U.PORTO

MESTRADO INTEGRADO EM MEDICINA

Can the metabolic gastric bypass counteract the negative impact of dysglycaemia on weight loss?

Inês Portugal Mascarenhas do Amaral Lucas

M

2022

Can the metabolic gastric bypass counteract the negative impact of dysglycaemia on weight loss?

Inês Portugal Mascarenhas do Amaral Lucas

portugalmascarenhas.ines@gmail.com

MESTRADO INTEGRADO EM MEDICINA

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR, UNIVERSIDADE DO PORTO

Orientadora

Professora Doutora Lídia Mariana Rodrigues Pereira Monteiro

Professora Associada com Agregação

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Coorientadora

Professora Doutora Sofia Daniela da Silva Pereira

Professora Auxiliar

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Junho 2022

Porto, 3 de junho de 2022

Inês Portugal Mascarenhas do Amaral Lucas
____

Inês Portugal Mascarenhas

____

Professora Doutora Mariana P. Monteiro

Sofia Pereira
____

Professora Doutora Sofia S. Pereira

À minha mãe

Acknowledgements

Uma casa começa a ser construída pelos alicerces, assim como o conhecimento. Os anos pré-clínicos têm uma importância indubitável, e foi durante este período que o meu interesse na área da endocrinologia, mais especificamente no tratamento da obesidade se desenvolveu, por intermédio da Professora Mariana Monteiro. À mesma agradeço a oportunidade de poder explorar esta área, assim como a experiência e conhecimento transmitidos.

À Professora Sofia Pereira, um verdadeiro exemplo de dedicação, agradeço todo o aconselhamento, que ultrapassa o território deste trabalho, e se aplica a trabalhos de investigação científica.

À Professora Marta Guimarães agradeço a disponibilidade e oportunidade da realização do acompanhamento do percurso dos seus doentes em consulta de cirurgia bariátrica e pela aprendizagem teórica e prática que fomentou neste âmbito.

À Professora Sara Andrade agradeço a acessibilidade para o apoio da realização do presente projeto e pelo auxílio na fase preliminar da criação da base de dados incluída no estudo.

A Fundação para a Ciência e Tecnologia (FCT) apoiou este trabalho através dos seguintes fundos: UIDB/00215/2020, UIDP/00215/2020 e PTDC/MEC-CIR/3615/2021.

The Foundation for Science and Technology (FCT) supported this work through the following funds: UID/MULTI/0215/2016, UID/Multi/00215/2019, UIDB/00215/2020 and UIDP/00215/2020.

"De sonhar ninguém se cansa, porque sonhar é esquecer, e esquecer não pesa e é um sono sem sonhos em que estamos despertos"

Fernando Pessoa

Resumo

<u>Introdução:</u> O bypass gástrico Roux-en-Y (RYGB) é um tipo de cirurgia bariátrica com elevada taxa de perda ponderal e melhoria das comorbilidades associadas, como a diabetes tipo 2 (T2D). O RYGB metabólico com uma ansa biliopancreática (BPL) de 200cm, demonstrou apresentar melhores resultados clínicos quando comparado com a técnica clássica, com ansa BPL de 100cm. Estudos anteriores indicaram que, os indivíduos com alterações no perfil glicémico, têm uma menor probabilidade de atingir o seu peso ideal após cirurgia bariátrica.

<u>Objetivo:</u> Avaliar se o perfil glicémico pré-operatório influencia a perda ponderal obtida após o RYGB clássico e metabólico.

<u>Métodos:</u> Foram incluídos, neste estudo, indivíduos submetidos a RYGB com pelo menos dois anos de seguimento. Foram recolhidos dados clínicos e antropométricos nos períodos pré- e pós-operatórios (3, 6, 12, 18 e 24 meses). Os indivíduos foram classificados como euglicémicos (EUG), na ausência de alterações na homeostase glicémica, ou disglicémicos (DYSG), incluindo doentes pré-diabéticos (PT2D) e T2D. As variáveis, peso perdido, índice de massa corporal (IMC) perdido, percentagem de perda de peso total (%TWL) e percentagem de IMC em excesso perdido (%EIMCP), foram calculadas.

<u>Resultados:</u> Na nossa coorte (n=183), 129 indivíduos foram submetidos ao RYGB clássico e 54 ao RYGB metabólico. Entre estes doentes, 85 eram EUG e 98 eram DYSG (51 com PT2D e 47 com T2D), 25 dos quais tinham síndrome metabólica. Os doentes com PT2D submetidos a RYGB metabólico apresentaram uma %EIMCP significativamente maior aos 12 e 18 meses, quando comparados com o grupo EUG. Indivíduos com uma duração de T2D superior, submetidos ao RYGB clássico, apresentaram uma %EIMCP maior após os 6 meses ($p<0.05$). Contrariamente, observou-se uma correlação negativa entre a duração da T2D e %TWL, aos 12 e 24 meses, no grupo RYGB metabólico ($p<0.05$). Os indivíduos mais velhos apresentaram uma menor perda ponderal e de BMI, aos 6, 12, 18 e 24 meses, no grupo RYGB metabólico ($p<0.05$). Adicionalmente, observou-se uma correlação negativa ($p<0.05$) entre a idade e %TWL aos 24 meses, no grupo RYGB clássico.

<u>Conclusão:</u> A disglicemia não teve um impacto negativo na perda de peso até 24 meses após nenhuma das técnicas RYGB, uma vez que não houve diferenças significativas nos resultados da perda de peso entre pacientes com estados glicémicos diferentes. Além disso, a %EIMCP após o RYGB metabólico foi significativamente mais elevada nos pacientes mais jovens e naqueles com PT2D, em comparação com indivíduos euglicémicos ou com T2D.

<u>Palavras-chave:</u> Obesidade, Cirurgia Bariátrica, *Bypass* Gástrico, Disglicemia, Perda de peso

Abstract

Introduction: Roux-en-Y gastric bypass (RYGB) is a bariatric surgery procedure that results in high rates of short- and medium-term weight loss and improvement of obesity-associated comorbidities, such as Type 2 diabetes (T2D). Metabolic RYGB, defined by a biliopancreatic limb (BPL) of 200 cm, was described to result in better clinical outcomes when compared to the classical technique, with a BPL of 100 cm. Previous studies postulated that individuals with altered glycaemic profiles are less likely to reach an ideal weight after RYGB.

Aim: To assess if the pre-operative glycaemic profiles influence the weight loss after classical and metabolic RYGB.

Methods: Patients previously submitted to RYGB with at least two years of follow-up were included in this study. Pre-operative and post-operative (3, 6, 12, 18 and 24 months) clinical and anthropometric data were collected. Patients were classified as euglycaemic (EUG), if no alterations in the glycaemic homeostasis were present, or dysglycaemic (DYSG), in the presence of abnormal glucose homeostasis, which includes patients with pre-diabetes (PT2D) and T2D. Considering the anthropometric data collected, weight loss, body mass index (BMI) loss, percentage of total weight loss (%TWL) and percentage of excess BMI loss (%EBMIL) were calculated.

Results: From our cohort (n= 183), subjects were submitted to classical (n=129) or metabolic RYGB (n=54). Among patients, 85 were EUG and 98 were DYSG, 51 with PT2D and 47 with T2D, 25 of whom had metabolic syndrome. Patients with PT2D submitted to metabolic RYGB presented a significantly higher %EBMIL at 12 and 18 months when compared with EUG group. Patients with longer T2D duration, submitted to classical RYGB had a higher %EBMIL at 6, 12, 18 and 24 months ($p<0.05$). Contrarily, there was a negative correlation between T2D duration and %TWL at 12 and 24 months in the metabolic RYGB group ($p<0.05$). Older patients presented less weight and BMI loss at 6, 12, 18 and 24 months, in the metabolic RYGB group ($p<0.05$). Similarly, a negative correlation ($p<0.05$) between age and %TWL at 24 months was observed in the classical RYGB group.

