strong link to type 2 diabetes. It is also a risk factor for cardiovascular disease and some cancers. It is estimated that the direct economic cost of obesity to the UK National Health Service (NHS) amounts to around £3.2 billion.

Because of the health and economic burden of obesity, efforts to tackle this growing problem have increased. Unfortunately, calorie restricted diets have not been shown to be an effective route to long-term weight loss in obese patients, with little evidence of significant health improvements and up to two-thirds of patients regaining more weight than they lose. This has led to a growth in the popularity of weight-loss bariatric surgery.

Bariatric surgery is an effective treatment for obesity. The American Association of Clinical Endocrinologists recommends that bariatric surgery is considered for obese patients with a body mass index (BMI) of greater than 40, or for patients with a BMI of greater than 35 with serious co-existing medical conditions, including diabetes.

There have been numerous operations proposed for weight loss. These are broadly defined as restrictive procedures, where a physical restriction to the gastrointestinal tract in the form of a band is used to make a smaller stomach, or reducing surgery, such as the Roux-en-Y gastric bypass, where parts of the stomach and small bowel are permanently bypassed. These methods have been proven to result in sustained weight loss and reduced mortality. It is thought that these operations do not work by reducing the absorptive capacity of the bowel but, rather, affect the complex gut hormonal profile, improving weight regulation mechanisms. Various hormones have been implicated, including peptide YY, which is believed to reduce appetite.

Gastric banding is an important restrictive technique widely employed for weight loss. An inflatable band is placed around the upper part of the stomach, which limits the amount of food which can be consumed at any given time, and allows a sense of satiety to be met. It is less invasive than a gastric bypass and most modern bands can be adjusted post-procedure. It is effective in both achieving weight loss and in improving metabolic parameters, including diabetes.

A systematic review has suggested that gastric banding is not
as effective as bypass surgery, with gastric bands achieving 50% of their excess weight loss in two years compared to 70% with bypass surgery. For both gastric banding and bypass procedures, a significant proportion (79%) of patients regain some weight post-bariatric surgery, with a small proportion regaining all of the initial weight.

Unfortunately, there are many obese patients who are unfit to undergo bariatric surgery. Furthermore, surgery can carry significant long-term complications, both in terms of short-term morbidity post-operatively and in terms of long-term complications, including significant malnutrition. Bariatric surgery is irreversible, which means these problems cannot be easily reversed. There is an issue with weight regain after bariatric surgery in a significant proportion of patients, with currently very few options for rescue therapy. Some patients simply do not want to undergo surgery because of these problems. Bariatric surgery is expensive, and in this current era of austerity there is inadequate capacity in most countries to meet the projected need for bariatric surgery. There is therefore a clinical need for minimally invasive and cost-effective methods both to reduce weight and, more importantly, improve metabolic parameters and reduce mortality. This has led to the development of endoscopic devices to facilitate weight loss.

Various approaches have been taken, including gastric balloons and helicosphere bags, with some evidence of benefit. These are all restrictive procedures with some evidence of efficacy. However, these techniques have been limited by non-tolerance, spontaneous deflation and small bowel obstruction, with little evidence of sustained weight loss compared to conventional management (diet therapy).

The Endobarrier is an endoluminal device which is placed endoscopically into the duodenum. It acts as a physical barrier between the intestinal wall and luminal contents, potentially delaying digestion and altering the activation of hormonal signals. It has been hoped that in this way it may mimic the effects of reductive surgery.

This article aims to examine the evidence behind the Endobarrier.

There have to date been six studies examining the efficacy of Endobarrier. Four of these were open-label prospective cohort studies and two were randomised controlled trials. Outcome measures included weight loss, safety and improvement in metabolic parameters, including glycaemic control, lipid profile and blood pressure.

