Changes in circulating sirtuin 1 after bariatric surgery

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Abstract *Background and aims:* Obesity is associated with chronic inflammation and oxidative stress. Weight loss after bariatric surgery improves the inflammatory state and risk of cardiovascular disease. Improvement in metabolic dysfunction might be associated with changes in the activity of sirtuin 1 (SIRT1) and we aimed to investigate the effect of bariatric surgery on its circulating levels.

Methods and results: This is a sub-study of a prospective cohort study, including 110 subjects with morbid obesity. The surgical procedure was either laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG). Blood was sampled at inclusion and six and 12 months after surgery. SIRT1 was measured in EDTA plasma with an enzyme-linked immunosorbent assay. The mean age in the population was 43 years, 80% were women and mean body mass index (BMI) was 38.8 kg/m^2. RYGB and SG were performed in 89 and 21 subjects, respectively. SIRT1 concentration was significantly reduced from baseline to six and 12 months after surgery, with mean values (SD) 156.8 (82.6), 119.5 (65.6) and 94.9 (45.6) ng/mL, respectively, (p $\leq$ 0.002, all), accompanied by significant reductions in C-reactive protein (CRP), BMI and triglycerides from inclusion (p < 0.001, all). Type of surgery did not differently modify SIRT1 levels (p = 0.09). CRP and triglycerides were both positively predictive of SIRT1 levels (p $\leq$ 0.001, both).

Conclusion: SIRT1 concentration was significantly lower six and 12 months after bariatric surgery. CRP and triglycerides independently predicted SIRT1 levels, suggesting that reduction in SIRT1 levels might not intrinsically be related to weight reduction, but to improvement in metaflammation.

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Acronyms

AMP	Adenosine monofosfat	Lp(a)	Lipoprotein (a)
AMPK	AMP activated protein kinase	mRNA	Messenger RNA
ApoA1	Apolipoprotein A1	miR	Micro RNA
ApoB	Apolipoprotein B	NF-κB	Nuclear factor kappa B
BMI	Body mass index	PPAR	Peroxisome proliferator-activated receptor
CRP	C-reactive protein	PGC	Peroxisome proliferator-activated receptor-gamma coactivator
CVD	Cardiovascular disease	RYGB	Laparoscopic Roux-en-Y gastric bypass
EDTA	Ethylenediaminetetraacetic acid	RNA	Ribonucleic acid
ELISA	Enzyme-linked immunosorbent assay	SD	Standard deviation
HbA1c	Glycated haemoglobin	SG	Sleeve gastrectomy
HDL	High-density lipoprotein	SIRT1	Sirtuin1
LDL	Low-density lipoprotein	T2DM	Type 2 diabetes mellitus

1. Introduction

The prevalence of obesity, defined as body mass index (BMI) $\geq$ 30 kg/m^2, has escalated worldwide [1]. Obesity is characterized by a higher incidence of chronic inflammation and oxidative stress, with subsequent increase in metabolic complications including cardiovascular disease (CVD), diabetes type 2 (T2DM), the metabolic syndrome, hypertension, dyslipidaemia and several types of cancers [2–4].

Weight loss is associated with improvement in metabolic function, and bariatric surgery is considered a reliable treatment to achieve consistent weight loss. Laparoscopic Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are both considered effective procedures. The large weight loss provided by bariatric surgery in subjects with morbid obesity affects both the amount and structure of the adipose tissue, and may reduce the chronic inflammatory state [5] and the risk of CVD [6].

Sirtuin 1 (SIRT1) belongs to a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases, and is the most investigated sirtuin subtype in humans [7]. Its activity has been associated with longevity and protection against metabolic and chronic degenerative diseases [8]. Recent studies have shown that SIRT1 induces both cellular and systemic protective effects in the cardiovascular system [9]. Experiments in genetically modified mice have also highlighted the role SIRT1 in metabolic disorders, and SIRT1 has been suggested to be a potent protector against age-associated pathologies [10]. With its nuclear localization, SIRT1 regulates gene expression through its activity on histones and transcription factors [7]. SIRT1 is also able to inhibit NF-κB signalling and thus suppress inflammation [11]. In contrast, being a multifaceted intracellular player, upregulation of SIRT1 has been reported in certain type of cancers, possibly reflecting a compensatory protective process or other not fully understood underlying mechanisms [12].