Conclusion: Dysglycaemia did not have a negative impact on weight loss up to 24 months after neither RYGB technique, as there were no significant differences in weight loss outcomes between patients with different glycaemic status. Moreover, the %EBMIL after metabolic RYGB was significantly higher in younger patients and those with PT2D as compared to individuals with euglycemia or T2D.

Keywords: Obesity, Bariatric Surgery, Gastric Bypass, Dysglycaemia, Weight Loss

Abbreviations

BMI	Body mass index
BPL	Biliopancreatic limb
CHEDV	Centro Hospitalar de Entre o Douro e Vouga
DYSG	Dysglycaemic
EUG	Euglycaemic
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
PT2D	Pre-Type 2 Diabetes
RYGB	Roux-en-Y Gastric Bypass
T2D	Type 2 Diabetes
%EBMIL	Percentage of excess body mass index loss
%TWL	Percentage of total weight loss

Index

Table list

Figure list

Introduction

Obesity is a complex multifactorial disease resulting from the interaction between environmental, social, behavioural and genetic factors, which prevalence has been increasing exponentially in recent decades, constituting a public health problem[1,2]. Overweight and obesity are major risk factors for several comorbidities, affecting the individuals' quality of life and possibly leading to a reduction in average life expectancy, namely through the development of cardiovascular disease[3,4]. Among the comorbidities reported as being associated to obesity, those included in the metabolic syndrome stand out, namely arterial hypertension, dyslipidemia and type 2 diabetes (T2D) [5].

Weight loss is the cornerstone for improving obesity-related comorbidities, and consequently reducing morbimortality, especially when it comes to cardiovascular disease[4,6,7].

Therefore, treatment may involve two distinct approaches: conservative therapy, which includes lifestyle modifications and pharmacological therapy, and bariatric surgery[6]. Regarding conservative therapy, in most cases the weight loss obtained is not significant and sustained, and the weight lost is usually recovered in the medium to long term, without being associated with remission of the metabolic syndrome[6]. On the other hand, bariatric surgery represents the most effective treatment for severe obesity in terms of significant and sustained weight loss, with improvement of related comorbidities, and quality of life, as well as reduced mortality[6,8,9]. In regards to comorbidities, dysglycaemia is worth highlighting, which clinical remission may be obtained in a short post-operative period, being this effect attributed to the anatomical rearrangement of the gastrointestinal tract induced by surgery and consequent changes in gastrointestinal hormones[10,11,12].

In fact, the Roux-en-Y gastric bypass (RYGB) is one of the most frequently performed bariatric techniques due to its efficacy. It consists on the reduction of the gastric volume, with the exclusion of the duodenum and proximal jejunum, and in the creation of three new intestinal limbs: the alimentary limb, the biliopancreatic limb (BPL) and the common limb[10,13]. RYGB has a high rate of short- and medium-term successful weight loss and obesity-associated comorbidity improvement. However, as for long-term follow-up, the results are not as satisfactory. A study of our research group found that 10 years after surgery, 20.5% of the patients that had short- and medium term T2D remission, experienced T2D relapse[14].

In order to improve the surgical outcome in individuals with dysglycaemia, a modified RYGB was introduced, which is defined by the creation of a BPL of 200 cm, when compared to the classical method, in which this same loop measures approximately 100 cm[10]. The RYGB with a 200 cm BPL (named metabolic RYGB) was demonstrated to result in a higher rate of weight loss and T2D remission[10]. In fact, a distinctive hormone profile favoring improved metabolic profiles with increased post-prandial glucagon-like peptide-1 (GLP-1) and neurotensin responses in individuals who were submitted to the metabolic RYGB when compared to the classical technique was also observed[15].

Although bariatric surgery is effective in the majority of the patients with obesity, 10 to 20% of individuals undergoing this surgical intervention do not reach their ideal weight, which is defined as the weight loss of at least 50% of their excess weight[16,17,18,19,20]. Indeed, several studies postulate that individuals with pre-operative dysglycaemia are less likely to reach their ideal weight, as well as having a higher risk of gaining weight during follow-up[20,21].

The aim of this research study is to assess if the pre-operative glycaemic profiles influence the post-bariatric weight loss after classic and metabolic RYGB.

Methods

Subjects' selection and data collection

Subjects were selected from the cohort of patients undergoing bariatric surgery at Centro Hospitalar de Entre o Douro e Vouga (CHEDV), during the period between January 1st 2017 and February 27th 2020. In order to compare the weight loss in euglycaemic (EUG) and dysglycaemic (DYSG) individuals after RYGB, data pertaining to these patients was collected before surgery and in the post-surgical period (3, 6, 12, 18 and 24 months) using the Medtrix platform. The aforementioned data will refer to nearest hospital visit to date of the surgery and scheduled post-surgical follow-up visits. The study protocol including access to the patient register for data analysis were approved by the CHEDV Ethical Review and Executive Boards (Nº: CA-0033/ 2022-0t_MP/ CC). Pre-surgical data, included anthropometric parameters height, weight and body mass index (BMI), previous bariatric surgery, blood pressure, and presence, duration and ongoing medication of comorbidities, including T2D, arterial hypertension, dyslipidemia or other. In addition, routine blood biochemical parameters were included, these being glucose, glycated hemoglobin (percentage and mmol/mol), total cholesterol, HDL, LDL and triglycerides.

As for the subsequent visits, anthropometric data (weight and BMI), blood pressure, status of previously existing comorbidities and ongoing medication was retrieved, as well as the biochemical study consisting of the same parameters mentioned above.

In the process of collecting the data, all patients whose surgical procedure was not the RYGB, who had previously undergone bariatric surgery and female individuals who became pregnant during the 24 months of follow-up were excluded. The considered data referred to patients either submitted to the classical RYGB, characterized by the creation of a BPL of approximately 100 cm, or the metabolic RYGB, defined by the creation of a BPL of 200 cm[10].

Thereafter, patients were classified as: EUG, in the absence of alterations of glucose homeostasis, presenting a fasting glycaemia (FPG) under 100 mg/dL or a glycated hemoglobin (HbA1c) under 5.7%, without the concomitant use of any glucose lowering drug; or DYSG, in the presence of an abnormal glucose homeostasis, including patients with pre-diabetes (PT2D) (FPG greater than or equal to 100 mg/dL and less than 126 mg/dL or a HbA1c greater than or equal to 5.7% and less than 6.5%) and with T2D (FPG greater than or equal to 126 mg/dL or a HbA1c greater than or equal to 6.5%)[5].

A patient was considered as being in T2D remission whenever HbA1c was under 6.5% during an extended period of time, without the need for pharmacological therapy[20].

Regarding the anthropometric data, the weight loss at each follow-up visit (3, 6, 12, 18 and 24 months) was obtained for each patient, to calculate BMI loss, percentage of total weight loss

(%TWL) and percentage of excess body mass index loss (%EBMIL). In order to obtain the %TWL, a formula was applied which corresponds to the percentage obtained by dividing the difference between the initial weight and weight at the defined visit and the initial weight, and the %EBMIL, which is equivalent to the percentage obtained by dividing the difference between the initial BMI and BMI at the defined visit and the difference between the initial BMI and 25[22,23].

Statistical analysis

The statistical analysis of the data was performed using the Microsoft Office Excel and the GraphPad Prism software version 8.01.

In this analysis, the anthropometric data evaluated at the different visits of the follow-up were compared as regards the classic and metabolic RYGB, being the normality of the sample assessed using the D'Agostino & Pearson test. In the presence of variables with Gaussian distribution, a parametric test was implemented, namely the Unpaired T test, while in variables without Gaussian distribution, a non-parametric test was applied, this being the Mann-Whitney test.