Randomised controlled trials

A randomised controlled trial examined 41 patients, 30 of whom underwent sleeve implantation. It was a multi-centre study where all patients initially followed a low-calorie diet during the study period. The initial mean BMI of the cohort was 48.9 kg/m² and 47.4 kg/m² for the device and control patients, respectively. The key endpoints were safety and efficacy of the device. In total, 26/30 (87%) were successfully implanted. The device took a mean of 35 minutes to install (range 12–102 minutes), with no procedure-related adverse events. During the study period, all of the 26 duodenal-jejunal bypass sleeve patients (100%) had at least one adverse event, mainly abdominal pain and nausea during the first week after implantation. In 4/26 (15%) of cases, the device had to be removed. These included one episode of sleeve migration, one dislocation of the sleeve from its anchor, one sleeve obstruction and one episode of unresolvable abdominal pain. After three months, there was a mean loss of excess weight of 19.0% for device patients versus 6.9% for control patients (p<0.002), with an absolute change in BMI at three months of 5.3 kg/m² and 1.9 kg/m², respectively. The study examined impact on metabolic parameters. Type 2 diabetes mellitus was present at baseline in eight patients in the device group. This improved in seven patients during the study period (lower glucose levels, HbA1c, and medication requirements). The authors concluded that the Endobarrier is a feasible and safe non-invasive device with excellent short-term weight loss results. The device also appeared to have a significant positive effect on type 2 diabetes mellitus, although it should be noted that the numbers are very small and larger studies would be needed to confirm if this is truly the case. The effects were measured while the device was in situ, so this study does not give us any information on long-term benefit nor the lack of it and the device was removed at three months.

A further randomised controlled trial has examined the efficacy of Endobarrier in achieving improved glycaemic control in obese patients with type 2 diabetes. This exploratory trial randomised 18 patients to either Endobarrier or a sham procedure. Endpoints included weight, HbA1c, fasting glucose, and glucose profiles. Subjects had a BMI of 38.9 kg/m², with a baseline HbA1c of 9.1% (76 mmol/mol). In total, 12 patients received the Endobarrier. A change in fasting glucose in the Endobarrier arm was -55±21 mg/dl versus +42±30 mg/dl in the sham arm. Likewise, the glucose profiles were reduced in the patients receiving Endobarrier but not in the sham arm. While the mean postprandial glucose area under the curve was reduced in the Endobarrier arm by 20%, it increased by 17% in the sham arm. This difference was statistically significant. There was a significant improvement in the change in HbA1c, with a reduction of 2.4% in the Endobarrier arm and 0.8% in the sham arm. Again, like the previous study, an improvement in glycaemic control is potentially clinically important. However, the results need to be interpreted carefully. Study size was very small and how sustained this response is cannot be determined from this study.

Cohort studies

All of the cohort studies examined metabolic parameters. The results from three of these cohort studies are summarised in Table 1. All of these studies showed an improvement in metabolic status, including improved glycaemic control, lipids and blood pressure.

The largest cohort study examined 42 subjects over a one-year period. These patients were morbidly obese, with a mean BMI of 43.7 kg/m². In total, 39/42 underwent sleeve insertion, with three
subjects unable to undergo implantation due to a short duodenal bulb. The mean implantation time was 24 minutes. Again, no procedure-related complications were encountered. However, there were 15 (39%) early sleeve removals. Eight were removed due to device movement/migration, three for device obstruction and two for abdominal pain. There was one episode of acute cholecystitis necessitating removal, and one was removed due to the patient’s request. The primary endpoint was safety and weight change, with secondary endpoints of a change in metabolic parameters, including waist circumference, blood pressure, lipids, glycaemic control and the metabolic syndrome. In the 52-week completer population, the total body weight change from baseline was -22.1 ± 2.1 kg (p < 0.0001). This represented a 19.9 ± 1.8% reduction in total body weight and a 47.0 ± 4.4% loss of excess weight. There was a significant improvement in waist circumference, blood pressure, total and low-density lipoprotein cholesterol, triglycerides, and fasting glucose.

