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Layton, Georgia R.; Bhanderi, Shivam; Sahloul, Mohamed; Charalampakis, Vasileios; Daskalakis, Markos; Singhal, Rishi

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# Challenges and outcomes for bariatric surgery in patients with paraplegia: Case series and systematic review

Georgia R. Layton<sup>1</sup>  | Shivam Bhanderi<sup>2</sup> | Mohamed Sahloul<sup>3</sup>  |  
Vasileios Charalampakis<sup>4,5</sup> | Markos Daskalakis<sup>3,5</sup> | Rishi Singhal<sup>3,5</sup>

<sup>1</sup>Leicester General Hospital, University Hospitals Leicester NHS Trust, Leicester, UK

<sup>2</sup>Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

<sup>3</sup>Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

<sup>4</sup>Warwick Hospital, South Warwickshire NHS Foundation Trust, Warwick, UK

<sup>5</sup>Healthier Weight Centre, Birmingham, UK

## Correspondence

Mr. Rishi Singhal, Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.  
Medical Director, Healthier Weight  
Email: singhal\_rishi@hotmail.com

## Summary

**Introduction:** Obesity contributes to a plethora of significant chronic diseases. Bariatric surgery has been demonstrated to be the most cost-effective treatment for severe obesity and significantly reduces morbidity and mortality from metabolic syndrome. Patients with paraplegia have significantly impaired mobility and are therefore at a much higher risk of developing severe obesity and its sequelae. Bariatric surgery may bring significant improvements to mobility, morbidity and quality of life for patients with paraplegia, but evidence in the literature is poor for this group of patients.

**Methods:** A systematic review was conducted conforming to PRISMA guidelines. The MEDLINE and Cochrane databases were searched for all articles published prior to April 2019 matching all of the keywords 'bariatric', 'paraplegia' and 'spinal cord'. Articles were assessed for relevance and full texts reviewed.

In addition, clinical records were reviewed for three patients who underwent bariatric surgery at a single UK private institution. Non-identifiable demographic, clinical, operative and outcome data were obtained from electronic records.

**Results:** Twenty seven articles were retrieved from the initial database search, of which nine eligible full texts were reviewed. Eight articles were case reports or case series and the final article was a systematic review. All cases reported had positive outcomes with significant weight loss, improvement in mobility and increased quality of life. Outcomes from the three diversely aged patients in our case series were similarly positive, with no significant post-operative complications.

**Discussion:** Patients with obesity and paraplegia may significantly benefit from bariatric surgery. There is a need for multi-centre cohort studies to evaluate outcomes and the choice of bariatric intervention. UK guidelines do not include criteria based on mobility or neurological deficit, resulting in a potential missed opportunity to offer a cost-effective treatment that can significantly improve quality of life for patients with severe obesity and paraplegia.

## KEYWORDS

bariatric surgery, gastric bypass, obesity surgery, paraplegia, sleeve gastrectomy

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## 1 | INTRODUCTION

### 1.1 | Obesity and paraplegia

Obesity remains one of the western world's most pressing health challenges. It is associated with a plethora of comorbidities<sup>1-3</sup> including diabetes, cardiovascular disease and cancer. It has been widely proven that sustained weight loss significantly reduces risk of both acquisition of these chronic health problems and improves outcomes from their treatment.<sup>4-6</sup>

There is a much higher risk of obesity, and therefore its sequelae, amongst patients with paraplegia.<sup>7,8</sup> The odds ratio for obesity in patients with paraplegia has been previously reported as 2.5 times higher than adults with other non-disabling conditions.<sup>9</sup> The true prevalence of obesity amongst patients with paraplegia however is difficult to define as traditionally accepted metrics such as body mass index (BMI) may not be applicable to this subpopulation. Nevertheless, there is evidence that patients with paraplegia may have more morbidity from metabolic diseases. A 2011 cross-sectional study demonstrated that at least 10% of young people with spinal cord injury are at moderate to high risk of adverse cardiometabolic events as well as those patients with neurological deficit and obesity experiencing higher levels of pain, higher rates of unplanned hospitalization and reduced social inclusion.<sup>10</sup>

