Title

Endoscopic Trans-Oral Outlet reduction in Combination with Gastroplasty (TORe-G) is a Novel Technique that is Highly Efficacious and Safe for Weight Loss in Patients with Failed Roux-en-Y Gastric Bypass (RYGB)

Author

Goyal, Deepinder

Publication Date

2016

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

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A thesis submitted in partial satisfaction of the requirements for the degree Master of Science in Clinical Research

by

Deepinder Goyal

2016

ABSTRACT OF THE THESIS

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by

Deepinder Goyal
Masters of Science in Clinical Research
University of California, Los Angeles, 2016
Professor Gang Li, Chair

Background: Enlargement of the remnant gastric pouch and gastro-jejunal (GJ) stoma are associated with weight regain after RYGB surgery. Current evidence suggests an excess weight loss (%EWL) of 12-25% with GJ outlet reduction (TORe) alone. However, the efficacy of a combined approach using endoscopic trans-oral outlet reduction (TORe) in combination with Gastroplasty of the entire gastric pouch from the gastro-esophageal (GE) junction to the GJ stoma (TORe-G) is unknown.

Methods: Patients who experienced inadequate weight loss (<50% EWL) or weight regain (>25% EWL from nadir) post-RYGB along with evidence of dilated GJ stoma and gastric pouch underwent a combined GJ stoma reduction and gastroplasty. The procedure involved ablation of the peristomal mucosa and gastric pouch using APC and placement of interrupted and running full-thickness plications (Overstitch, Apollo Endosurgery, Austin Tx) for a targeted GJ diameter of ~5-8 mm and significant reduction of gastric pouch volume.

Results: 40 patients (78% females) with age 53±10 years, BMI 41±9 kg/m^2, and time since RYGB 10±4 years were prospectively studied. Significant weight loss (>5% TBWL) was seen in 90% patients. Post Tore-G, mean (95% CI) %TBWL observed at 1, 3, 6, 9 and 12 months follow up was 7.6 (5-10.1), 10.4 (8.1-12.8), 12.3 (9.6-14.9), 13.3 (10.4-16.2), and 14.1 (10.9-17.2) respectively. Corresponding %EWL was 24.1 (15.9-32.3), 31.3 (23.7-38.9), 35.9 27.3-44.4), 38.5 (29.1-47.9), and 40.4 (30.2-50.6); and %RWL was 39.6 (22.1-57), 52.1 (35.5 -68.8), 60.1 (41.9-78.3), 64.7 (45-84.5), and 68 (47-89) respectively. No covariates including age, sex, interval time since RYGB, % weight regained were significantly associated with weight loss over time. No serious adverse events were observed.

Conclusions: We demonstrate for the first time the efficacy and safety of TORe-G to re-establish weight loss in patients with failed RYGB using a full thickness endoscopic suturing device. TORe-G resulted in robust weight loss and superior outcomes compared with published data with TORe alone.

The thesis of Deepinder Goyal is approved

Joseph Pisegna

David Elashoff

Gang Li, Committee Chair

University of California, Los Angeles

2016

ACKNOWLEDGEMENTS

Mentors:

Joseph Pisegna, MD

Rabindra Watson, MD

David Elashoff, PhD

This work received grant support from Human Studies CORE through CURE: Digestive Diseases Research Center supported by NIH grant P30DK41301; UCLA CTSI; NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124, the American College of Gastroenterology Pilot grant (ACG-CR-039-2014), and the Department of Veterans Affairs RR&D Merit Review (JP)

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CHAPTER 1. MANUSCRIPT

ABSTRACT

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INTRODUCTION

Obesity and diabetes are the leading causes of cardiovascular mortality and pose a major public health challenges. Together, they pose a significant burden on healthcare resources both in terms of direct and indirect costs [1, 2]. Roux-en-Y gastric bypass (RYGB), the most commonly performed weight loss procedure in the United States, is characterized by a marked and sustained loss of 65 to 75% of excess body weight and remission of diabetes in more than 75% of individuals [3, 4, 5]. However, more than 20% of patients experience significant post-operative weight regain, and risk recurrence or worsening of comorbid conditions such as diabetes, hypertension and obstructive sleep apnea [6]. An additional 20-35% patients who undergo this operation fail to achieve the target weight loss of >50% excess weight body weight (EWL) at one year [6]. Although the etiology of weight regain and treatment failure is likely multi-factorial including both behavioral factors and adaptive changes in energy expenditure and satiety hormone secretion, enlargement of the remnant gastric pouch and gastro-jejunal (GJ) stoma post-RYGB have been identified as independent predictors of weight regain [7, 8].

With the widespread use of RYGB for the treatment of obesity, weight regain is an increasingly a common referral indication for revision operations, which carry significant morbidity and mortality to the patient [9]. Due to the risks and complexity of using a surgical approach to correct the anastomosis, several endoscopic suturing techniques and platforms have been and are being

developed that provide both a minimally invasive as well as safe approach for stomal revisions [10]. Although level 1 evidence exists regarding the efficacy of endoscopic trans-oral outlet reduction (TORe), efficacy of gastric pouch revision in terms of weight loss is still unclear. Current evidence suggests an excess weight loss (%EWL) of 12-25% with GJ outlet reduction (TORe) alone [11-15].

We hypothesized that gastric pouch volume restoration in addition to GJ outlet reduction would have an additive effect to help achieve greater and more sustained weight loss in patients with weight regain or RYGB failure. Therefore, in order to further understand the efficacy and safety of combined endoscopic TORe and gastroplasty (TORe-G) on body weight in RYGB patients who either experience a significant weight regain or fail to achieve target weight loss we conducted the following study. Our objectives were: (i) To evaluate the outcomes of TORe-G with respect to percentage of total body weight loss (%TBWL), excess weight loss (%EWL), regained weight loss (%RWL) and, (ii) To identify predictors of weight loss following TORe-G.

METHODS

The Institutional Review Board (IRB) at UCLA Medical Center provided approval for the study. A review of a prospectively collected database was conducted for all patients who underwent endoscopic revision of RYGB during 2014-2015 at UCLA Medical Center. Variables collected from electronic patients' charts included age, sex, interval time since RYGB, pre-surgical weight, nadir weight post RYGB, percent weight regained since RYGB, procedural data, and post-procedure weight at 1, 3, 6 and 9, and 12 month follow up intervals. Subjects were evaluated at scheduled post-procedure visits and were contacted via telephone to obtain individual progress

reports. Patients were weighed on a single scale throughout the study, and were queried regarding exercise and activity levels, diet, satiety levels and gastrointestinal symptoms.

Patients: All male and female subjects between the ages of 18 and 65 years who underwent a combined GJ stoma reduction and gastroplasty for inadequate weight loss (< 50% EWL) or weight regain (>25% EWL from nadir) post-RYGB, along with evidence of GJ diameter of ≥ 2cm and dilation of gastric pouch were included in the study.

