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Changes in Telomere Length 3-5 years after Gastric Bypass Surgery

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Abstract

Increased inflammation and oxidative stress associated with obesity can accelerate aging. Telomere length (TL) has the capacity to serve as an aging indicator at the cellular level. Obesity has a known association with shorter TL. This study evaluated TL of immune cells in a population of obese individuals who underwent gastric bypass surgery. Pre and post-operative DNA samples were available for 50 subjects who had gastric bypass surgery. DNA was analyzed via quantitative polymerase chain reaction (q-PCR) to determine TL. Changes in TL were evaluated by comparing TL at baseline to TL at 3-5 years post gastric bypass surgery. Sixty percent of the individuals in the study observed an increase in TL. Significant lengthening was observed for those with the shortest baseline TL ($p=0.0011$), but not for those with intermediate baseline TL ($p=0.411$) or longest baseline TL ($p=0.207$). Change in TL was negatively correlated with age and triglycerides but not correlated with weight loss induced by bariatric surgery. This study confirms that TL lengthening is observed post bariatric surgery and is the first to detect TL lengthening 3-5 years after surgery.

Introduction

Telomeres are specialized structures, consisting of repetitive nucleotide sequences, localized at the natural end of eukaryotic chromosomes (1). The function of these DNA caps is to protect the genetic information by preventing DNA terminal degradation (2). For vertebrates, the repeating sequence of nucleotides in telomeres is TTAGGG (2,3).

Under normal circumstances during cell division, DNA polymerase fails to copy entire stands of telomeric DNA, thus shortening telomere length with each cell division (4.) This progressive telomere shortening with cell divisions is felt to limit cell renewal capability and may serve as a marker of longevity (5). Numerous controlled studies have demonstrated that

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obesity is associated with a shorter telomere length (6-10). These observations raise questions concerning the relationship between obesity, shortened telomere length, and the aging process.

Metabolic surgery is now recognized as the treatment of choice for severe obesity. Numerous studies have documented the health benefits, which include remission or improvement in comorbid disease and resolution of metabolic dysfunction. Previous long-term studies have demonstrated that metabolic surgery is associated with telomere lengthening, (11) but not within the first year after surgery (12). The purpose of this study is to provide additional information regarding the time course of telomere lengthening after metabolic surgery and its association with patient characteristics and surgical weight loss.

Methods

DNA and patient data were selected using a convenience sample from a previously described, IRB approved research study (13). Selected patients included those with readily available DNA from blood collected before surgery and DNA from blood collected between 3 to 5 years after surgery. DNA was diluted to a working concentration of 5ng/ul. TL analysis was run in triplicate and implemented via quantitative PCR (qPCR) on Advanced Biosystem 7500. qPCR was performed as previously delineated in (14), with cycle conditions of: 50°C for 2 minutes, 95°C for 10 minutes, followed by 35 cycles of 95°C for 15 seconds and 60°C for 1 minute. Primers (telomere forward/reverse and single copy gene 36B4 forward/reverse) and standards (telomere and single copy gene 36B4) were obtained from Integrated DNA Technologies. Primer and standard oligomer sequences are previously described (14). Serial dilutions of telomere standard and single copy gene standard were utilized to procure a standard curve to which a value for telomeric DNA and diploid genome copies of 36B4 was formulated by the AB7500 software. The aforementioned values were divided to calculate TL. The AB7500 software flagged any samples with high standard deviation. The throughput for sample analysis was refined so any sample analyzed was not flagged for high standard deviation.

Wilcoxon signed rank tests were used to evaluate changes in TL for the overall cohort and after stratifying by baseline TL (using tertiles). The correlation of change in TL with age, sex, baseline clinical variables (e.g. BMI, waist circumference, blood pressure, lab results), and weight loss induced by bariatric surgery was evaluated using Pearson's correlation (overall and stratified by baseline TL). SAS version 9.4 was used for statistical analysis and p-values <0.05 were considered significant.

Results

The study cohort included 50 patients with Roux-en-Y gastric bypass surgery with baseline clinical parameters described in Table 1. The mean baseline age was 46.8 years (SD=10.3, range=[23, 66]), 82% were female (n=41), and 100% white (49 non-Hispanic and 1 Hispanic). The mean baseline BMI was 50.3 kg/m² (SD=11.2, range=[37.0, 94.3]). A history of smoking was present for 38% (n=19) and 42%, 34%, and 38% had pre-operative hypertension, hyperlipidemia, and diabetes, respectively.