A significant part of both obesity prevention and treatment focuses on exercise and mobility, however patients with paraplegia face evident difficulties with this aspect of weight management due to restrictions on mobility that preclude adequate participation into conventional physical activity programs. It has been demonstrated that patients with paraplegia may have a lower resting metabolic rate than age-matched individuals with no neurological deficit.<sup>11,12</sup> This is thought to be partly due to the fact that atrophied muscle starts to be infiltrated by adipose tissue, which undergoes less metabolism and thus results in a net reduction in metabolic rate.<sup>12</sup>

Weight loss achieved following bariatric surgery could reduce morbidity and mortality for patients with paraplegia,<sup>7</sup> whilst also allowing them to transfer to and from the bed and mobilize with a wheelchair more easily, potentially leading to improved quality of life and reduced dependence on carers. This would also translate into better quality of work for carers and reduced burden for the immediate family environment. In the United Kingdom, NICE guidelines<sup>13</sup> for provision of bariatric surgery do not specify any criteria based on mobility and focus solely on BMI and the presence of obesity-related metabolic comorbidities. A 2017 review<sup>7</sup> concluded that further research is required to establish the most appropriate metrics to use in order to correctly identify and categorize obesity for patients with paraplegia.

This article reviews the current literature with regards to bariatric surgery for patients with paraplegia and reports on a case series of three patients in order to add to the evidence base for bariatric surgery in this group.

## 2 | METHODS

A systematic review of the literature was performed in line with PRISMA guidelines,<sup>14</sup> in addition to compiling a case series of

### What is already known about this subject

- There is a much higher risk of obesity for patients with paraplegia than patients in the general population.
- Traditional methods of weight loss such as exercise can be challenging for patients with paraplegia.
- Bariatric surgery for this cohort of patients can offer significant weight loss, improved mobility and a better quality of life.

### What this study adds

- Bariatric surgery can be safely performed in patients with obesity and paraplegia.
- Patients with severe obesity and paraplegia require a more tailored approach to surgery than the general population.

patients with paraplegia who underwent bariatric surgery at our centre.

### 2.1 | Data source

The MEDLINE and Cochrane databases were searched for all articles published up to 1 April 2020 including the search terms 'bariatric', 'paraplegia' and 'spinal cord'.

### 2.2 | Study selection

All articles written in English were eligible for review. Abstracts returned from the initial search were all screened for relevance. All articles found to pertain to bariatric surgery for patients with paraplegia or spinal cord injury had their full texts reviewed.

Articles that were not based on human subjects or that were focused on non-surgical management of obesity were excluded. Two authors separately conducted the literature search, and where discrepancies were present these were resolved through discussion with the senior author.

### 2.3 | Case series

Demographic information for three patients with paraplegia who underwent bariatric surgery in a large UK private institution (Healthier Weight, Birmingham) were obtained from electronic health records. No electronic records from the NHS were accessed. Consultation notes, operation notes and follow-up weight measurements were

reviewed and excess weight losses calculated. Additional follow-up appointments or telephone calls were not conducted as part of compiling case reports so as to avoid deviations from usual post-operative care.

### 3 | OUR CASE SERIES

To add to the limited existing body of published cases, we present the cases of three patients with paraplegia who underwent bariatric surgery at a UK private institution.

#### 3.1 | Patient 1

A 34-year-old female full time student, who was a wheelchair user due to paraplegia following a spinal cord injury at L1 since the age of 4 years, was evaluated for bariatric surgery. She had intact bowel function and her overactive bladder symptoms were managed with oxybutynin. In addition, she was on diazepam for spasmodic back pain. In clinic, her baseline weight was 76.6 kg with a BMI of 39.0 kg/m<sup>2</sup>.