Patients who required concomitant gastro-gastric fistula closure were excluded from the study. Furthermore, patients were excluded if they had recent change in social behavior including smoking, alcohol, substance abuse and active use of medications known to cause either weight gain or weight loss within 3 months.

Endoscopic procedure: All procedures were performed by two endoscopists (RW, DG) using an FDA approved endoscopic suturing device (Overstitch, Apollo Endosurgery Inc, Austin, Tx). All procedures were performed in an endoscopy suite with anesthesia assistance (general anesthesia or modified anesthesia care) per standard clinical practice. Gastric pouch length was measured from the squamo-columnar junction to the rim of the GJ anastomosis. As previously described, a gastric pouch of length of ≥ 6 cm together with the ability to easily perform retro-flexion in the pouch was considered diagnostic of gastric pouch dilation [16]. The GJ stoma diameter was assessed during the endoscopy using a through the scope standard calibrated round snare device.

Argon plasma coagulation (APC) was used to ablate the mucosa of the stoma and gastric pouch to expose the substrate collagen required for durable tissue apposition [11, 18]. This technique also served to map the predicted pouch plication sites. Interrupted plications using 2-0 prolene suture were placed in sequential fashion across the stoma to achieve a targeted immediate post-

procedure GJ diameter of approximately 5-8 mm. Interrupted plications in a triangular stitch pattern running from the anterior gastric wall to greater curvature to the posterior gastric wall were then placed in a distal to proximal fashion from just above the revised GJ anastomotic junction to the gastric fundus immediately below the GE junction resulting in significant reduction of gastric pouch volume **(Figure 1)**. Patients were recovered in the post anesthesia care unit per standard practice and furnished with analgesia and anti-emetics as needed.

Post-operatively, patients remained NPO on the day of procedure, followed by a clear liquid diet for two days, full liquid diet for two days, mechanical soft diet for two days, and advancement as tolerated thereafter.

Statistical Analysis: Weight loss (WL) was calculated by subtracting follow-up weight from the operative weight. The outcomes were reported as %TBWL = WL/(operative weight) × 100, %EWL = WL/(excess weight based on BMI of 25) × 100, and %RWL = WL/(regained weight post RYGB nadir) × 100.

Linear mixed effect model with random intercept for each subject was used for determining weight loss over time. This approach takes into account the correlations between observations within the same subject. It also provides valid estimates when missing data was assumed to be missing at random. Several functional forms such as linear, quadratic, square root and logarithm were examined for incorporating time into the mixed effect model. By comparing Akaike's information criterion, logarithm function was seen to best capture the relationship between time and weight loss outcomes. After the best model specification was chosen, restricted maximum likelihood was used to obtain the final model parameter estimates. Furthermore, by examining

residual versus fitted plots, observations for which models fit poorly were identified and sensitivity analysis was performed by removing these outliers and refitting the model.

The effect of covariates such as age, BMI, years since RYGB and gender and the interaction term gender x time on weight loss over time was tested by Wald test. R software (R version 3.2.3) was used for analysis. A p value < 0.05 was considered statistically significant.

RESULTS

40 patients (78% females) with age 53±10 years, BMI 41±9 kg/m2, and time since RYGB 10±4 years were included in the study. Technical success was achieved in 100% of the patients. The duration of maximum follow up was 1, 3, 6, 9 and 12 months for 40, 31, 14, 10 and 9 patients respectively. The number of data observations available at the above follow up intervals were 31, 27, 11, 3 and 9 respectively.

Post- TORe-G weight loss over time was significant during one year follow up period ($p < 0.001$). The weight loss results in terms of %TBWL, % EWL, and %RWL are described in three different formats as: 1) sample mean with 95% confidence intervals (95% CI) based upon the available data only and ignoring the missing data [**Table 1, 2, and 3]**; 2) model estimates with 95% CI taking into account the missing data and within subject weight correlations [**Table 1, 2, 3] [Figure 2 A, B, C**], and 3) model estimates after removing all the outliers in order to avoid biased results from skewed weight loss observations reported in few subjects. **[Table 4]** No covariates including age, sex, interval time since RYGB, percent weight regained were significantly associated with weight loss over time.

No major adverse events were observed in any of the patients and most patients were discharged home the same day. One fourth of all patients required more than 24 hours of observation post-

procedure. After the procedure, the most commonly reported adverse event consisted of mild abdominal pain and nausea which were managed successfully with analgesics and antiemetics. All reported symptoms resolved after an average of one week.

DISCUSSION

Historically, greatest proportion of obese patients underwent gastric bypass surgery in the last two decades. This has led to an ever-increasing population of patients encountering weight relapse as a medically challenging and emotionally frustrating problem [19]. Enlargement of the remnant gastric pouch or gastro-jejunal (GJ) stoma post-RYGB has been demonstrated to be an independent predictor of weight regain in multiple studies [19]. In one study, at 5 years after RYGB, each 10 mm increase in the GJ stoma diameter was associated with an 8% increase in the percent of maximal weight lost after RYGB that was regained [7]. In another report of 380 patients, at a mean of 6 years after RYGB, pouch length, volume, and stoma diameter correlated inversely with excess weight loss. Stomas >2 cm in diameter were considered enlarged, and pouches >6 cm in length or >5 cm in width were considered enlarged. A multivariate analysis revealed stoma diameter to be independently associated with weight regain. In the 175 patients with successful weight loss, a majority (63.4%) had normal pouch and stoma size. By contrast, in the 205 patients referred for weight regain, only 28.8% had normal pouch and stoma size (P <.001) [8].

Several endoscopic suturing strategies have been described as revision therapies for weight regain after gastric bypass. Using a suction based endoscopic suturing system (Bard EndoCinch by C.R. Bard, Inc, Murray Hill, NJ), Thompson, et. al. established the efficacy of endoluminal intervention for GJ stoma reduction in a multicenter randomized sham controlled trial involving 77 patients. In this study, the investigators showed greater weight loss in the

subjects that received sutured trans-oral outlet reduction (TORe) (3.5 % (95% confidence interval [CI], 1.8%-5.3%) than controls (0.4%; 95% CI, 2.3% weight gain to 3.0 % weight loss) (p=0.02) [11]. Subsequently, the investigators published superior results in two case series with a full thickness endoscopic suturing device (Overstitch, Apollo Endosurgery, Austin Tx) that was designed to overcome the limitations of suction-based tissue acquisition via a curved suturing arm. In one study, 20% EWL was seen at 6 months in 59 patients with GJ outlet revision [12]. In another smaller study involving 25 patients who underwent outlet reduction for dilated GJ stoma, a mean weight loss of approximately 11 kg was seen at 3 months which was sustained for 6 months. In this study, 13 of 25 patients also received few additional stitches in the distal pouch to re-inforce the anastomotic reduction. The authors however did not differentiate between the outcomes of GJ outlet reduction compared to those receiving additional distal gastric pouch revisions [13]. More recently, the above group published their long term outcomes in the largest case series involving 150 patients demonstrating sustained weight loss post TORe of % EWL 24.9% and 19.2 % at 1 and 3 years respectively. No significant difference in weight loss was seen without or without pouch reduction in this cohort; however, these patients did not receive gastroplasty of their entire gastric pouch [15]. A separate group of investigators in a 16 patient study have reported more modest outcomes in patients undergoing endoscopic GJ stoma reduction using the Overstitch device with an average %EWL of 12.4 % at 6 months [14]. The absolute weight loss from baseline achieved in their cohort was mean 5.6 kg at 6 months. The majority of the weight loss observed in these studies occurred in the first 3-6 months after the procedure [12-15].