At 3-5 years after surgery, 30 of the 50 individuals had a lengthening of TL (60%, 95% CI=[45%, 74%]). In the overall group, the median TL from baseline to follow-up increased but was not significant (Figure 1, baseline median TL = 5.00 versus follow-up median TL = 6.07, $p=0.167$). However, significant lengthening was observed for those with the shortest baseline TL (baseline median TL = 1.07 versus follow-up median TL = 2.59, $p=0.0011$), but not for those with intermediate baseline TL ($p=0.411$) or longest baseline TL ($p=0.207$).

Age and triglycerides were positively correlated with baseline TL and negatively correlated with change in TL but not significantly correlated with sex, BMI, waist circumference, blood pressure, glucose level, serum insulin, hbA1c, cholesterol, HDL, or LDL (Table 1). Bariatric surgery induced weight change (Table 1, including nadir weight loss, 3-year weight loss, or weight regain from nadir to 3-years) was not correlated with baseline TL or change in TL (Table 1).

Discussion

Telomere attrition of leukocytes can be exacerbated in individuals with obesity (6-10). Here we delineate 50 adults with obesity, 60% of which experienced an amelioration of telomere attrition 3-5 years after gastric bypass surgery. Significant lengthening occurred in the group with the shortest baseline telomere length but not for those with intermediate to long baseline telomere lengths.

Only one study has shown the recovery of TL in obese adults who have lost weight through caloric restriction (15). Another study showed increases in telomere length 10 years after bariatric surgery (11). Formichi and colleagues conducted a similar study to the present study and they concluded weight loss associated with bariatric surgery did not amend shortened telomeres (12). They did admit, however, that their short follow up window of only one year could have impacted results. Furthermore, in a review by Epel, an ideal window of 2-6 years to observe telomere lengthening is outlined (16). Based on the 2-6 year optimal window for lengthening and the prior study showing lengthening at 10 years after surgery, the present study of measuring TL in a timeframe of 3-5 years post-operatively holds merit when searching for increases in TL.

Several mechanisms for telomere lengthening have been proposed. The first via telomerase as previously mentioned (2-4). Garcia-Calzon, et al. conducted an interventional study that measured baseline TL in overweight adolescents along with a second TL measurement after a strict diet and exercise change (17). The diet and exercise intervention was successful at lengthening telomeres, potentially linked to an increase in telomerase activity. Additionally, exercise was determined to be a key component to increased telomerase activity in a rodent model (18). In a population of obese men, TL was determined to increase if more weight and body fat was lost due to a calorie restricted diet (15). In the present study, increases in TL were observed, but there was no statistical correlation between the extent of weight lost and telomere lengthening (Table 1). A possible explanation for our finding that 60% of individuals had increases in TL is that diet after gastric bypass surgery together with an increase in physical activity may have resulted in an increase in telomerase activity. A future

study focused on telomerase levels could provide valuable insight to the overall mechanism contributing to TL variations.

The second telomere lengthening mechanism is considered quasi-lengthening due to altered concentrations of cell populations (16). TL can change in an oscillatory fashion based on distribution of young and old cells (16). TL can be distinguished by the average assortment of all immune cells in a sample studied (18). Oxidative stress has been delineated to be deleterious to TL, especially in obese individuals (6). Chronic stress limits the amount of cells circulating in the body (19), thus impacting the oscillatory based distribution of young versus old cells. A recent study identified a DNA polymerase that may mediate this process of telomere lengthening (20). A follow-up time of 3-5-years after post gastric bypass surgery is ample time for individuals to decrease obesity related stress. In return, a rejuvenated redistribution of younger immune cells may contribute to increased TL.

Major weaknesses for this study include the relatively small sample size and the lack of a control group. For this study, those with shorter baseline telomere lengths significantly increased after surgery and those with long baseline telomere lengths had a non-significant decrease in telomere length. A control group would help evaluate whether these results are explained by regression to the mean. A strength of this study is the intermediate follow-up time (3-5 years after surgery) for telomere lengthening, which has not been previously studied.

Conclusion

A majority of telomeres will naturally shorten over time with increased age. Obesity has been documented to accelerate the shortening process of telomeres. Gastric bypass patients hope to mitigate obesity related comorbidities and lose excess weight. Weight loss from gastric bypass impacts TL. To our knowledge, no other study has demonstrated telomere regrowth within 3-5 years after gastric bypass surgery.