The comparison of anthropometric data in each of the surgical groups was made between EUG, PT2D and T2D individuals, as well as EUG and DYSG individuals, and individuals without metabolic syndrome and with metabolic syndrome, using the Two-way ANOVA test. Using this tool, we also compared the anthropometric data of EUG, PT2D and T2D individuals, as well as EUG and DYSG individuals, and individuals without metabolic syndrome and with metabolic syndrome regarding the type of surgical technique implemented. In the analysis of the remission of T2D in individuals with T2D prior to the surgical procedure, Fisher's exact test and Chi-square test were performed. Correlations between age and T2D duration, and the post-operative weight and BMI loss were performed using the Pearson or Spearman correlation tests, depending on the normality of the variables.

Throughout the statistical analysis, a p-value < 0.05 was considered statistically significant.

Results

Our cohort includes 183 individuals, of which 143 are female (75%) and 40 are male (21%), aged between 22 and 63 years, corresponding to an average age of 44.1 ± 0.7 years. As to the anthropometric data, weights ranged between 76 and 170 Kg, with an average of 107.96 ± 1.2 Kg, resulting in a BMI between 32 and 60.4 Kg/m^2, with an average of 40.24 ± 0,3 Kg/m^2. Concerning the division of these patients by the surgical procedure, 129 individuals were submitted to classic RYGB and 54 individuals to metabolic RYGB. Respecting the classification of patients according to glycaemic status, 85 patients were EUG and 98 were DYSG, 51 of whom had PT2D and 47 T2D, 25 of the latter group with metabolic syndrome. Preoperative BMI was similar between the surgical groups. Thus, we obtained 4 groups: EUG individuals submitted to classical RYGB (n=73), DYSG individuals submitted to classical RYGB (n=56), including PT2D (n=42) and T2D (n=14), EUG individuals submitted to metabolic RYGB (n=12) and DSG individuals submitted to metabolic RYGB (n=42), including PT2D (n=9) and T2D (n=33) (Table I).

The statistical analysis of anthropometric data (weight loss, BMI loss, %TWL and %EBMIL), comparing the two surgical approaches, in EUG/PT2D/T2D, EUG/DYSG, and With metabolic syndrome/ Without metabolic syndrome groups, showed that there were no significant differences between groups. The curves obtained for each of the anthropometric parameters are practically overlapping (Figures 1, 2 and 3).

As for the anthropometric data related to each surgical technique, comparing the EUG/PT2D/T2D, EUG/DYSG, and With metabolic syndrome/Without metabolic syndrome groups, there were no significant differences and the curves obtained are practically overlapping, except for the %EBMIL obtained after metabolic RYGB (Figure 4, Figure 5 and Figure 6). Patients with PT2D submitted to metabolic RYGB presented a significantly higher %EBMIL at 12 and 18 months when compared to EUG subjects (110.6 ± 5.41* vs. 89.89 ± 5.66* [p=0.046] and 111.1 ± 5.18* vs. 92.17 ± 5.19* [p=0.048]) (Figure 4H). At 3 months after surgery, patients with T2D submitted to metabolic RYGB had a significantly higher %EBMIL when compared with EUG subjects (61.79 ± 3.42* vs. 45.20 ± 3.67* [p=0.014]), being that the differences between groups were no longer significant at later time points (Figure 4H).

Patients with longer T2D duration, submitted to the classical RYGB procedure presented greater %EBMIL at 6, 12, 18 and 24 months ($p<0.05$). Contrarily, a negative and significant correlation was detected between the T2D duration and the %TWL at 12 and 24 months in the metabolic RYGB group ($p<0.05$) (Table II).

In addition, older patients presented less weight and BMI loss at 6, 12, 18 and 24 months, in the metabolic RYGB group ($p<0.05$). Similarly, a negative correlation ($p<0.05$) between age and %TWL at 24 months was observed in the classical RYGB group (Table III).

T2D remission rate was not significantly different between the surgical variants, at all timepoints evaluated (Table IV).

Discussion

RYGB is associated with a significant and sustained weight loss and improvement of obesity-related comorbidities, achieved by the combination of a restrictive procedure and malabsorption, as well as the change in hormonal mechanisms and basal metabolic rate[14,24].

The introduction of metabolic RYGB created a new paradigm in the treatment of obesity and metabolic syndrome[10]. The literature indicates that the creation of a 200 cm BPL is associated with a gut hormone profile distinct from what is observed after classical RYGB. Taking into consideration the "Foregut" and "Hindgut" hypotheses, either isolated or acting synergistically, these differences may be justified[10]. The "Foregut" hypothesis postulates the concept that surgically induced duodenal-jejunal exclusion from the intestinal transit prevents the release of a metabolic signal with anti-incretin action, leading to normalization of the sensitivity to glucose-dependent insulinotropic peptide (GIP). In contrast, the "Hindgut" hypothesis states that early arrival of poorly digested nutrients to the distal ileum is associated with increased release of incretin and anorexigenic hormones such as GLP-1[10]. Actually, the location of cells secreting different intestinal hormones is not homogeneous throughout the digestive tract. The density of GLP-1 and YY peptide-secreting cells is higher at the distal level, therefore the metabolic RYGB with a longer BPL limb, results in an earlier stimulation of these cells, whereas the classical RYGB procedure results in early nutrient arrival to the proximal small intestine, where GIP-secreting cells predominate [10,15].

Our current study showed that both classical and metabolic RYGB are associated with a weight loss, BMI loss, %TWL and %EBMIL that do not diverge significantly between patient groups EUG, PT2D and T2D, as well as when aggregated as EUG and DYSG, which indicates that in this study the surgical outcomes were not dependent on the surgical technique implemented. However, a previous analysis carried out by our research group enrolling a larger group of patients and over a 60-month period showed that the BMI was significantly lower at 36 and 48 months of follow-up in the group of individuals who underwent metabolic RYGB, and the %TWL and %EBMIL were significantly higher in this same group as of 24 months and 12 months, respectively[10]. It should be noted that the present study did not assess patients after 24 months, and it may be after this period that the differences described become evident, as previously documented[10].

The existence of obesity comorbidities may also affect surgical outcomes, in the sense that in the absence of comorbidities or presence of mild comorbidities, patients tend to have better outcomes[21]. Notwithstanding, in this analysis, the coexistence of T2D, hypertension and dyslipidemia (metabolic syndrome), did not significantly affect the surgical outcomes, either when the subjects underwent classical or metabolic RYGB[21]. As regards the postoperative results of each surgical technique, whichever the individual's glycaemic status, one technique does not seem to upstage the other. Nevertheless, the existence of a small group of patients with diabetes who underwent classical RYGB should be considered. This disparity is due to the change in the standard operating procedures implemented at CHEDV, since the metabolic RYGB is the recommended procedure for patients with T2D. It should be noted that regarding the %EBMIL in metabolic RYGB, the PT2D group stands out significantly from the EUG group at 12 and 18 months, with no significant differences in relation to the classical RYGB or when comparing the two surgical techniques in each of the glycaemic status.

Bearing in mind that the follow-up corresponds to 24 months, some of these individuals presented environmental and social conditions different from normality in the first 2 years after surgery, given the impact of the Covid-19 pandemic and consequent confinement in the eating and activity level of individuals, which may have conditioned the surgical results [18,25]. Therefore, and considering the importance of the individuals' lifestyle for weight loss, it would be important to further study this topic in future evaluations.