There is limited data demonstrating the efficacy of gastric pouch reduction alone by using an older endoscopic tissue approximation device that uses H-fasteners (StomaphyX by Endogastric Solutions, Redmond, WA) in small case series [20, 21, 22]. However, there are no

published results studying the efficacy of TORe in combination with gastroplasty of the entire gastric pouch from the GE junction to the GJ stoma (TORe-G) utilizing an endoscopic full thickness suturing device.

Our study demonstrates, for the first time, the efficacy and safety of the combined approach of endoscopic GJ stoma revision and gastroplasty (TORe-G) in patients experiencing weight regain post RYGB. TORe-G appears to result in greater weight loss as compared to published data on GJ stoma revision alone. The %EWL observed in our study even by most conservative estimates was above 35% at 12 months as compared to approximately 12-25 % reported with TORe alone at similar follow up intervals. Corresponding total body weight loss was robust at above 10% and loss of regained weight more than 50%. The results did not change significantly with implementation of statistical modeling accounting for the missing data as well as after removing outliers from the analysis who reported unexpected excessive weight loss as compared to rest of the cohort. We hypothesize that the greater weight loss observed with our technique may be secondary to greater gastric volume restriction, reduced gastric emptying times, and higher baro-receptor stimulation of stretch receptors thereby inducing satiety. Although we did not study the levels of various gastro-intestinal orexigenic and anorexigenic hormones, an altered release pattern could have also played an important role in the success of this procedure. A prospective study evaluating the underlying physiological mechanisms of this endoscopic bariatric procedure is currently underway.

Importantly, weight loss was seen in every patient who underwent TORe-G regardless of their age, sex, interval time since RYGB, and percent weight regained since the surgery. The procedure was well tolerated by all patients. No patient required prolonged hospitalization or re-admission for any endoscopic procedure related adverse event. However, our study is limited by

small sample size, short follow up period, missing data, lack of standardized measurement of post-revision gastric pouch size, lack of specific measures for dietary compliance post procedure and the role that it might have played in these results. Furthermore, no routine post-procedure endoscopic or radiological assessment was conducted to evaluate the durability of the gastric volume reduction.

In summary, we demonstrate the efficacy of a novel approach to the treatment of weight regain following RYGB. The combination of gastroplasty in addition to GJ stoma reduction appears to result in the induction of robust weight loss in the setting of weight regain and RYGB failure using a full thickness endoscopic suturing device. Larger, multi-center, prospective studies with longer follow up are needed to conclusively establish the superiority of this endoscopic revision technique.

Figure 1

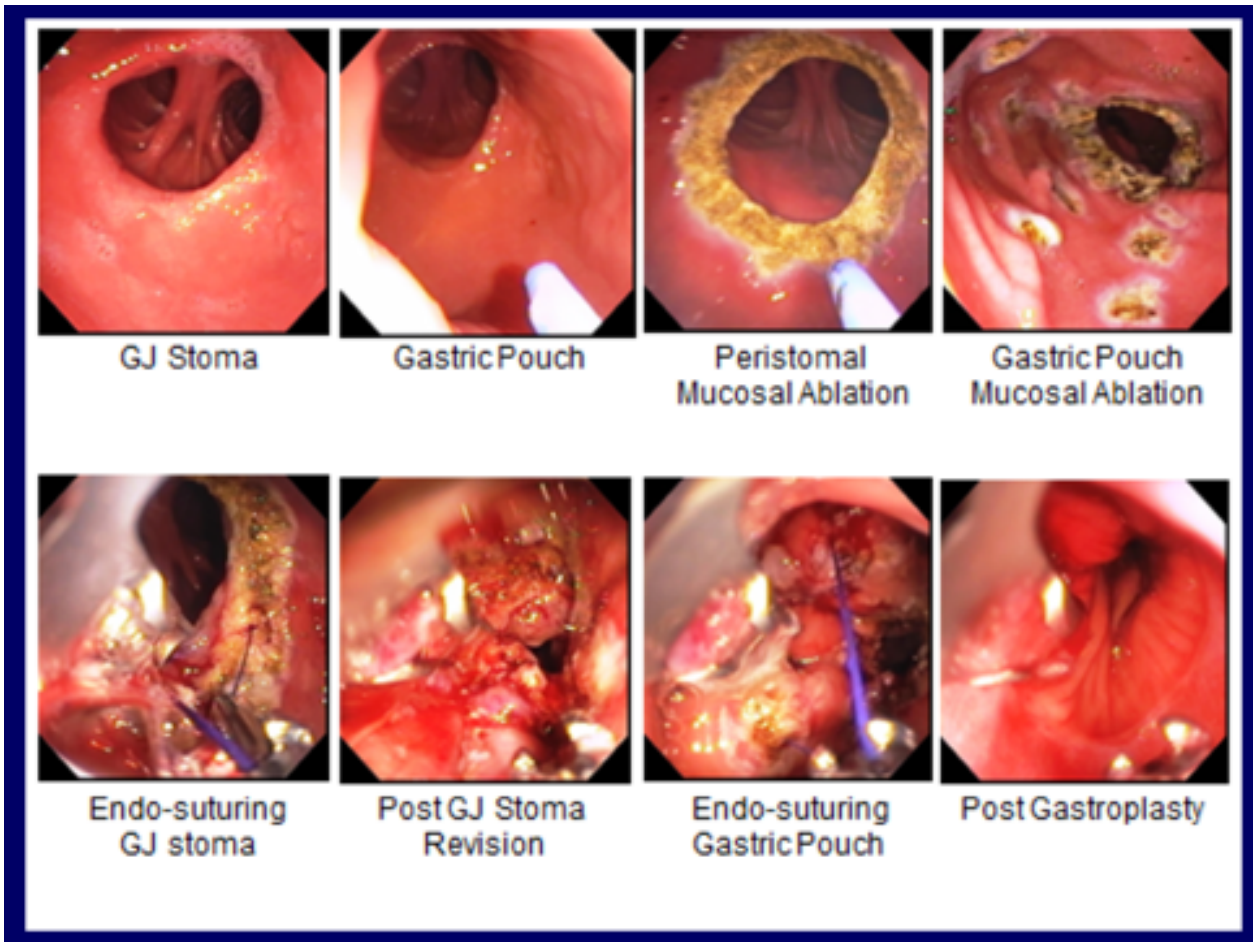

GJ Stoma
Gastric Pouch
Peristomal Mucosal Ablation
Gastric Pouch Mucosal Ablation
Endo-suturing GJ stoma
Post GJ Stoma Revision
Endo-suturing Gastric Pouch
Post Gastroplasty

Figure 2A.