These results were echoed in a second, similar study which examined 22 patients with type 2 diabetes and a mean BMI of 44.8 kg/m². Again, the device was implanted for one year in a prospective, open-label study. In this study, the endoscopic device was implanted under general anaesthesia. The primary endpoints were changes in fasting blood glucose and insulin levels and changes in HbA₁c, with the Endobarrier removed endoscopically at the end of the study. In total, 13/22 (59%) subjects completed the 52-week study, with 41% having the device removed before the endpoint due to adverse events. Reasons for removal included device migration (n = 5), gastrointestinal bleeding (n = 1), abdominal pain (n = 2), principal investigator request (n = 2), or the discovery of an unrelated malignancy (n = 1). In total, there were 30 procedure-related complications: 11 cases of upper abdominal pain, five cases of back pain, seven episodes of nausea and seven cases of vomiting associated with the device. There were statistically significant reductions observed in fasting blood glucose (-30.3 ± 10.2 mg/dl), fasting insulin levels (-7.3 ± 2.6 μU/ml), and HbA₁c (-2.1 ± 0.7%). At the end of the study, 16 of the 22 subjects had an HbA₁c < 7% compared with only one of 22 at baseline. The authors concluded that the Endobarrier improves glycaemic status in obese subjects with diabetes. Similar results were seen in a smaller pilot study.

It is important to note that all of these cohort studies reflect similar findings to those seen in the two randomised controlled trials previously discussed. Complications were very similar and the effects observed in terms of improved glycaemic control were the same. It is unclear if further cohort studies conducted in this way will add much more to the data already collected. We feel that, if further cohort studies are conducted, they will need to be much larger and address issues around long-term benefits/problems beyond one year of follow up. A potential route to obtaining this kind of data would be through the formation of multicentre research registries for patients undergoing Endobarrier implantation. We consider this should be a research priority.

Table 1. Summary of key findings from studies on Endobarrier for weight loss and diabetes management

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>BMI (kg/m²)</th>
<th>Procedure time (min)</th>
<th>Weight loss</th>
<th>Complication rate</th>
<th>Change in HbA₁c / improvement in glycaemic control</th>
<th>Stent removal rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schouten R, et al.²²</td>
<td>RCT</td>
<td>41; 30 received treatment</td>
<td>49 device; 47 control</td>
<td>35</td>
<td>19% device; 6.9% control (p &lt; 0.002)</td>
<td>100% minor</td>
<td>Diabetes present in 8 patients at baseline. Improved in 7 during study period</td>
<td>15%</td>
</tr>
<tr>
<td>Rodriguez L, et al.²³</td>
<td>RCT</td>
<td>18; 12 received treatment</td>
<td>39</td>
<td>31±4</td>
<td>-10.2 ± 1.3 kg in treatment arm vs 7.1±4.3 kg in sham arm at week 12. Not reported for week 24. (p &gt; 0.05)</td>
<td>100% minor</td>
<td>9.1±7.8% baseline. Change of HbA₁c at 24 weeks: -2.4±0.7% treatment; -0.8±0.4% control. (p &gt; 0.05)</td>
<td>25%</td>
</tr>
<tr>
<td>Escalona A, et al.²⁴</td>
<td>Cohort</td>
<td>42; 39 received treatment</td>
<td>44</td>
<td>24</td>
<td>19.9±1.8% of total body weight (p &lt; 0.0001)</td>
<td>Minor</td>
<td>Fasting glucose 102.3 mg/dl at baseline falling to 92.9 mg/dl (p = 0.044)</td>
<td>39%</td>
</tr>
<tr>
<td>de Moura EG, et al.²⁵</td>
<td>Cohort</td>
<td>22</td>
<td>45</td>
<td>Not recorded</td>
<td>Not an endpoint</td>
<td>41%</td>
<td>-2.1% drop in HbA₁c. -30.3 mg/dl drop in fasting blood glucose. 16/22 had an HbA₁c of &lt;7% at end of study (1/22 at baseline)</td>
<td>41%</td>
</tr>
<tr>
<td>Escalona A, et al.²⁶</td>
<td>Cohort</td>
<td>10</td>
<td>41</td>
<td>Not recorded</td>
<td>16.7% total weight loss</td>
<td>70%</td>
<td>Not an endpoint</td>
<td>0%</td>
</tr>
</tbody>
</table>
Endobarrier: a viable alternative to gastric bypass surgery?