She underwent a sleeve gastrectomy (LSG). Her immediate recovery was uneventful and she was given 7 days of low-molecular weight heparin (LMWH) following surgery to reduce her risk of venous thromboembolism (VTE). She was re-admitted to hospital 2 weeks later with constipation. This settled conservatively. Her BMI decreased to 28.7 kg/m<sup>2</sup> after 17 months of follow-up, giving an excess BMI loss of 73%. No changes to her bowel or bladder function were reported and although not measured objectively, the patient has self-reported improvements to her mobility and sleep quality (she does not have a diagnosis of obstructive sleep apnoea).

#### 3.2 | Patient 2

A 64-year-old female disability panel member who had spinal surgery in 1965 with subsequent paraplegia presented seeking bariatric surgery. She had had two previous lower midline laparotomies as part of a previous cystectomy and ileal conduit. Her remaining medical history included dyslipidaemia, previous VTE (both deep vein thrombosis and pulmonary embolism) and gastro-oesophageal reflux disease due to a small hiatus hernia for which she was dependent on proton-pump inhibitors.

Her baseline weight was 77.1 kg with a BMI of 36.0 kg/m<sup>2</sup>. A sleeve gastrectomy was performed in order to avoid adhesions from the previous abdominal surgery, but despite her history of reflux. The hiatus hernia was not repaired and her post-operative recovery was uneventful. Due to her previous history of VTE, however, she was given extended prophylaxis of LMWH injections for 28 days. Her weight reduced to 54.43 kg with an excess BMI loss of 98%. BMI reduced to 25.2 kg/m<sup>2</sup> after 12 months of follow-up. Although still dependent on the same dosage of proton pump inhibitors for reflux as she was pre-operatively, the patient reported no subjective

increase in her reflux symptoms following sleeve gastrectomy, and stated that her improved mobility allowed her to manage the stoma of her ileal conduit more comfortably.

#### 3.3 | Patient 3

A 27-year-old female social worker who had been paraplegic since birth due to spina bifida and hydrocephalus was evaluated for bariatric surgery. She had a baseline weight of 107.95 kg with a BMI of 60.1 kg/m<sup>2</sup>. She had had more than 25 previous neurosurgical procedures for spina bifida and hydrocephalus, including a functioning ventriculo-peritoneal shunt. This patient was a wheelchair user and reported symptoms of stress incontinence. She was on long-term prophylactic antibiotics in order to reduce risk of shunt infection and urinary tract infection. She was dependant on proton-pump inhibitors for moderate gastro-oesophageal reflux disease and on Continuous Positive Airway Pressure for Obstructive Sleep Apnoea.

A sleeve gastrectomy was performed in order to reduce the risk of infection to her ventriculo-peritoneal shunt despite the history of gastro-oesophageal reflux disease.

Her operation was technically more difficult due to multiple adhesions in the upper abdomen as a result of her previous ventriculo-peritoneal shunts. In addition, despite an extended very low calorie diet (VLCD) for 6 weeks, she had a very steatotic and enlarged liver. Post-operatively, she had CO<sub>2</sub> retention and required 24 hours of Non Invasive Ventilation in High Dependency Unit (HDU)/ Intensive Care Unit (ITU). A 3 day course of intravenous antibiotics was given as additional prophylaxis against shunt infection. An extended Deep Venous Thrombosis (DVT) prophylaxis of 28 days on LMWH was prescribed.