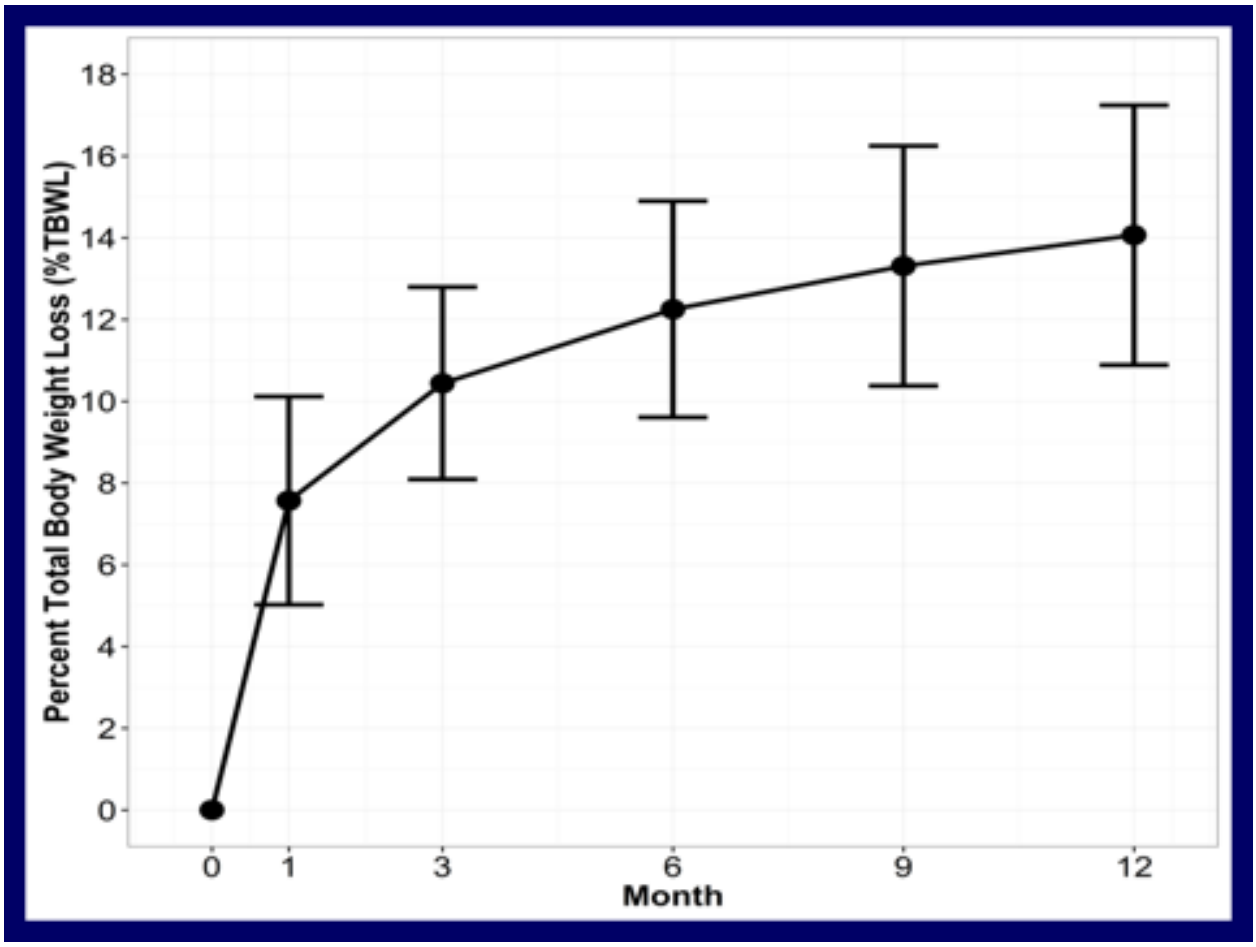

Percent Total Body Weight Loss (%TBWL)
18
16
14
12
10
8
6
4
2
0
0
1
3
6
9
12
Month

Figure 2B.