Impact of Endobarrier on metabolic parameters

Many of the studies previously described demonstrated benefits in terms of glycaemic control and metabolic parameters. Because of the observed effects on metabolic parameters, a further study has examined the impact of Endobarrier on the key gut hormones GLP-1 and PYY (glucagon-like peptide 1 and peptide YY). These hormones are felt to be of central importance for the pathogenesis of obesity. In this prospective cohort study, 17 obese patients with type 2 diabetes mellitus were examined. Patients had the Endobarrier inserted and were put onto a low-caloric diet for 24 weeks. Weight, HbA1c, fasting and post-prandial glucose, insulin, GLP-1, and PYY were measured. It was found that the intervention resulted in a total weight loss of 12.7±1.3kg (29.8±3.5% reduction in excess weight). Fifteen of 17 patients reported increased satiety, with all patients reporting reduced caloric intake. There were increased levels of postprandial GLP-1 and PYY secretion, and changes in fasting and postprandial ghrelin levels. There were decreased fasting leptin levels which positively correlated with BMI (rs=0.58, p<0.05). Of note, no hormonal changes were observed after the device was removed, suggesting that benefits are not sustained after device removal. The abstract did not comment on complication rates. The authors felt that a possible explanation for the weight loss was that the device was affecting satiety and food intake, probably via triggering of the ileal-brake, as indicated by the increased GLP-1 and PYY levels. (See Figure 1.) The increased ghrelin levels were felt to be secondary to the reduced caloric intake.

It has been generally accepted that many of the benefits of definitive anti-obesity surgery are driven from a change in metabolic parameters rather than from reduced absorption. While the mechanisms are complex and incompletely understood, these findings would be consistent with this view. It is important to appreciate that this study does not attempt to explain how the Endobarrier drives these changes. It is reasonable to postulate that part of its mode of action prevents the mixing of bile and pancreatic digestive enzymes with food contents in the proximal duodenum, but this does not directly explain the findings described here. What is apparent from this study is that the effects of Endobarrier are likely to be far more complex than simply inducing malabsorption. This is beneficial but also raises questions around its effects and safety if used on a long-term basis.

Endobarrier in patients who are not morbidly obese

Because of the proposed benefits in glycaemic control, there has been a study examining Endobarrier in patients with type 2 diabetes who are not obese. This pilot study examined patients with type 2 diabetes of ≤10 years’ duration, with an HbA1c of >7.5% (58mmol/mol) and <10% (86mmol/mol), and a BMI of 26–50kg/m². The main outcome measure was fasting plasma glucose levels, HbA1c, and change in body weight. In total, 20 patients underwent device implantation. The mean BMI of the cohort was 30.0kg/m², suggesting patients were obese, but not as large as those examined in the previous studies. Sixteen of 20 completed the study. Fasting plasma glucose levels dropped from 207mg/dl at baseline to 139mg/dl at one week. This reduction was sustained throughout the study. HbA1c fell from 8.7% (72mmol/mol) at baseline to 7.5% (58mmol/mol) at week 52. While the mean body weight declined, this was not significantly associated with the change in fasting plasma glucose. This would suggest that the benefits may extend beyond simple weight loss and provides a rationale for performing further studies in patients where the obesity is not so pronounced.

This supports the points made surrounding the previous study. It is generally felt that diabetes forms part of a metabolic syndrome, and weight gain may be more of a symptom of this condition than simply a cause for worsening insulin insensitivity. While the subjects in this study were overweight, the changes in blood glucose were observed within a week, too early to be driven by weight loss alone. This study would suggest that in some (unknown) way Endobarrier alters the gut hormones to improve blood glucose regulation. A future area for research into Endobarrier will be into investigating how it alters metabolic parameters and gut hormones. If this could be understood better, we may understand better who would potentially gain the most from Endobarrier.