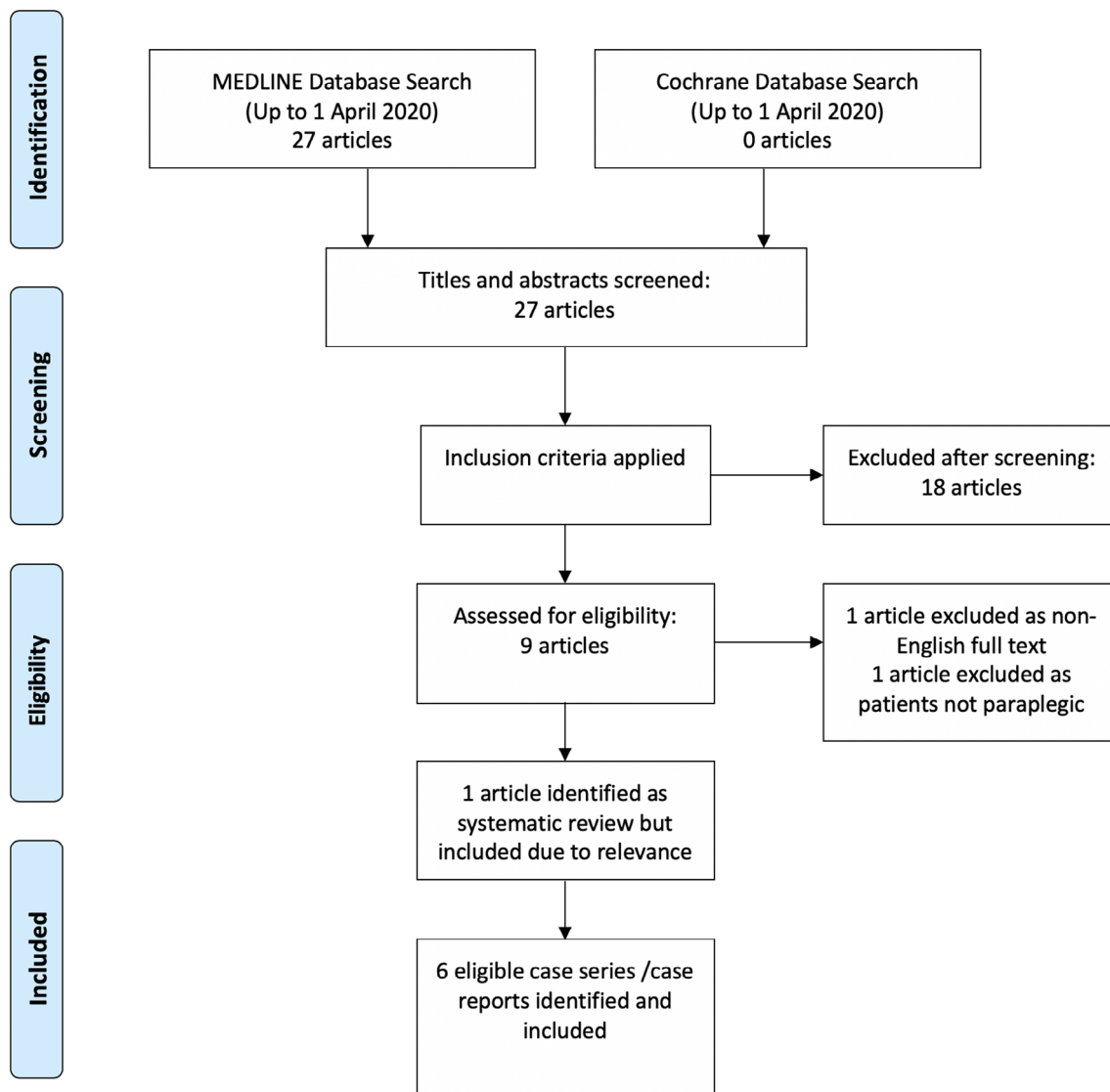
After 4 months of follow-up, she had gained a small amount of weight up to 116 kg, producing a BMI of 64.0 kg/m<sup>2</sup>. The patient has since been lost to follow-up and therefore her BMI and any further subjective information regarding her mobility or additional symptoms after a longer period post sleeve gastrectomy are not known. All reasonable attempts were made to contact the patient and her carers. Communication was also established with the General Practitioner to extend psychological support to the patient but the patient did not want to engage with weight management services at this point.