When taking into account the impact of T2D duration on anthropometric data obtained after performing classical RYGB and metabolic RYGB, we concluded that T2D duration did not influence the results obtained, with the exception of the %EBMIL. In fact, regarding the trend towards greater %EBMIL in individuals with longer lasting T2D at 6, 12, 18 and 24 months in the classical RYGB group, its assessment should take into account that only 14 of 129 patients who underwent classical RYGB had T2D, this numerical disproportion is likely to have influenced these results.

Regarding confounding factors, the absence of significant differences in BMI of individuals belonging to the group of patients undergoing classical and metabolic RYGB excludes the influence of this factor on surgical outcomes, corroborating results obtained in previous studies[24]. In fact, literature indicates that this may be one of the determining factors for the variety of anthropometric results obtained. It has been postulated that individuals with higher preoperative BMI are less likely to achieve normal weight and a BMI>50 Kg/m^2 is defined as a risk factor for surgical failure[18,21].

Another important factor to be highlighted is age. It has been described that in general, younger individuals present better surgical results as far as weight loss is concerned, as older individuals are more likely to have more comorbidities, limitations in adapting eating habits and physical activity levels, besides possessing a clear reduction in basal energy expenditure and lipolytic activity[18,21]. In the present study, the evaluation of weight loss and BMI loss revealed a significant increase in weight loss and consequently BMI as from 6 months of follow-up only in metabolic RYGB in younger individuals. Critically, the sample size could be questioned, and research could be progressed by increasing the number of patients under study. Furthermore, two strands could be explored, these being the individual’s lifestyle habits and the hormonal profile of the different age groups.

Regarding the latter, it should be noted that the inhibition of the body's response to intestinal hormones, namely peptide YY and GLP-1, is associated to worse surgical results, since the increased secretion of these hormones, which are generally reduced in individuals with altered glycaemic status, is associated to an absence of appetite reduction and consequent increase in food consumption, which may culminate in hindered weight loss or weight regain [24].

With respect to all patients with T2D (n=47), 72.3% had remission of T2D at 3 months, 83% at 6 months, 89.3% at 12 months, 91.5% at 18 months and 87.2% at 24 months (2 patients in remission were lost to follow-up). Comparing the surgical techniques, there were no significant differences, but it is noteworthy that at 18 months, all T2D individuals who underwent classical RYGB showed remission of T2D. Previous studies showed that individuals with T2D who underwent metabolic RYGB had a significantly higher T2D remission rate as of 36 months[10]. It should be noted that the follow up in the present study is shorter and the group of T2D individuals who underwent classical RYGB is smaller compared to the other technique.

Conclusion

Dysglycaemia did not have a negative impact on weight loss up to 24 months after neither RYGB technique, as there were no significant differences in weight loss outcomes between patients with different glycaemic status. Moreover, patients with PT2D achieved a greater %EBMIL after metabolic RYGB as compared to individuals with euglycemia or T2D. In contrast, age was a preponderant factor for weight loss after metabolic RYGB that favoured younger individuals.

Appendix

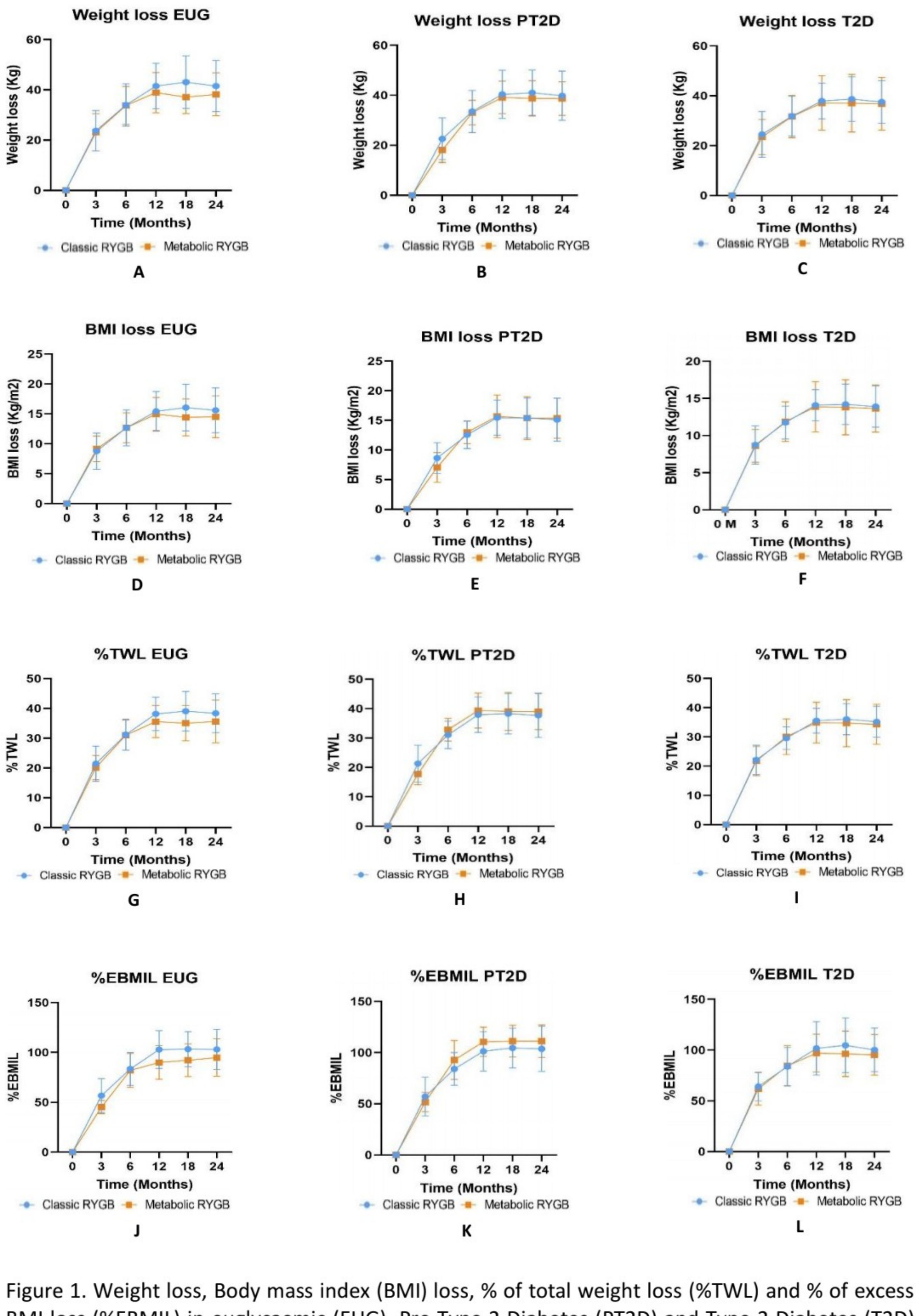

Figure 1. Weight loss, Body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) in euglycaemic (EUG), Pre-Type 2 Diabetes (PT2D) and Type 2 Diabetes (T2D) patients, achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques (* $p<0.05$: Classic RYGB vs. Metabolic RYGB, Two-way ANOVA test).