Several studies have reported that caloric restriction induces SIRT1 activity [13] also in clinical settings [14,15]. Whether bariatric surgery has the same beneficial effects on SIRT1 levels is less known. We have previously reported differentiated effects on circulating SIRT1 after caloric restriction according to sex and BMI [16]. Obesity was previously reported to reduce SIRT1 expression in subcutaneous adipose tissue of obese women [17].

The main aim of the present study was to assess alterations in SIRT1 plasma concentration six and 12 months after bariatric surgery in subjects with obesity. Secondary outcomes included potential differences in SIRT1 levels between the RYGB and SG procedures and any association of SIRT1 with age, sex, C-reactive protein (CRP), BMI, T2DM, and cardiovascular risk assessed by the lipid profile.

2. Methods

2.1. Study population

The present investigation is a sub-study of a prospective cohort study performed at Innlandet Hospital Trust, Gjøvik, Norway, between 2012 and 2014 [18]. Subjects aged 18–60 years eligible for bariatric surgery, due to a BMI >40 kg/m^2 or a BMI >35 kg/m^2 with serious weight related comorbidities, such as T2DM and CVD, were consecutively recruited into the study. Exclusion criteria were previous surgery due to obesity, other major abdominal surgery, major psychiatric disorder and serious somatic pathological conditions not related to obesity, and alcohol or drug addiction.

An initial dietetic counselling was given to all included subjects six months before surgery, including an eight week-course on life-style changes. Bariatric surgery was performed in accordance with current guidelines, either as standard RYGB [19] or SG [20], the allocation to the operative method being done by the surgeons. Both techniques resulted in reduced size of the stomach followed by earlier satiety, and thus restricted food intake and less to absorb from the small intestine.

Clinical data were registered, and blood sampled at baseline and at the follow-up visits at six and 12 months postoperatively. Subjects with comorbidity received standard medication, and the participants' condition was provided on a case report form. The protocol was approved

by Regional Committee for Medical and Health Research Ethics (REK), Region South-East, Norway, ref. Numbers 2012/966 and 2012/1394. The study conformed to the Declaration of Helsinki, and written informed consent was obtained from all subjects upon enrolment.

2.2. Blood sampling and analysis

Fasting whole blood samples were collected between 8:00 and 10:30 a.m. immediately before surgery and at six and 12 months postoperatively. Routine analyses were carried out by conventional methods. Pre-chilled ethylenediaminetetraacetic acid (EDTA) vials were centrifuged at 3000 g, for 10 min at +4 °C, and EDTA plasma was separated and stored at −80 °C until SIRT1 analysis. The Human SIRT1 ELISA kit from LSBio LifeSpan BioSciences (lnc, Seattle, USA) was used for the SIRT1analysis, performed at baseline before the surgery, and six and 12 months after surgery. Samples collected at different timepoints from the same individual were analysed on the same ELISA plate to minimize the effect of assay variability between runs. SIRT1 was successfully measured in all available samples except for one. The inter-assay correlation of variation was 13%.

2.3. Statistics

Descriptive data were reported as mean with standard deviation (SD) and number (%). Comparisons between men and women at inclusion were analysed with t-test, unadjusted changes in the variables from before to after surgery with paired t-test, and correlations with Pearson's correlation test. The difference in SIRT1 levels after surgery was calculated from baseline to: 1) six months and 12 months, respectively, 2) the combined results after six and 12 months and 3) the change from six to 12 months. All multivariable analyses were performed with a linear mixed regression model for repeated measurements. Predictors of SIRT1 levels were adjusted for sex, age, type of surgery, time, and one by one of the other variables followed by stepwise forward regression adding one covariate at the time starting with the one with lowest p-value. The statistical analyses were reported as unstandardized coefficients (B-values), with 95% confidence intervals. P-values <0.05 were considered statistically significant. SPSS version 27 (SPSS Inc., IL, USA) was used for all statistical analyses.

3. Results

Out of 152 subjects included in the preoperative lifestyle intervention, 121 completed this initial conservative intervention period and were eligible for bariatric surgery. Subjects with at least one measurement of SIRT1 during the study period were included ($n = 110$). Of these, the numbers of available samples at baseline, and six and 12 months after surgery were 100, 97, and 88, respectively. Baseline characteristics of the 110 study participants are presented in Table 1, showing a dominance of women (80%), a mean age of 43 years and a mean BMI of 38.8 kg/m². There was an overweight of subjects selected to RYGB ($n = 89$) compared to SG ($n = 21$). Mean values for lipids,

Table 1 Subject characteristics before bariatric surgery.