### 4 | LITERATURE REVIEW

#### 4.1 | Search results

The initial database searches returned 27 articles. Nine articles within the MEDLINE database were relevant to the study objective and therefore had their full texts reviewed. No relevant systematic reviews were found in the Cochrane database. Figure 1 shows a PRISMA flow diagram of the search results.

In total, our search retrieved eight case reports or case series and one published systematic review. A single case report was excluded as although the abstract was in English, the full text was published in



**FIGURE 1** PRISMA diagram summarizing literature review

Spanish. One case series involved patients with neurological motor syndromes such as multiple sclerosis and post-polio syndrome rather than true paraplegia and was therefore excluded following full text review. Details of the included case reports and case series are summarized in Figure 2. We also did not include the cases from the systematic review in our analysis to avoid duplication of data since no extra cases had been identified in this review. Thus eventually, six case series were reviewed.

The low number of cases and the heterogeneity in outcome reporting meant that any form of meta-analysis was deemed unfeasible by the study authors as results would likely be insufficiently reliable.

## 4.2 | Review of published literature

Overall, only 11 cases of bariatric surgery in patients paraplegia have been reported throughout the published literature.

In the first reported case of bariatric surgery on a patient with paraplegia, Alaedeen and Jasper<sup>15</sup> described the case of a 51-year-old veteran with paraplegia who lost 15 BMI points following a Roux-en-Y gastric bypass (RYGB) in 2004, who subsequently no longer required any of his oral hypoglycaemic medicines for type 2 diabetes mellitus. They reported that this patient had improvements in his mobility, participation in exercise, quality of life and positive effects on sleep apnoea and gastro-oesophageal reflux disease.

The only reported case of a patient with paraplegia undergoing a duodenal switch procedure was published by Lutrzykowski in 2008.<sup>16</sup> This was a 49-year-old diabetic lady with paraplegia below the T8 spinal level. She underwent the procedure with a BMI of 47.7 kg/m<sup>2</sup>, was normoglycemic on discharge post-operatively and at 4 years had lost 91.6% of her excess BMI down to 25.0 kg/m<sup>2</sup>. The author reported that this patient did not report any undue diarrhoea or flatulence.

Miyano et al<sup>17</sup> reported a case of a young 15-year-old male who had paraplegic from birth with spina bifida. He had a RYGB and

**FIGURE 2** Table of reports obtained from literature review. % EWL, percentage excess weight loss; BMI, body mass index; LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass

Author & Year	Operation(s)	Weight Loss Reported
Aladeen & Jasper, 2006 <sup>[17]</sup>	1 x RYGB	52% BMI loss at 1 year (48kg/m <sup>2</sup> to 23kg/m <sup>2</sup> )
Lutzykowski, 2008 <sup>[18]</sup>	2 x Duodenal Switch	51% BMI loss at 1 year (56.8kg/m <sup>2</sup> to 8kg/m <sup>2</sup> )  42% BMI loss at 1 year (47.7kg/m <sup>2</sup> to 27.6kg/m <sup>2</sup> )
Miyano et al, 2009 <sup>[19]</sup>	1 x RYGB	35% BMI loss at 1 year (60.4kg/m <sup>2</sup> to 39.4kg/m <sup>2</sup> )
Wong et al, 2013 <sup>[20]</sup>	1 x RYGB	17% BMI loss after 7 months (59.8kg/m <sup>2</sup> to 49.8kg/m <sup>2</sup> )
Williams et al, 2014 <sup>[21]</sup>	5 cases (RYGB or LAGB)	Weight loss outcomes for patients with paraplegia could not be extracted.
Perrault et al, 2016 <sup>[22]</sup>	1 x LAGB	BMI reduction of 34.3% after 12 months (no baseline BMI reported)

attained an 83.8% excess weight loss for 2 years. He too showed improvements in insulin resistance, sleep apnoea and gastro-oesophageal reflux. In addition, the improvement in his mobility allowed him to be able to self-catheterize once again to manage his neurogenic bladder, resulting in much greater independence and improved quality of life. The authors add that with survival rates of spina bifida improving, concomitant obesity will become a problem for which these patients may require treatment.