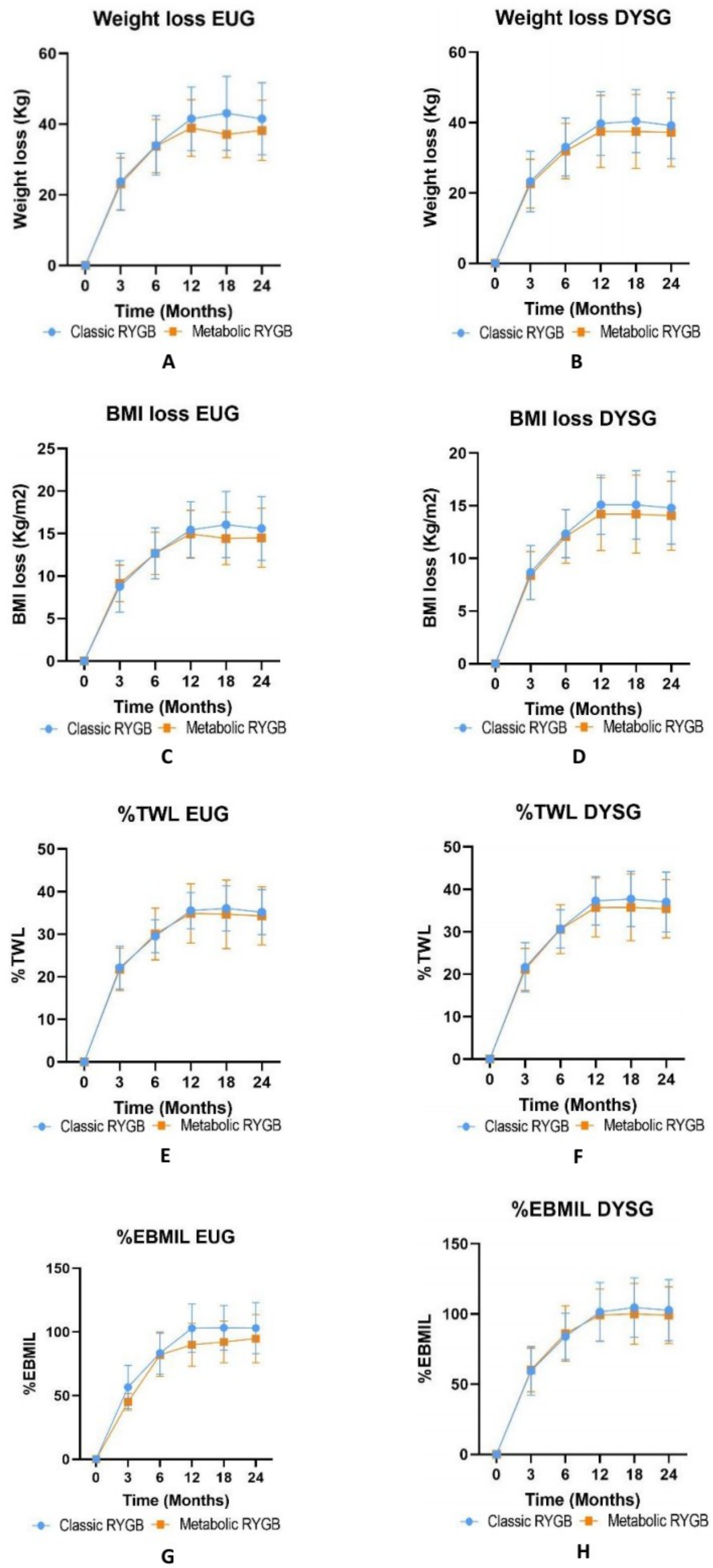

Figure 2. Weight loss, Body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) in euglycaemic (EUG) and dysglycaemic (DYSG) patients, achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques (* p<0.05: Classic RYGB vs. Metabolic RYGB, Two-way ANOVA test).

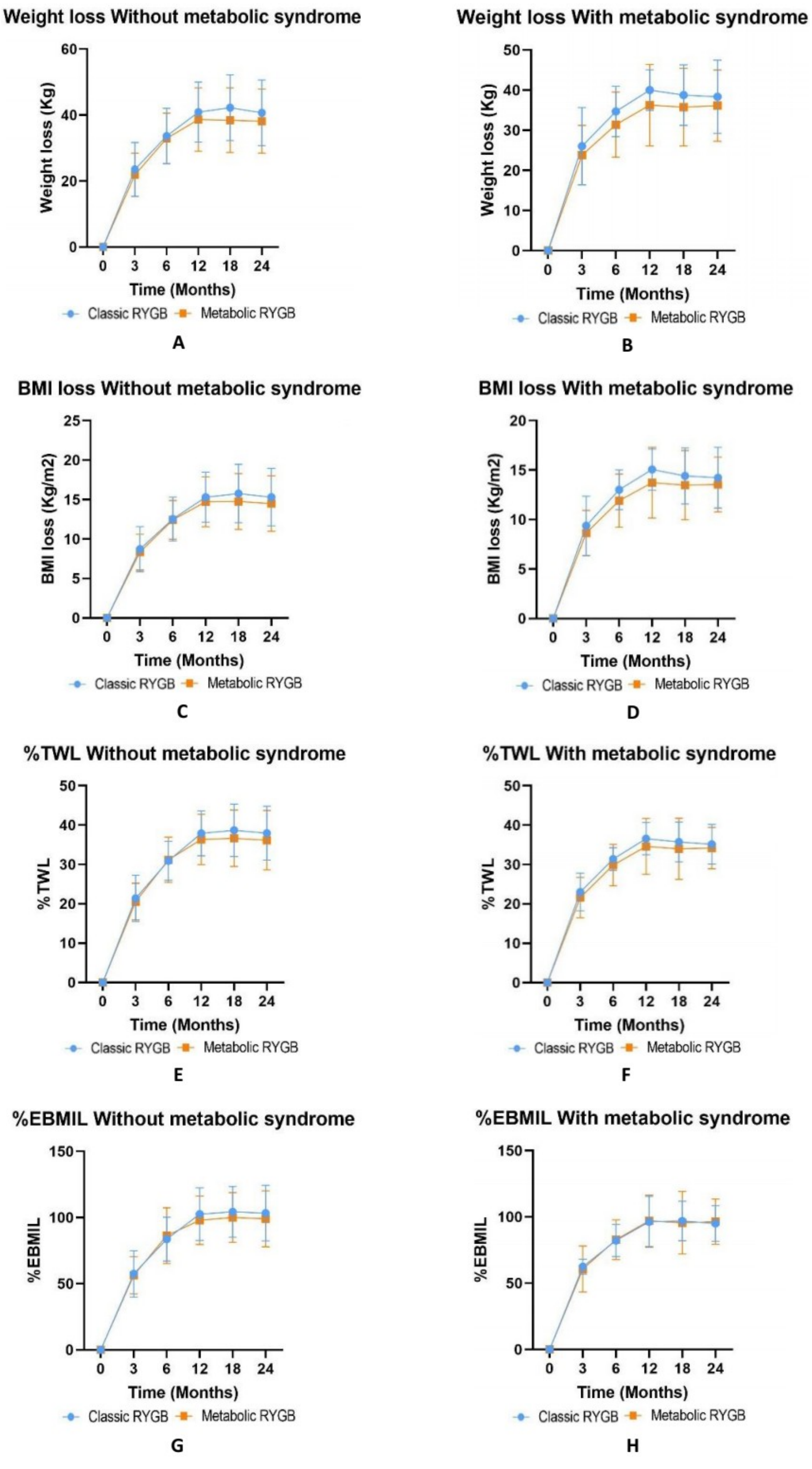

Figure 3. Weight loss, Body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) in patients with and without metabolic syndrome, achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques (* $p<0.05$: Classic RYGB vs. Metabolic RYGB, Two-way ANOVA test).