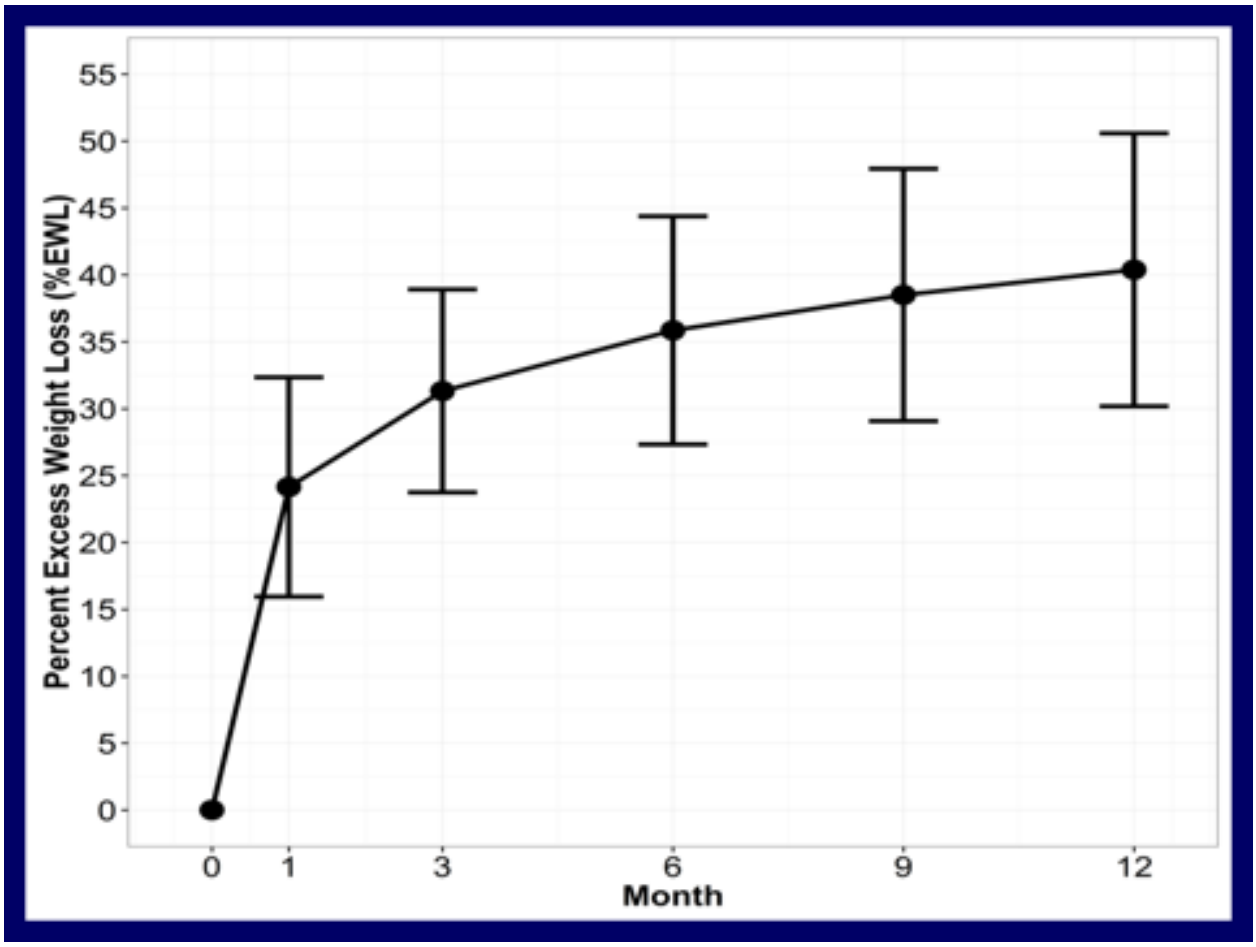

Percent Excess Weight Loss (%EWL)
55
50
45
40
35
30
25
20
15
10
5
0
0
1
3
6
9
12
Month

Figure 2C.

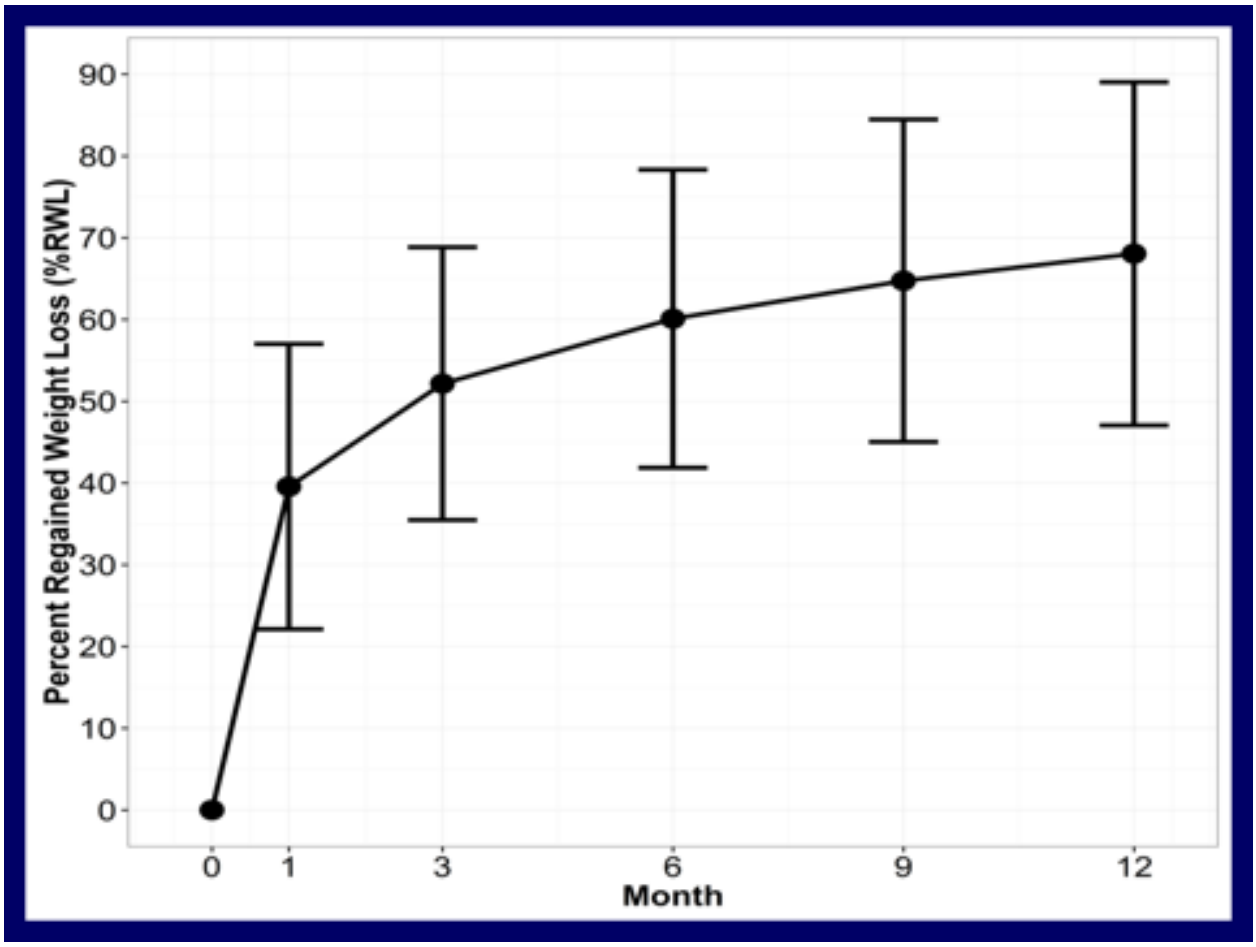

Percent Regained Weight Loss (%RWL)
90
80
70
60
50
40
30
20
10
0
0
1
3
6
9
12
Month

Table 1

Month	% Total Body Weight Loss			
	Sample Mean	95% CI	Model Estimate	95% CI
1	7.1	[5.6, 8.7]	7.6	[5.0, 10.1]
3	10.3	[7.8, 13.7]	10.4	[8.1, 12.8]
6	11.7	[7.7, 16.1]	12.3	[9.6, 14.9]
9	16.8	[11.2, 25.0]	13.3	[10.4, 16.2]
12	13.4	[6.3, 21.3]	14.1	[10.9, 17.2]

Table 2

Month	% Excess Weight Loss			
	Sample Mean	95% CI	Model Estimate	95% CI
1	23.3	[16.2, 32.4]	24.1	[15.9, 32.3]
3	32.7	[25.0, 42.3]	31.3	[23.7, 38.9]
6	33.7	[19.6, 48.8]	35.9	[27.3, 44.4]
9	49.1	[22.4, 76.0]	38.5	[29.1, 47.9]
12	35.3	[18.9, 56.7]	40.4	[30.2, 50.6]

Table 3

Month	% Regained Weight Loss			
	Sample Mean	95% CI	Model Estimate	95% CI
1	31.7	[23.5, 40.7]	39.6	[22.1, 57.0]
3	55.2	[37.3, 79.9]	52.1	[35.5, 68.8]
6	74.7	[38.8, 124.9]	60.1	[41.9, 78.3]
9	145.5	[58.1, 254.5]	64.7	[45.0, 84.5]
12	82.2	[49.7, 116.1]	68.0	[47.0, 89.0]

Table 4

Month	%TBWL		%EWL		%RWL	
	All Data	No Outlier	All Data	No Outlier	All Data	No Outlier
1	7.6	7.3	24.1	21.0	39.6	30.2
3	10.4	9.0	31.3	28.1	52.1	41.9
6	12.3	10.1	35.9	32.7	60.1	49.2
9	13.3	10.7	38.5	35.3	64.7	53.5
12	14.1	11.2	40.4	37.2	68.0	56.6

CHAPTER 2: STATISTICAL APPENDIX

Missing Data

The data set had 81 follow up measurements from 40 subjects. The tables below summarize the number of observations at each follow up time, and the distribution of the number of follow up from each subject. Two subjects were missing regained weight and were removed from %RWL analyses.