Interestingly, Wong et al reported a case in 2013<sup>[18]</sup> of a 28-year-old man who was admitted for rehabilitation following thoracolumbar spinal cord injury from a gunshot wound. In this instance, his severe obesity presented a barrier to his rehabilitation and functional recovery. He continued to gain weight following his injury with no improvements using dietetic and pharmacological strategies. As his neurological recovery potential was still deemed favourable, he underwent a RYGB as an adjunctive therapy towards improving functional recovery from his spinal cord injury. The authors reported positive outcomes from this intervention, with a 16.7% reduction in BMI after 7 months. The authors emphasized the effect of surgery on his neurological recovery, identifying his bariatric surgery as a significant contributor to his ability to be able to manage stairs with aids.

Williams et al<sup>[19]</sup> reported a case series of 15 patients who were wheelchair users of varying aetiologies and who had bariatric surgery in a tertiary centre in London. Only five of these patients had severe mobility impairment of a spinal aetiology. Operative data and outcomes

could not be specifically extracted for these five particular patients from the published manuscript. The five patients underwent either laparoscopic adjustable gastric banding (LAGB) or RYGB as their primary bariatric procedure. No sleeve gastrectomies were reported in this cohort. Post-operative complications reported for the entire cohort included lower respiratory tract infection, internal hernia, gastrojejunal anastomotic stricture and a single case of a marginal ulcer due to long term steroid use (the patient had severe rheumatoid arthritis). Importantly relevant to this current literature review, the authors reported that two of their patients who had spinal cord pathology had improvements in weight but not in mobility. No association was deemed to be present between the aetiology of mobility impairment and improvement in either weight or mobility post-operatively. It is unclear from the reported data what operations the two patients with paraplegia had undergone, but the authors reported that of the four patients within the whole series who had no improvement in mobility, three of these had adjustable gastric banding as their primary procedure.

Finally, in 2016 Perreault et al<sup>[20]</sup> reported the case of a 47-year-old man who was tetraplegic following a motor accident in 2005. Following several multidisciplinary strategies to reduce his weight which were unsuccessful, he underwent gastric banding for his severe obesity. This achieved a 34.3% reduction in BMI at 1 year. It should be noted that there is no evidence whether patients with tetraplegic neurological deficit may or may not achieve the same expected outcomes as patients with paraplegia.



In summary, our literature search retrieved reports of 11 previous bariatric operations performed on patients with paraplegia. Most operations were gastric bypass (3, 27%), followed by gastric banding (1, 9%) with the remaining two operations being duodenal switches (18%) with a further five patients in one series<sup>21</sup> having undergone a LAGB or RYGB (45%). Weight loss data could not be analysed collectively from these cases due to heterogeneity in reporting.

Four of the aforementioned case reports were included in a relatively recent 2017 systematic review of management strategies for obesity in those with spinal cord injury.<sup>7</sup> This review found that of the conservative, medical and surgical therapies studied, bariatric surgery delivered the most superior results. This conclusion was delivered with the caution however that only case reports formed the current evidence base for bariatric surgery in patients with paraplegia.

## 5 | DISCUSSION

### 5.1 | Patient selection and paraplegia specific considerations

There is a deficiency of evidence regarding bariatric surgery for patients with paraplegia. The literature available fails to meet a consensus of the most effective or appropriate management of this patient cohort as there is no high level evidence produced by randomized trials to support what are largely anecdotal findings. Furthermore, we were unable to identify any studies assessing the use of LSG in a cohort of patients with paraplegia. We present a case series of three patients with significant mobility limitations due to paraplegia whom have all safely undergone bariatric surgery in the UK private sector. Notably, our series is the first to report on patients with paraplegia specifically undergoing LSG as a primary bariatric procedure.