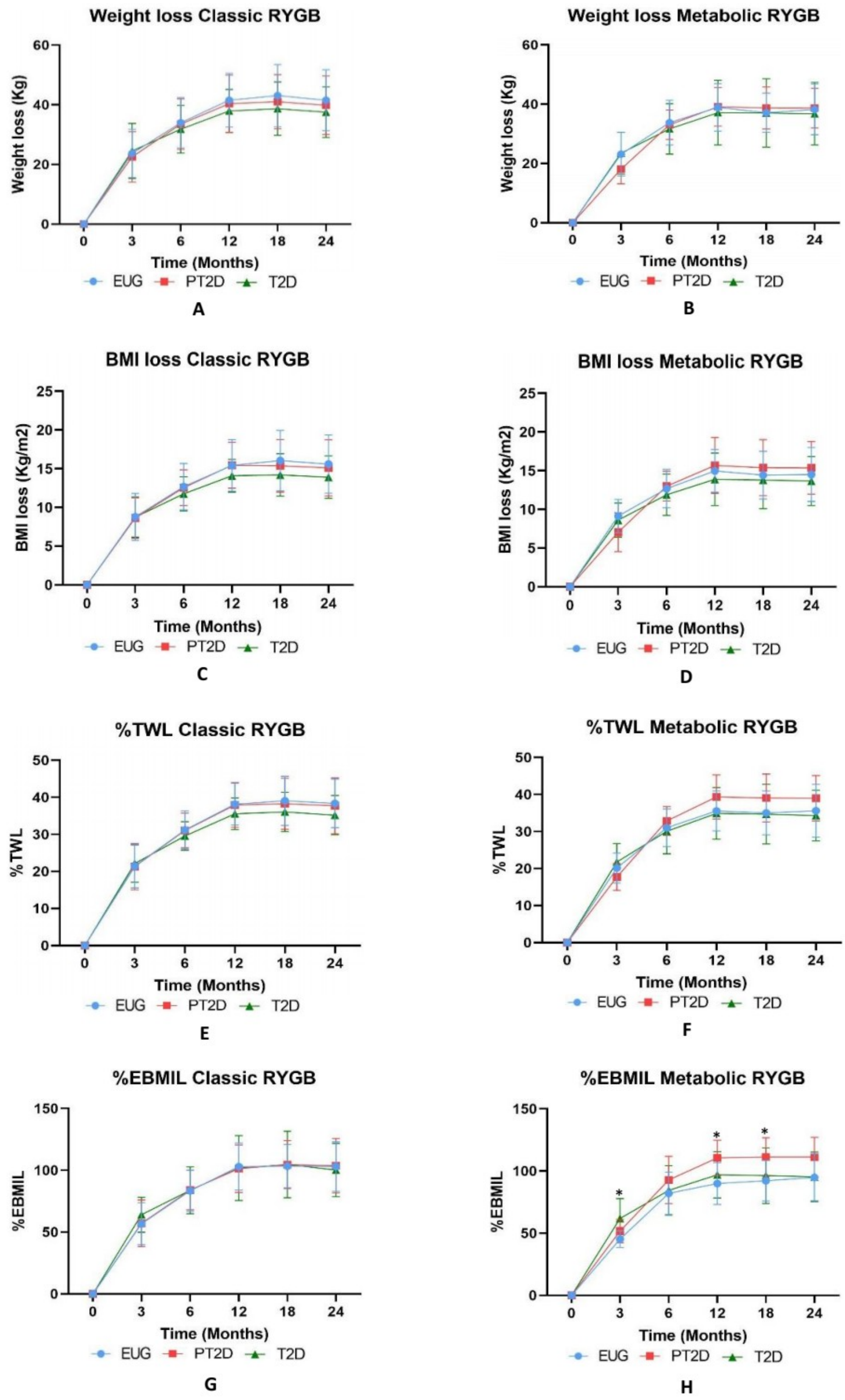

Figure 4. Weight loss, Body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques for euglycaemic (EUG), Pre-Type 2 Diabetes (PT2D) and Type 2 Diabetes (T2D) patients. (* $p<0.05$: EUG vs PT2D and T2D, Two-way ANOVA test).

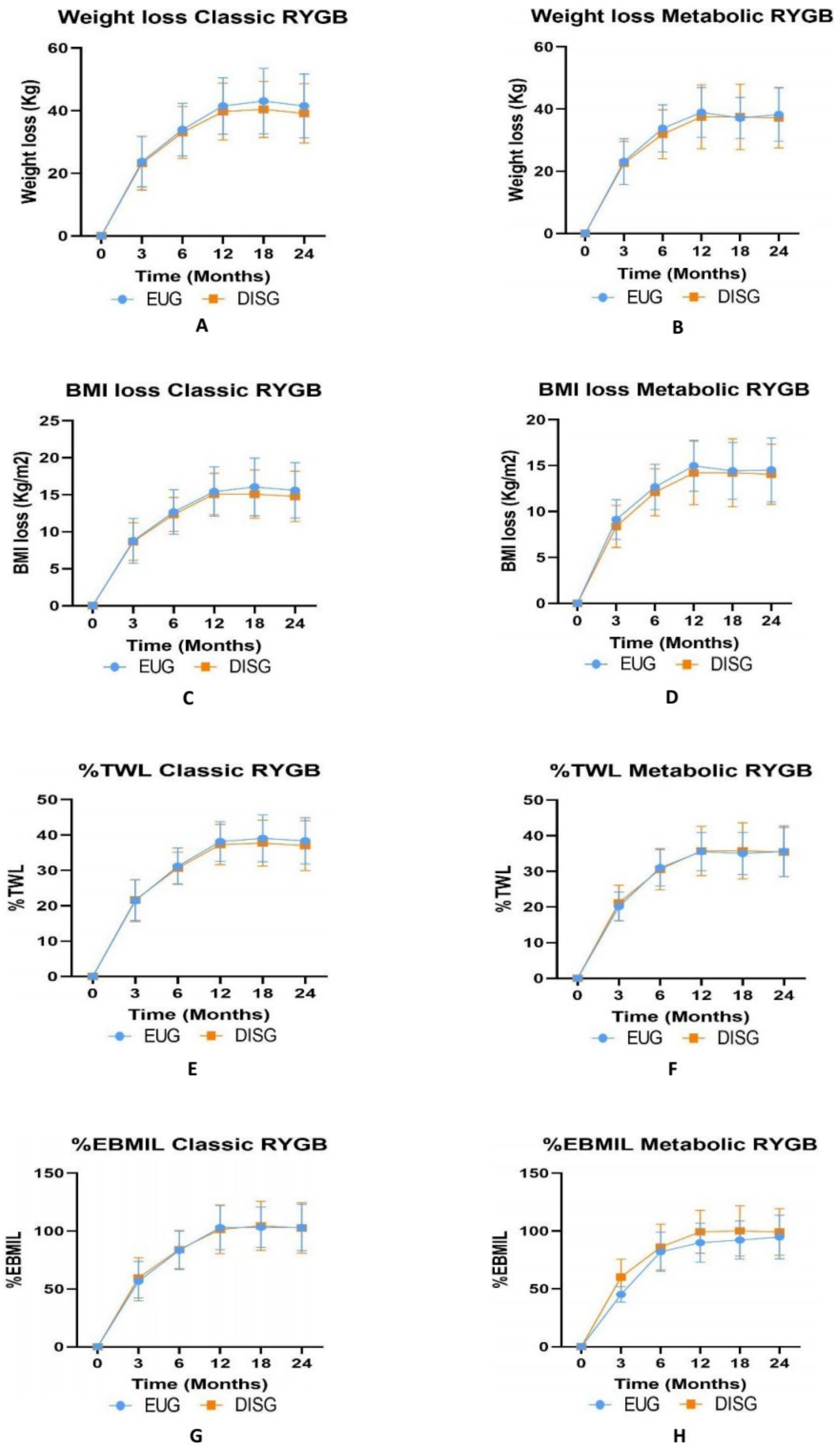

Figure 5. Weight loss, Body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques for euglycaemic (EUG) and dysglycaemic (DYSG) patients (* $p<0.05$: EUG vs DYSG, Two-way ANOVA test).