Number of observations at each follow up time

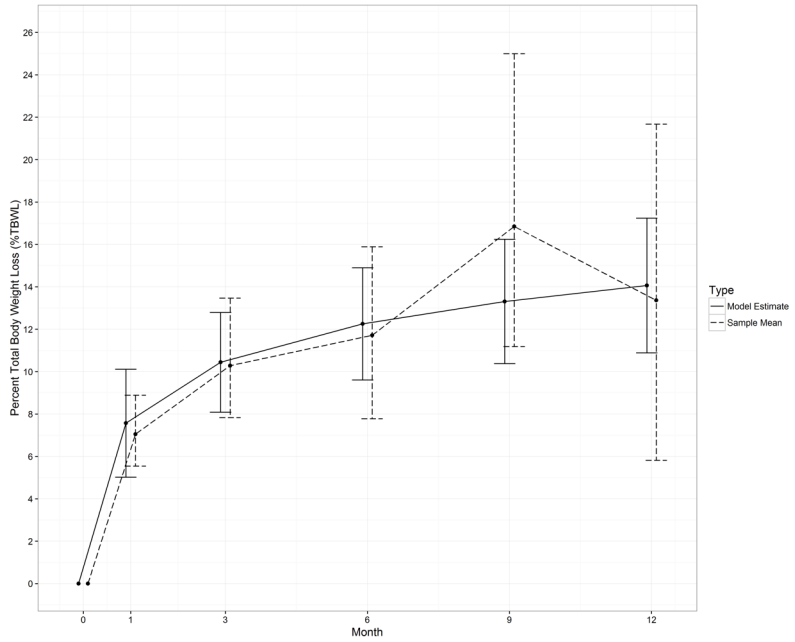
Month	1	3	6	9	12
No. Observations	31	27	11	3	9

Distribution of the number of follow up from each subject

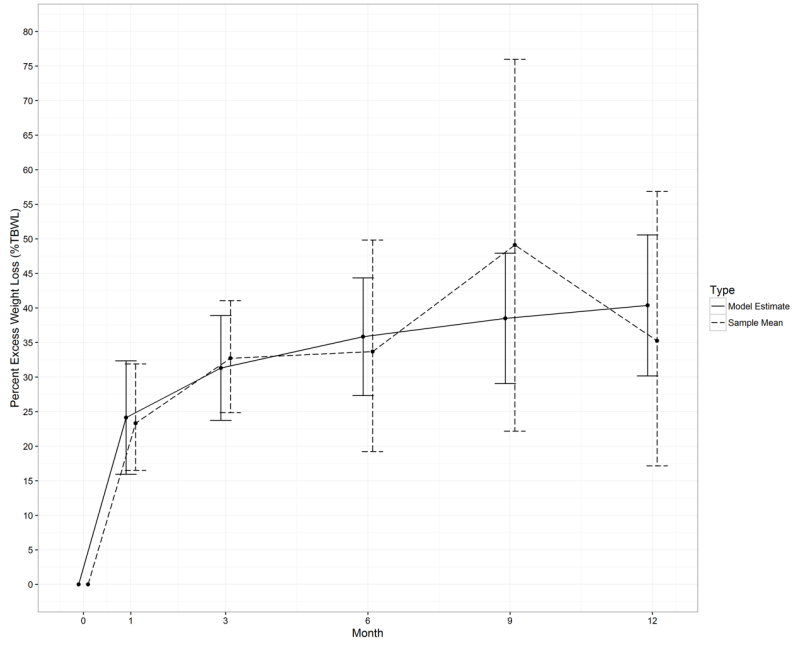
No. Follow up	1	2	3	4	5
No. Subjects	11	20	7	1	1

Results Objective 1: The following graphs compare the sample means of %TBWL, % EWL and %RWL based upon the available data versus the mixed effect model estimate with their 95% confidence intervals. Sample mean was obtained by averaging observations at a specific follow up time. It disregarded the missing data issue. For sample mean, Bootstrap (2000 bootstrap samples) percentile confidence interval was used due to the small sample size. Both parameters give fairly similar results except the confidence intervals were much narrower for model estimates suggesting a good model fit.