Characteristics	Result	Male/Female[a]	Reference values
Sex (male/female)	22 (20)/88 (80)		
Age (years)	42.9 (8.2)	43.4 (7.6)/42.8 (8.4)	
BMI (kg/m²) (n = 95)	38.8 (3.8)	39.9 (3.6)/38.5 (3.8)	
Diabetes (n = 104)	18 (17)	5 (25)/13 (16)	
RYGB/GS	89 (81)/21 (19)		
HbA1c in % (n = 100)	5.47 (0.87)	5.46 (0.57)/5.48 (0.93)	4−6
CRP (mg/L)	4.44 (3.92)	3.32 (2.63)/4.72 (4.15)	<5
Triglycerides (mmol/l) (n = 100)	1.33 (0.52)	1.39 (0.62)/1.31 (0.49)	0.5−2.6
Cholesterol (mmol/L) (n = 100)	4.38 (0.87)	4.33 (0.93)/4.40 (0.85)	18−29 years: 2.9−6.2 30−49 years: 3.3−6.9 ≥50 years: 3.9−7.8
HDL (mmol/L) (n = 100)	1.11 (0.30)	0.94 (0.21)/1.15 (0.31) p = 0.001	Women: 1.0−2.7 Men: 0.8−2.1
LDL (mmol/L) (n = 100)	2.80 (0.80)	2.86 (0.91)/2.78 (0.78)	18−29 years: 1.5−4.2 30−49 years: 1.9−4.8 50−79 years: 2.1−4.9)
LDL/HDL ratio (n = 100)	2.74 (1.16)	3.31 (1.38)/2.60 (1.06) p = 0.013	
ApoA1 (g/L) (n = 99)	1.14 (0.19)	1.04 (0.12)/1.16 (0.19) p = 0.001	Women: 1.1−2.3 Men: 1.0−2.0
ApoB (g/L) (n = 99)	0.86 (0.21)	0.88 (0.26)/0.85 (0.20)	0.5−1.3
Lp(a) (nmol/L) (n = 99)	53.6 (63.0)	68.1 (77.0)/50.0 (59.0)	<75
ApoB/ApoA1 ratio (n = 99)	0.77 (0.23)	0.87 (0.29)/0.75 (0.21) p = 0.047	
SIRT1 (ng/ML)	156.5 (82.9)	167.8 (92.3)/153.7 (80.7)	

Values are presented as mean (SD) or number (%). Number is given if less than 110.
BMI: body mass index, RYGB: Roux-en-Y gastric bypass, SG: sleeve gastrectomy, HbA1c: glycated haemoglobin, CRP: C-reactive protein, HDL; high-density lipoprotein, LDL; low-density lipoprotein, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Lp(a): lipoprotein (a).
[a] p-values are given for statistically significant differences between male and female.

fasting glucose, and glycated haemoglobin (HbA1c) were in the normal range (Table 1).

3.1. SIRT1 concentration

SIRT1 concentration in plasma was significantly reduced from baseline to six and 12 months after surgery (Table 2), with mean values (SD) 156.8 (82.6), 119.5 (65.6) and 94.9 (45.6) ng/mL, respectively, (p $\leq$ 0.002, between all time-points), accompanied by reduction in BMI from 38.8 (3.8) to 30.2 (3.7) and 28.3 (3.9) kg/m^2, CRP from 4.44 (3.92) to 1.90 (2.46) and 1.07 (1.33) mg/L, and triglycerides from 1.33 (0.52) to 1.03 (0.38) and 0.93 (0.33) mmol/L, respectively (p < 0.001, in changes from baseline).

The reductions in SIRT1 concentration (presented as delta values) were significant from baseline to six and 12 months after surgery, respectively, and also between SIRT1 at baseline and six and 12 months levels combined (p < 0.001, in all), and between six to 12 months levels (p = 0.002) (Table 2). The changes in SIRT1 levels between investigational time-points did not vary between gender (p > 0.25, all), and type of surgery techniques did not significantly modify SIRT1 levels (p = 0.09). In Fig. 1, the violin plot visualizes median and dispersal of SIRT1 levels before, six and 12 months after surgery, with comparisons between time-points (p $\leq$ 0.002, for all).