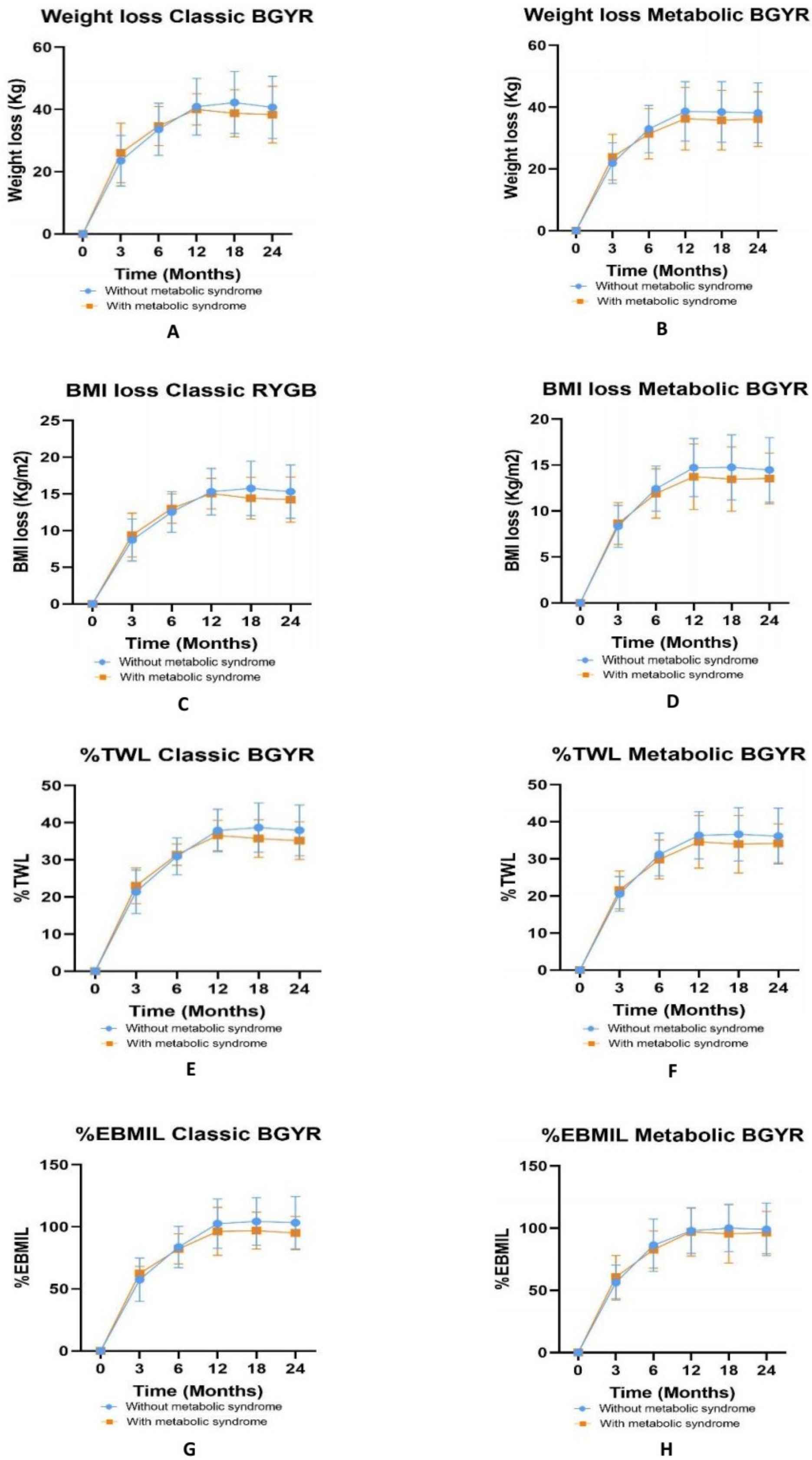

Figure 6. Weight loss, Body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques for patients with and without metabolic syndrome. (* $p<0.05$: With metabolic syndrome vs Without metabolic syndrome, Two-way ANOVA test).

Table I- Demographic, anthropometric, and clinical features of the individuals subjected to classical Roux-en-Y Gastric Bypass (RYGB) and metabolic RYGB.

	Classical RYGB	Metabolic RYGB
Gender (F/M)	101/28	42/12
Age (mean ± SEM years)	42.3 ± 0.81	48.6 ± 1.12
Weight (mean ± SEM Kg)	108.9 ± 1.47	105.7 ± 2.16
BMI (mean ± SEM Kg/m^2)	40.4 ± 0.35	39.9 ± 0.49
EUG, n (%)	73 (57%)	12 (22%)
PT2D, n (%)	42 (33%)	9 (17%)
T2D, n (%)	14 (11%)	33 (61%)
Hypertension, n (%)	36 (28%)	39 (72%)
Dyslipidemia, n (%)	46 (36%)	39 (72%)
Metabolic syndrome, n (%)	6 (5%)	19 (35%)

SEM: Standard error of the mean; BMI: Body mass index, EUG: Euglycaemia; PT2D: Pre-Type 2 Diabetes; T2D: Type 2 Diabetes

Table II- Correlations between the Type 2 Diabetes (T2D) duration and the post-operatory weight loss, body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques.

	Checkpoint	Classical RYGB		Metabolic RYGB	
		p value	r	p value	r
Weight loss (Kg)	3 months	0.2656	-0.3897	0.0843	0.3764
	6 months	0.2448	-0.3831	0.4693	0.1551
	12 months	0.4266	-0.2674	0.1736	0.2466
	18 months	0.2082	-0.4357	0.1801	0.2659
	24 months	0.2052	-0.3762	0.5606	0.1149
BMI loss (Kg/m^2)	3 months	0.1288	-0.5170	0.0843	0.3763
	6 months	0.0926	-0.5359	0.2785	0.2305
	12 months	0.4480	-0.2541	0.5835	0.1007
	18 months	0.1983	-0.4451	0.4995	0.1358
	24 months	0.2141	-0.3681	0.7541	-0.0620
%TWL	3 months	0.6839	-0.1477	0.3970	-0.1900
	6 months	0.3517	-0.3095	0.1346	-0.3144
	12 months	0.7207	0.1204	**0.0462**	-0.3549
	18 months	>0.9999	0	0.1929	-0.2585
	24 months	0.8153	-0.0721	**0.0143**	-0.4578
%EBMIL	3 months	0.1284	0.5141	0.8759	0.0354
	6 months	**0.0025**	0.8100	0.6599	-0.0947
	12 months	**0.0003**	0.8852	0.3261	-0.1793
	18 months	**0.0432**	0.6469	0.9100	-0.0228
	24 months	**0.0234**	0.6214	0.2505	-0.2246

Table III- Correlations between the patient's age and the post-operatory weight loss, body mass index (BMI) loss, % of total weight loss (%TWL) and % of excess BMI loss (%EBMIL) achieved after both Roux-en-Y Gastric Bypass (RYGB) techniques.