There are several specific considerations when reviewing the appropriateness of bariatric surgery for patients with obesity and paraplegia. Fundamental differences in metabolic physiology and physical mobility<sup>7</sup> suggest that current measurements used to evaluate obesity, such as BMI or waist to hip ratio, may not be valid for patients with paraplegia. Neurological impairment signals a radical change in body composition as soon as 6 months after a spinal cord injury. Patients lose lean mass<sup>21</sup> and therefore gain mass from fat and also experience reduction of their resting metabolic rate.<sup>22</sup> Each of these result in an excess of adipose tissue and therefore greater obesity than a patient without the same neurological injury. The inability of BMI to differentiate lean mass and mass from fat has long been a criticism of the other useful measurement of obesity. Therefore, it is likely that measuring BMI in patients with paraplegia underestimates their total body fat and therefore comorbid risk from obesity.<sup>8</sup> As such, we cannot use BMI to make the same assumptions about body composition as we can for patients without paraplegia. However, there is currently no validated classification system for obesity for patients with paraplegia and so selection of patients for bariatric intervention may need to be based upon different or new metrics compared to patients without neurological deficit.

As well as biological changes to adiposity and muscle composition, patients with paraplegia are likely to undertake less exercise.<sup>21</sup> Therefore, cardiorespiratory function in these patients may be underestimated in relation to their pre-operative BMI. This may translate to increased anaesthetic risk on top of that conferred by their severe and complex obesity.

All three patients in our series underwent an LSG. This was performed over a 34Fr bougie with an antral resection (first firing at <2.5 cm from the pylorus). The choice of the operation was mainly based on the author's preference and an informed discussion with the patient. This specially took into account the risk of chronic abdominal pain with LRYGB,<sup>23</sup> long term risk of re-operations (2.2% for LRYGB vs 0.85% for LSG<sup>24</sup>) and the risk of bowel frequency and small intestinal bacterial overgrowth with RYGB.<sup>25</sup> Although the risks of developing these problems are no higher in patients with paraplegia, the consequences of re-admissions and frequent presentations to the hospital in patients with poor mobility cannot be overemphasized.

### 5.2 | Pre-operative optimisation and patient consent

Given a lack of data supporting the post-operative outcomes of patients with paraplegia after weight-loss surgery, patients must be counselled about their specific circumstances. It is imperative that they are made aware of the lack of published data with regards to outcomes. It must be stressed that weight loss may not be comparable to published weight loss in healthy subjects due to differences in body composition and limitations on physical activity. Furthermore, specific procedural risks, such as the negative impact of quality of life with frequency of bowel motion<sup>25</sup> after LRYGB should be highlighted extensively to inform patient decision-making.

As with any patient undergoing invasive surgery, their peri-operative risk and unique intra-operative requirements should be considered and addressed where possible. VLCD is recommended for all patients prior to bariatric surgery.<sup>26</sup> The duration a VLCD may need to be modified for patients with paraplegia to adjust for their reduced physical activity levels. However, a significantly prolonged calorie deficit may begin to increase peri-operative risks if nutrition prior to surgery starts to become suboptimal. Adjuvant medical therapies such as glucagon-like-peptide-1 (GLP-1) receptor agonists which have been shown to aid weight loss prior to bariatric surgery<sup>27</sup> may also be helpful.