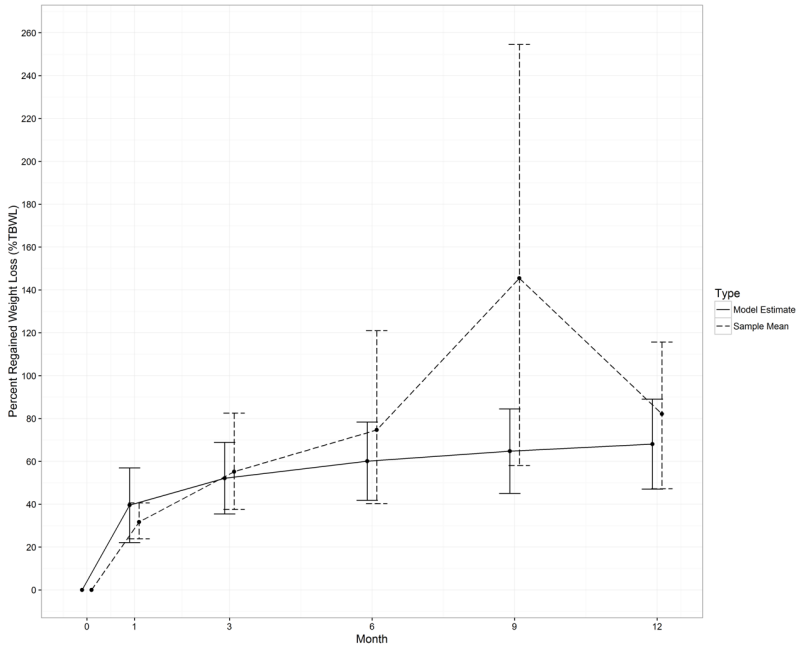
1. %TBWL


Percent Total Body Weight Loss (%TBWL)
Month
Type
Model Estimate
Sample Mean

2. %EWL

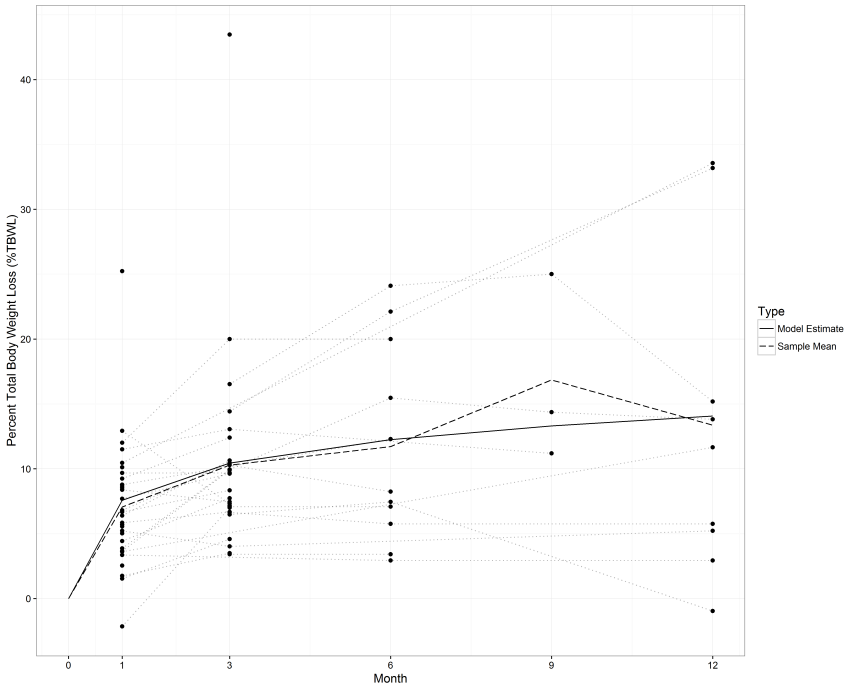

Percent Excess Weight Loss (%TBWL)
Month
Type
Model Estimate
Sample Mean

3. %RWL:

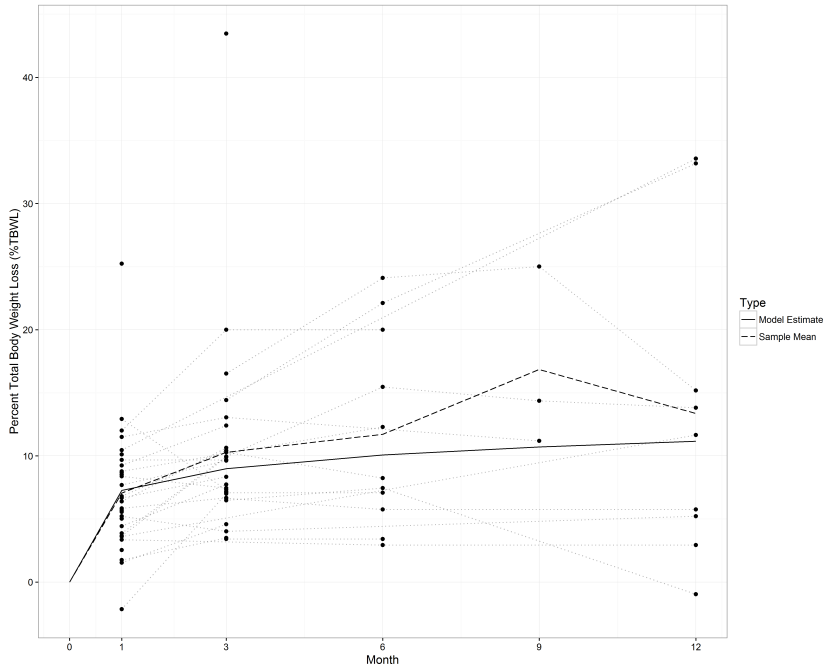

Percent Regained Weight Loss (%TBWL)
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0
1
3
6
9
12
Month
Type
Model Estimate
Sample Mean

Sensitivity Analysis: We examined the residual versus fitted plots and identified observations for which models fit poorly. Sensitivity analysis was performed by removing these outliers and the model was refitted. The following are the subject specific plots with and without outliers. The overall results did not change significantly after removing the outlier observations.