Figure 1. Effects of Endobarrier on gut hormones and insulin leading to weight loss and improved glycaemic control
Discussion

There is growing evidence that the Endobarrier duodenal-jejunal bypass is effective both in achieving weight loss and in improving metabolic parameters associated with long-term morbidity and mortality. In all of the studies, initial insertion was uncomplicated in the majority of cases. It is, however, associated with significant complications in many cases, with sleeve removal being required in up to 40% of cases. It is important to understand that the Endobarrier is a reversible procedure. This is in stark contrast to bariatric surgery, where complications cannot be resolved in such a simple manner as device removal.

It is currently unclear where Endobarrier fits into the clinical management of obesity and/or diabetes. While it is a device which shows considerable promise, both in achieving weight loss and in improving metabolic parameters, there have been no head-to-head comparisons with the established bariatric surgical techniques. Which patient population benefits greatest from Endobarrier is unclear and whether the gains made are sustained on a long-term basis are unknown. There are therefore many questions which still need to be answered.

It is unclear how long the optimum time is for Endobarrier to be in place. At present, the proposed strategy is to remove Endobarrier at one year. However, it may be that sustained benefit can be achieved by leaving it in for much longer, even permanently.

There is therefore a need for much larger clinical trials to investigate the true potential of these devices. There is no study to date with a follow-up period of greater than one year. This reflects the recent introduction of Endobarrier into the clinical arena. In particular, sustainability of the results seen in these studies needs to be assessed. Furthermore, the potential long-term problems which could arise have not yet been fully evaluated. This is not a problem restricted to Endobarrier and could be targeted at most of the commonly performed bariatric procedures. There are, however, much more long-term data available for gastric banding and restrictive surgery than there are for Endobarrier. It is interesting to note that all of the published studies investigating Endobarrier have shown similar results, both in terms of positive results and in adverse outcomes. Therefore it is reasonable to feel optimistic about Endobarrier, but this optimism must be tempered with caution.

We feel that Endobarrier is likely to be of greatest benefit to patients where the risks of surgery are high. There are many patients with life-threatening obesity who are simply not fit to undergo surgery. It is likely that Endobarrier could prove to be an attractive option in these patients to effectively ‘downstage’ their clinical risk prior to surgery. Even a modest reduction in weight and improvement in metabolic parameters can have an important effect on making surgery viable.

We feel the data on Endobarrier in patients with type 2 diabetes who are not morbidly obese are particularly interesting. There are many patients where the risk of permanent reductive surgery cannot be justified. However, where diabetic control is poor there is often a lack of options for these patients. Endobarrier may offer an effective way of achieving better glycaemic control. Again, further studies are needed to answer this question.

It is important to appreciate that all of the studies currently published are small. These provide a compelling argument for developing large clinical trials.

However, caution should be shown before widespread adoption into the routine management of diabetes or obesity. It is simply unclear at present what unforeseen problems may arise from use of the device, and these questions will only be answered through further research.

A significant limitation of the published literature has been that none of the studies have long-term follow up. It is therefore difficult to be certain that any of the gains seen are sustained. Furthermore, there has been no direct comparison of Endobarrier to the existing surgical techniques, or other available endoscopic treatments. Therefore establishing where Endobarrier fits into treatment algorithms is difficult. We feel this should also be a focus for future research.

Conclusions

Endobarrier is an exciting new device for weight loss in morbidly obese patients, and has the potential to improve glycaemic control and metabolic parameters. It can be fitted with minimal problems but is associated with significant complications, usually resolvable by sleeve removal. We feel this is a significant innovation ready for large-scale clinical trials before a mainstream introduction of this device into the management of diabetes or obesity.

It is our contention that Endobarrier should not be seen as a replacement for bariatric surgery, but as a useful additional therapy in challenging patient group. Its place in the clinical treatment pathways of obesity is currently unclear and should be a focus for future research.

Declaration of interests

There are no conflicts of interest declared.

References

References are available in Practical Diabetes online at www.practicaldiabetes.com.
References

2. www.foresight.gov.uk. Foresight, 1 Victoria Street, London SW1H 0ET. 2012.