Predictors of SIRT1 concentration are presented in Table 3, showing diabetes, CRP, triglycerides, HDL, and the
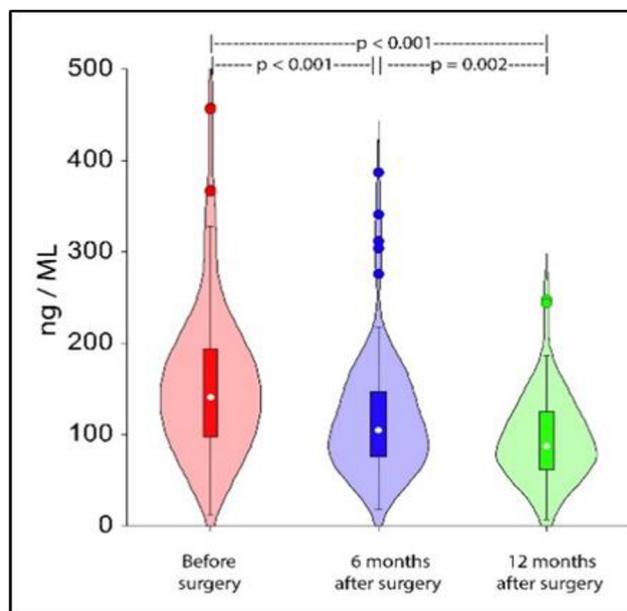
Figure 1 SIRT1 concentration (ng/mL) before surgery, and six and 12 months after surgery. Violin plot describing the median value, the interquartile range and peaks of the data at baseline preoperatively (red colour), 6 months after surgery (blue colour) and 12 months after the surgery (green colour).

LDL/HDL and ApoB/ApoA1 ratios to be predictive, when adjusting for age, sex, type of surgery and time (p $\leq$ 0.05, in all). Of the significantly related covariates, only HDL cholesterol was inversely associated to SIRT1. In stepwise forward regression, CRP and triglycerides remained statistically significant (p $\leq$ 0.001, for both, adjusted). Unadjusted analyses of the correlations (Pearson) between SIRT1 and CRP and triglycerides were r = 0.394, p < 0.001 and r = 0.346, p < 0.001, respectively.

4. Discussion

The main finding in this prospective study of subjects with morbid obesity was that bariatric surgery significantly reduced plasma SIRT1 levels six and 12 months postoperatively. The SIRT1 reduction was independent of type of surgery. BMI was significantly reduced from the morbid obese classification to simple overweight, along with significant reductions in CRP and triglycerides. CRP and triglycerides were independently associated with SIRT1, with stronger impact of CRP in men vs. women.

The beneficial health effects of increased intracellular SIRT1 activity are well known. Whether circulating SIRT1 reflects intracellular activity is not clear [21]. The observed reduction in SIRT1 plasma concentration was somewhat surprising, but the effect of bariatric surgery on SIRT1 has been insufficiently studied. Recently, a study performed only on women with morbid obesity reported an increase in adipose tissue SIRT1 expression after RYGB, with significant correlations between the delta SIRT1 mRNA level and BMI changes [22]. We have previously reported differentiated effect of sex on circulating SIRT1

Table 2 Changes in SIRT1 from before to six and 12 months after bariatric surgery.

Changes	B; 95% CI	p-value
Change from before to combined six and 12 months after surgery		
All participants	- 49.6 (−61.7; - 37.4)	**p < 0.001**
Change difference, RYGB compared with SG	27.2 (- 4.3; 58.6)	p = 0.090
Change difference, men compared with women	- 15.2 (- 45.6; 15.1),	p = 0.323
Change from before to six months after surgery		
All participants	- 39.2 (- 52.9; - 25.8)	**p < 0.001**
Change difference, men compared with women	- 18.5 (- 52.4; 15.5)	p = 0.505
Change from before to 12 months after surgery		
All participants	- 61.2 (−75.2; - 47.2)	**p < 0.001**
Change difference, men compared with women	- 11.8 (−46.9; 23.2)	p = 0.284
Change from six to 12 months after surgery		
All participants	- 21.9 (- 35.8; 9.0)	**p = 0.002**
Change difference, men compared with women	6.6 (- 41.4; 28.2)	p = 0.708

RYGB: Roux-en Y gastric bypass, SG: Sleeve gastrectomy.
Boldface type indicate p-values $\leq$ 0.05.
Mixed model linear regression analyses adjusted for age, gender, type of surgery and time. The results are reported as unstandardized coefficients (B-values) with 95% confidence intervals and p-values.

Table 3 Mixed model linear regression analyses with SIRT1 as the dependent variable.