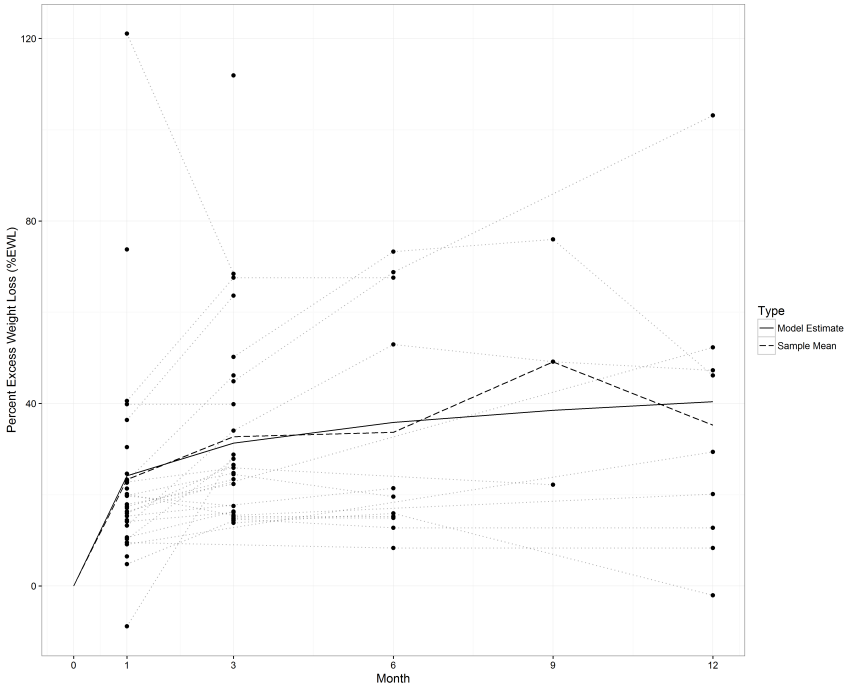
1a. % TBWL with outliers



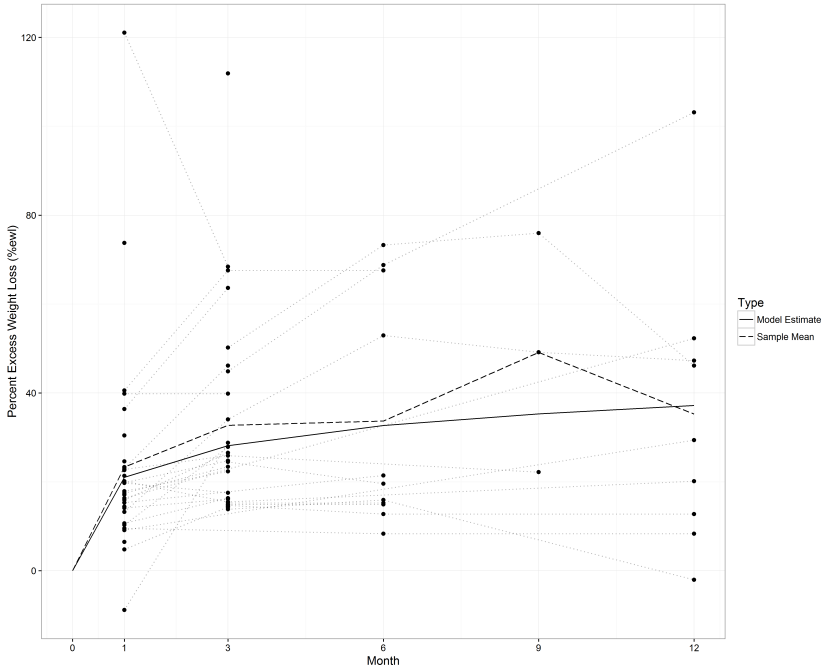
1b. % TBWL with-out outliers



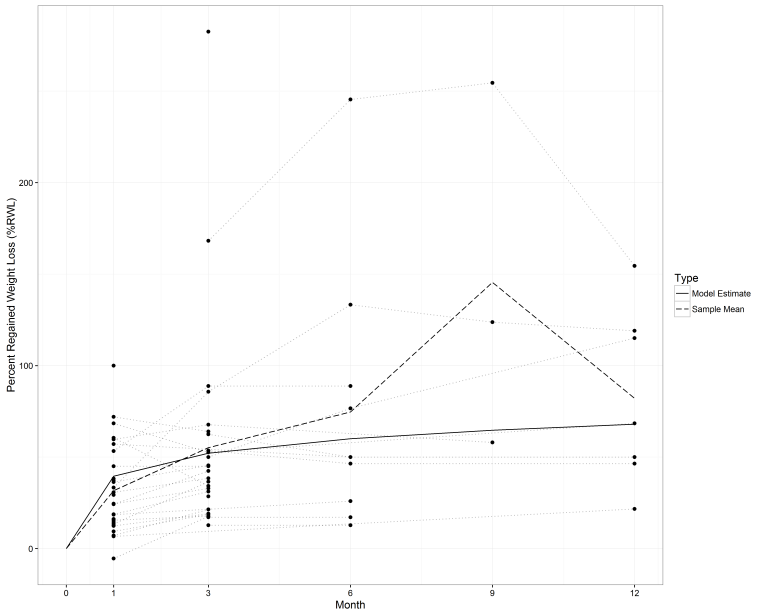
2a. % EWL with outliers



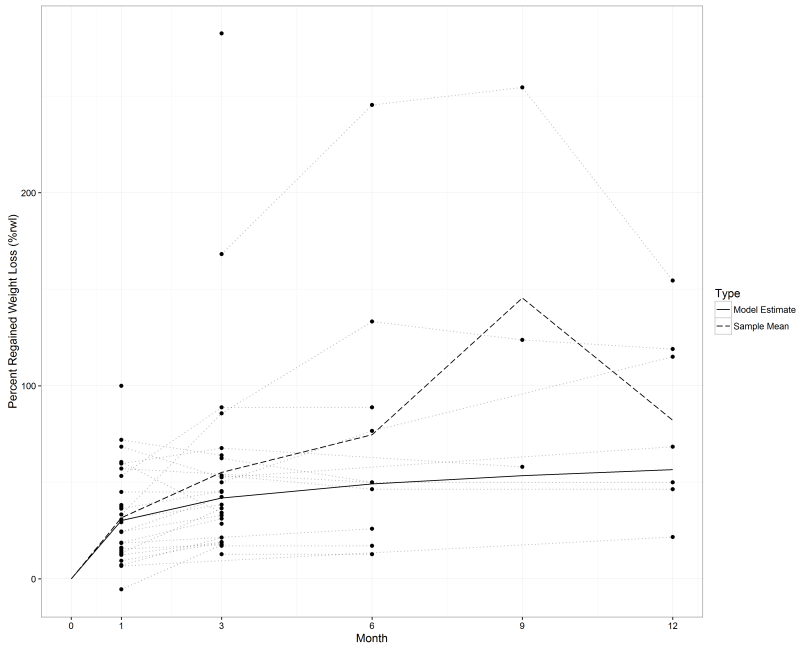
2b. % EWL with-out outliers



3a. % RWL with outliers



3b. % RWL with-out outliers



Objective 2: The effect of covariates including age, sex, BMI, years since RYGB and the interaction term gender x time on weight loss over time was tested by Wald test. The coefficient for log(time) was highly statistically significant. The %TBWL, % EWL and %RWL were significantly different from zero in a 1-year period. We failed to reject the null hypothesis that patient characteristics are associated with weight loss. The effect of interaction term $gender \times time$ was also not statistically significant suggesting no difference in %TBWL over time between genders.

1. Table comparing mixed effect model coefficients with and without covariate adjustments for %TBWL.

%TBWL	With Covariates		No Covariates	
	Coefficient	95% CI	Coefficient	95% CI
(Intercept)	0.073	[0.053, 0.093]	0.073	[0.055, 0.090]
log(time)	0.018	[0.006, 0.029]	0.016	[0.006, 0.026]
Age	-0.002	[-0.021, 0.017]	-	-
Sex = M	-0.002	[-0.043, 0.039]	-	-
Years since RYGB	0.004	[-0.013, 0.022]	-	-
Baseline BMI	0.004	[-0.013, 0.021]	-	-
log(time) : Sex = M	-0.009	[-0.034, 0.015]	-	-
P-value (LRT) comparing models with and without covariates = 0.92.				

2. Table comparing mixed effect model coefficients with and without covariate adjustments for % EWL.

%EWL	With Covariates		No Covariates	
	Coefficient	95% CI	Coefficient	95% CI
(Intercept)	0.20	[0.132, 0.267]	0.20	[0.137, 0.260]
log(time)	0.09	[0.051, 0.125]	0.07	[0.039, 0.106]
Age	-0.02	[-0.085, 0.046]	-	-
Sex = M	0.00	[-0.139, 0.137]	-	-
Years since RYGB	0.02	[-0.039, 0.078]	-	-
Baseline BMI	-0.06	[-0.118, 0.002]	-	-
log(time) : Sex = M	-0.07	[-0.154, 0.014]	-	-
P-value (LRT) comparing models with and without covariates = 0.19.				

3. Table comparing mixed effect model coefficients with and without covariate adjustments for RWL.

%RWL	With Covariates		No Covariates	
	Coefficient	95% CI	Coefficient	95% CI
(Intercept)	0.30	[0.180, 0.473]	0.30	[0.189, 0.446]
log(time)	0.12	[0.069, 0.228]	0.11	[0.058, 0.199]
Age	0.09	[-0.096, 0.195]	-	-
Sex = M	-0.04	[-0.360, 0.227]	-	-
Years since RYGB	-0.02	[-0.181, 0.078]	-	-
Baseline BMI	-0.01	[-0.167, 0.098]	-	-
log(time) : Sex = M	-0.08	[-0.271, 0.063]	-	-
P-value (LRT) comparing models with and without covariates = 0.16.				

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