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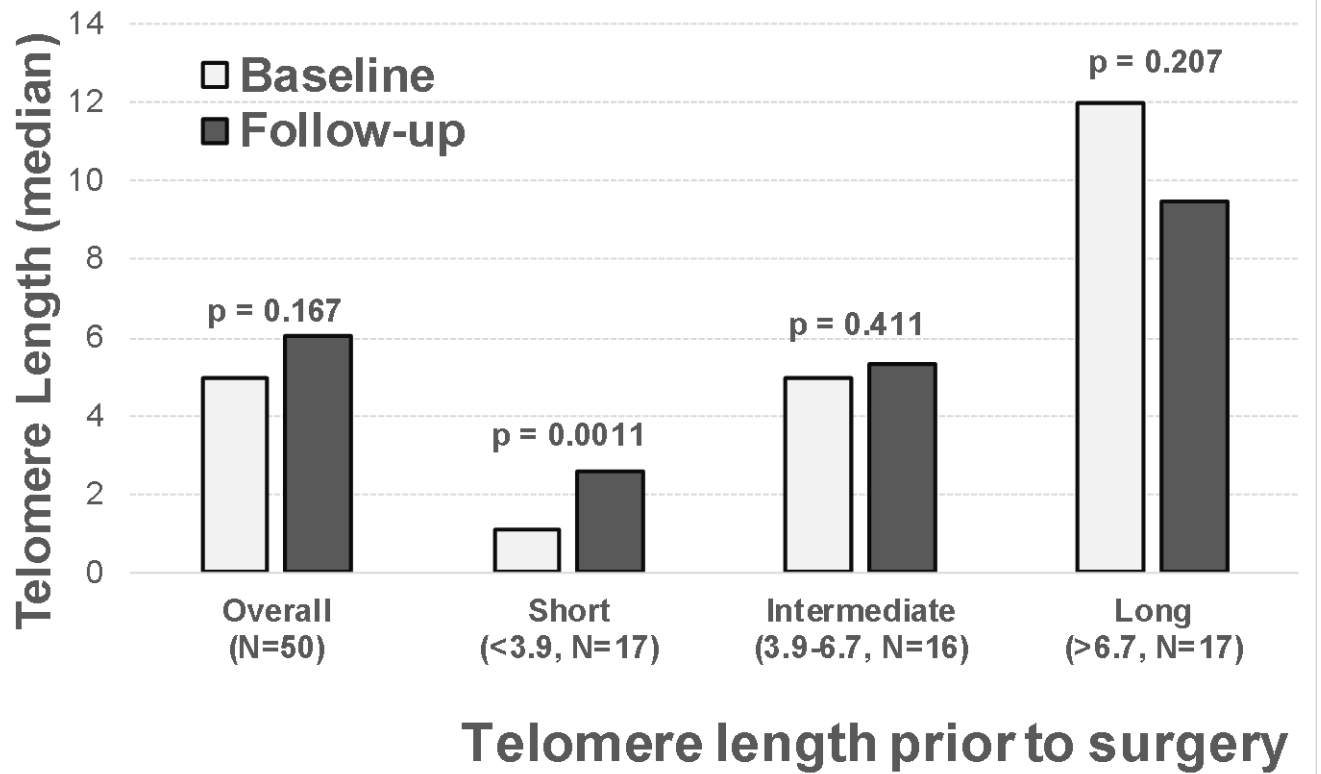


Figure 1.

Change in TL from pre-operative (baseline) and post-operative (follow-up). P-values resulted from signed rank test.

Table 1

Correlation of patient characteristics with baseline telomere length and change in telomere length.

Clinical parameter and weight loss	Correlation with baseline telomere length		Correlation with change in telomere length		
	Mean (SD)	r	p-value [†]	r	p-value [†]
Age, years	46.8 (10.3)	0.32	0.022	-0.31	0.027
Weight, kg	138.2 (35.9)	-0.04	0.786	0.01	0.959
BMI, kg/m ²	50.3 (11.2)	-0.01	0.956	0.02	0.906
Waist circumference, cm	135.6 (16.5)	0.02	0.866	0.03	0.840
Systolic BP, mmHg	130.2 (15.5)	0.23	0.101	-0.24	0.091
Diastolic BP, mmHg	74.2 (8.3)	-0.18	0.219	0.034	0.814
Glucose, mg/dL	93.9 (22.0)	0.06	0.661	0.00	0.976
Insulin, μ U/mL	25.0 (27.5)	-0.07	0.621	0.14	0.333
HbA1c, %	6.1 (1.1)	0.12	0.411	-0.04	0.769
Triglycerides, mg/dL	145.2 (60.9)	0.41	0.0033	-0.32	0.026
Cholesterol, mg/dL	185.9 (32.7)	0.05	0.724	0.10	0.480
HDL, mg/dL	48.4 (10.9)	-0.09	0.513	0.19	0.193
LDL, mg/dL	108.5 (28.4)	-0.08	0.601	0.18	0.206
Nadir %WL	36.4% (16.1)	-0.08	0.601	0.01	0.947
%WL 3-years	28.8% (11.4)	-0.05	0.750	-0.01	0.922
%WL regained	7.6% (5.2)	0.03	0.828	-0.05	0.740

[†]Pearson's correlation 0