	Checkpoint	Classical RYGB		Metabolic RYGB	
		p value	r	p value	r
Weight loss (Kg)	3 months	0.3731	0.1003	0.2538	-0.2150
	6 months	0.1394	-0.1425	**0.0378**	-0.3297
	12 months	0.1385	-0.1428	**0.0058**	-0.3926
	18 months	0.0922	-0.1702	**0.0462**	-0.2955
	24 months	0.1829	-0.1256	**0.0157**	-0.3469
BMI loss (Kg/m^2)	3 months	**0.0404**	0.2283	0.0686	-0.3369
	6 months	0.7116	-0.0358	**0.0124**	-0.3918
	12 months	0.8002	-0.0245	**0.0013**	-0.4502
	18 months	0.3463	-0.0957	**0.0479**	-0.2933
	24 months	0.5766	-0.0528	**0.0049**	-0.3993
%TWL	3 months	0.7982	0.0289	0.4416	-0.1459
	6 months	0.6020	-0.0505	0.9834	-0.0034
	12 months	0.5028	-0.0649	0.2433	-0.1717
	18 months	0.1467	-0.1469	0.6701	-0.0645
	24 months	**0.0294**	-0.2041	0.6998	-0.0571
%EBMIL	3 months	0.8037	0.0281	0.7283	-0.0662
	6 months	0.6382	-0.0456	0.7434	0.0534
	12 months	0.9684	0.0038	0.7894	-0.0396
	18 months	0.5865	-0.0553	0.6237	-0.0743
	24 months	0.2544	-0.1076	0.7099	0.0551

Table IV- Type 2 Diabetes (T2D) remission rates after each Roux-en-Y Gastric Bypass (RYGB) techniques.

		Classical RYGB	Metabolic RYGB	p value
3 months	Without remission	4 (28.6%)	8 (25%)	>0.9999
	With remission	10 (71.4%)	24 (75%)	
6 months	Without remission	1 (7.1%)	5 (16.1%)	0.6485
	With remission	13 (92.9%)	26 (83.9%)	
12 months	Without remission	1 (7.1%)	4 (12.1%)	>0.9999
	With remission	13 (92.9%)	29 (87.9%)	
18 months	Without remission	0 (0%)	4 (12.1%)	0.3024
	With remission	14 (100%)	29 (87.9%)	
24 months	Without remission	0 (0%)	3 (10%)	0.5402
	With remission	14 (100%)	27 (90%)	

Bibliography

1. The GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/nejmoa1614362
2. Yumuk V, Tsigos C, Fried M. European Guidelines for Obesity Management in Adults. *Obes Facts*. 2015;8(6):402-424. doi:10.1159/000442721
3. Nyberg ST, Batty GD, Pentti J, et al. Obesity and loss of disease-free years owing to major non-communicable diseases: a multicohort study. *Lancet Public Heal*. 2018;3(10):e490-e497. doi:10.1016/S2468-2667(18)30139-7
4. Powell-Wiley TM, Poirier P, Burke LE, et al. *Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association*. Vol 143.; 2021. doi:https://doi.org/10.1161/CIR.0000000000000973
5. Diabetes Canada Clinical Practice Guidelines Expert Committee, Punthakee, Z., Goldenberg, R., & Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. *Can J Diabetes*. 2018;42(1):S10-S15. doi:10.1016/j.jcjd.2017.10.003
6. Nora M, Guimarães M, Almeida R, et al. Excess body mass index loss predicts metabolic syndrome remission after gastric bypass. *Diabetol Metab Syndr*. 2014;6(1):1-7. doi:https://doi.org/10.1186/1758-5996-6-1
7. Clifton PM, Keogh JB. Effects of Different Weight Loss Approaches on CVD Risk. *Curr Atheroscler Rep*. 2018;20(6):27. doi:https://doi.org/10.1007/s11883-018-0728-8
8. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes. *N Engl J Med*. 2017;376(7):641-651. doi:10.1056/nejmoa1600869
9. Adams TD, Davidson LE, Litwin SE, et al. Weight and Metabolic Outcomes 12 Years after Gastric Bypass. *N Engl J Med*. 2017;377(12):1143-1155. doi:https://doi.org/10.1056/NEJMoa1700459
10. Nora M, Morais T, Almeida R, Guimarães M, Monteiro MP. Should Roux-en-Y gastric bypass biliopancreatic limb length be tailored to achieve improved diabetes outcomes? *Medicine (Baltimore)*. 2017;96(48):e8859. doi:https://doi.org/10.1097/MD.0000000000008859
11. Cummings DE, Rubino F. Metabolic surgery for the treatment of type 2 diabetes in obese individuals Biliopancreatic diversion DSS-II Second Diabetes Surgery Summit GLP-1 Glucagon-like peptide-1 LAGB Laparoscopic adjustable gastric banding NIH National Institutes of Health QALY Q. *Diabetologia*. 2018;61((2)):257-264. doi:https://doi.org/10.1007/s00125-017-4513-y
12. Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. *Lancet Diabetes Endocrinol*. 2014;2(2):152-164. doi:10.1016/S2213-8587(13)70218-3
13. Affinati AH, Esfandiari NH, Oral EA, Kraftson AT, Arbor A. Bariatric Surgery in the Treatment of Type 2 Diabetes. *Curr Diab Rep*. 2019;19(12):156. doi:10.1007/s11892-019-1269-4.Bariatric
14. Guimarães M, Osório C, Silva D, et al. How Sustained is Roux-en-Y Gastric Bypass Long-term Efficacy?: Roux-en-Y Gastric Bypass efficacy. *Obes Surg*. 2021;31(8):3623-3629. doi:10.1007/s11695-021-05458-y
15. Patrício BG, Morais T, Guimarães M, et al. Gut hormone release after gastric bypass depends on the length of the biliopancreatic limb. *Int J Obes*. 2019;43(5):1009-1018. doi:10.1038/s41366-018-0117-y
16. Wee CC, Jones DB, Apovian C, et al. Weight Loss After Bariatric Surgery: Do Clinical and Behavioral Factors Explain Racial Differences? *Obes Surg*. 2017;27(11):2873-2884. doi:10.1007/s11695-017-2701-y
17. Wharton S, Kuk JL, Luszczynski M, Kamran E, Christensen RAG. Liraglutide 3.0 mg for the management of insufficient weight loss or excessive weight regain post-bariatric surgery. *Clin Obes*. 2019;9(4):e12323. doi:10.1111/cob.12323
18. Cadena-Obando D, Ramírez-Rentería C, Ferreira-Hermosillo A, et al. Are there really any predictive factors for a successful weight loss after bariatric surgery? *BMC Endocr Disord*. 2020;20(1):20. doi:10.1186/s12902-020-0499-4

19. Livhits M, Mercado C, Yermilov I, et al. Preoperative Predictors of Weight Loss Following Bariatric Surgery: Systematic Review. *Obes Surg*. 2012;22(1):70-89. doi:https://doi.org/10.1007/s11695-011-0472-4
20. Hallberg SJ, Gershuni VM, Athinarayanan SJ. Reversing type 2 diabetes: A narrative review of the evidence. *Nutrients*. 2019;11(4):766. doi:https://doi.org/10.3390/nu11040766
21. Carbonell AM, Wolfe LG, Meador JG, Sugerman HJ, Kellum JM, Maher JW. Does diabetes affect weight loss after gastric bypass? *Am Soc Metab Bariatr Surg*. 2008;4(3):441-444. doi:https://doi.org/10.1016/j.soard.2007.10.001
22. Grover BT, Morell MC, Kothari SN, Borgert AJ, Kallies KJ, Baker MT. Defining Weight Loss After Bariatric Surgery: a Call for Standardization. *Obes Surg*. 2019;29(11):3493-3499. doi:10.1007/s11695-019-04022-z
23. Carbajo MA, Jiménez JM, Luque-De-León E, et al. Evaluation of Weight Loss Indicators and Laparoscopic One-Anastomosis Gastric Bypass Outcomes. *Sci Rep*. 2018;8(1):1961. doi:10.1038/s41598-018-20303-6
24. Furtado MCMB, Vermeulen KM, Bellot PENR, et al. Evaluation of factors that may influence in the insufficient weight loss in patients after two years of roux-en-y gastric bypass. *Nutr Hosp*. 2018;35(5):1100-1106. doi:10.20960/nh.1814
25. Zeigler Z. COVID-19 Self-quarantine and Weight Gain Risk Factors in Adults. *Curr Obes Rep*. 2021;10(3):423-433. doi:10.1007/s13679-021-00449-7