Peri-operative VTE prophylaxis may also require extending beyond routine protocol to compensate for increased venous thrombo-embolic risk conferred by immobilization.<sup>28</sup> Indeed, a 2017 American analysis of VTE events in patients undergoing bariatric surgery identified paraplegia specifically as a significant risk factor for an event within 30 days post-operatively.<sup>29</sup> In our series, two of our patients received VTE prophylaxis as daily LMWH injections for 7 days post-surgery. A third patient was given extended prophylaxis up to 28 days due to her previous history of both deep vein thrombosis and pulmonary embolism. Previous VTE has been identified as a

risk factor for further events following surgery,<sup>30</sup> with recommendations in the literature that these patients receive extended prophylaxis.<sup>31</sup>

Immobilization can make transferring patients between theatre tables and ward beds or for personal care reasons more difficult. Institutions may therefore require hoists capable of moving patients who are super-obese to be available not only within the bariatric operating theatres but within ward environments.

Finally, it is expected that the surgical procedure will be comparative to that in patients without neurological deficit. However, we hypothesize that there may be a higher risk of carbon dioxide retention secondary to the use of higher laparoscopic inflation pressures in the case of disproportionate growth of the abdomen when patients have had paraplegia since childhood. It is imperative that both surgical and anaesthetic teams are aware of this risk in order that it not only be identified in a timely manner but that post-operative high-dependency care is always available.

### 5.3 | Post-operative expectations

It remains unclear what percentage of excess weight loss should be expected for patients with paraplegia. Heterogeneity in the reporting of weight loss outcomes in the current literature precludes a current analysis to suggest a result for expected weight loss.

In our case series, two patients achieved excess BMI losses of 73% and 98%, respectively. However, a third patient with paraplegia had not achieved any weight loss after 8 months follow-up. This patient stopped engaging with the service four months following surgery and we wonder if that contributed to a lack of weight loss. However, given the lack of follow-up data for this patient, no specific causes for her weight gain can reasonably be inferred.

The absolute lack of statistical data for patients with paraplegia undergoing bariatric surgery results in no statistical evidence regarding outcomes in mobility and quality of life. Whilst the current literature significantly favours positive outcomes, analysis of larger data sets will enable more robust investigation of the therapeutic potential of bariatric surgery for patients with paraplegia. A core outcome set for research involving bariatric surgery has been suggested,<sup>32</sup> but some of the patient factors and outcomes discussed in this article are absent from this.

### 5.4 | Strengths and limitations

This systematic review provides an up to date summary of the current literature regarding bariatric surgery for patients with severe, complex obesity and paraplegia. In addition, we provide a case series of three patients with paraplegia undergoing LSG, which has not specifically been reported previously. However, there remains overall only low level evidence of the efficacy of bariatric surgery in this cohort due to heterogenous outcome reporting and the potential for bias that lies within case reports. Post-operative outcomes other than weight loss

have so far only been reported subjectively; however in our case, series outcomes such as mobility and presence of reflux symptoms are patient-reported.

## 6 | CONCLUSION

In summary, we report a series of three patients with obesity and paraplegia who safely underwent bariatric surgery and achieved favourable outcomes from their operations. Moreover, it establishes that such surgery can be safely catered for in the private sector provided HDU/ITU facilities are available on site. This case series and literature review focuses on the surgical management of obesity in patients with paraplegia and outlines more specific potential challenges for this patient cohort both surgically and post-operatively. Finally, we highlight that patients with severe obesity and paraplegia are a population who should receive greater and more tailored consideration of surgical management of their obesity and to minimize future cardiometabolic risks.

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R. S. conceived the study and is the study guarantor. G. R. L. and S. B. are joint first authors. R. S. obtained retrospective consent from all patients in the case series and S. B. retrieved demographic, outcome and operative data from electronic private medical records. Surgery was performed by R. S. along with M. S., V. C. and M. D. G. R. L. and S. B. conducted the literature review and prepared initial manuscript drafts, which were subsequently reviewed and edited by all authors. R. S., V. C. and M. D. provided further critical insight during drafts of the manuscript. All authors have agreed to the submission of this manuscript.

### CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

### ORCID

Georgia R. Layton  <https://orcid.org/0000-0002-2209-0559>

Mohamed Sahloul  <https://orcid.org/0000-0002-2751-1981>

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