Independent Variables	Unadjusted regression coefficients (B)				
	One by one [a]			Stepwise forward [b]	
	B; (95% CI)	p-value	Difference Male/female (p-value)	B; (95% CI)	p-value
Sex (men)	2.6 (- 25.8; 31.0)	0.856			
Age (years)	- 0.8 (- 2.2; 0.5)	0.221			
Type of surgery (RYGB)	9.6 (- 19.4; 38.6)	0.513			
BMI (kg/m^2)	- 0.5 (−3.0; 2.1)	0.715	**0.041**		
Male	1.7 (- 1.5; 4.9)	0.296			
Female	- 1.1 (- 3.7; 1.5)	0.406			
Diabetes	33.4 (2.5; 36.0)	**0.034**			
HbA1c	12.4 (- 1.1; 25.8)	0.071			
CRP	6.5 (3.8; 9.1)	**<0.001**	**0.015**	5.5 (2.8; 8.2)	**<0.001**
Male	14.6 (7.5; 21.6)	**<0.001**			
Female	5.7 (2.9; 8.4)	**<0.001**			
Triglycerides	40.6 (21.0; 60.1)	**<0.001**	0.240	32.1 (12.6; 51.6)	**0.001**
Male	33.9 (11.4; 56.4)	**0.003**			
Female	56.3 (23.5; 89.0)	**0.001**			
Cholesterol	5.8 (−4.7; 16.4)	0.278			
HDL	−32.2 (−64.3; −0.07)	**0.05**			
LDL	5.7 (−5.9; 17.3)	0.337			
LDL/HDL ratio	10.9 (0.7; 21.0)	**0.035**			
ApoA1	- 4.7 (- 49.2; 39.9)	0.837			
ApoB	40.1 (- 4.9; 85.0)	0.080			
ApoB/ApoA1 ratio	49.0 (2.3; 95.7)	**0.040**			
Lp(a)	- 0.01 (−0.19; 0.16)	0.853			

RYGB: Roux-en-Y gastric bypass, BMI: body mass index, HbA1c: glycated haemoglobin, CRP: C-reactive protein, HDL; high-density lipoprotein, LDL; low-density lipoprotein, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Lp(a): lipoprotein (a).
[a] In the column "One by one", the variables age, gender, type of surgery (RYGB) and time were included in all analyses, and in addition one by one of the variables from the line BMI to Lp(a).
[b] In the column "Stepwise forward", the variables age, gender, type of surgery and time were included in all analyses, and in addition a stepwise forward inclusion of the statistically significant variables in the column "One by one", starting with the lowest p-value. The statistically significant associations are shown.

after caloric restriction, with reduction in SIRT1 serum levels in women that simultaneously reduced their BMI markedly [16]. BMI was significantly reduced in the present investigation, but its impact on SIRT1 levels was not significant in the total cohort but differed significantly according to sex (Table 3). It might be speculated based on previous observations, that the BMI loss in women, constituting 80% of the investigated subjects, may indirectly have contributed to the observed reduced plasma SIRT1 values via metabolic changes. In accordance with this, it was recently reported that removal of visceral adipose tissue in rodents caused a decrease in serum SIRT1 concentration [23]. Interestingly, SIRT1 plasma levels were reported to be inversely and significantly associated with BMI and fat content in a cross-sectional study of underweight, normal weight and obese subjects [21]. Adipose tissue SIRT1 expression after RYGB has furthermore been reported increased in one small study ($n = 13$, mean age 37 years, 100% women, mean BMI 42.2 kg/m^2) [22], and both protein expression in the supernatant and mRNA levels in peripheral blood cells were observed increased after laparoscopic bariatric surgery in obese subjects with T2DM ($n = 124$, mean age 46 years, 63% women, mean BMI 32 kg/m^2) [24]. Whether circulating SIRT1 inversely reflects its gene-expression and intracellular SIRT1 activity is still questionable, although

previously indicated by our group [25,26]. The contribution of different adipose tissue depots and other organismal sources on circulating SIRT1 in human is not clear. However, a significant inverse correlation was found between serum concentrations and epicardial adipose tissue thickness in subjects with obesity [27].

The low-grade chronic inflammation accompanying obesity is often termed metaflammation, as it is orchestrated by dysmetabolic cell proliferation. Our population, with a massive amount of adipose tissue preoperatively, suffered from metabolic and hormonal dysfunctions, triggering a systemic inflammatory state. Postoperatively, we observed a significant reduction in CRP, predictive of SIRT1 levels, especially in men, with significant differences between sexes (Table 3). CRP has been shown to promote NF-κB activation [28], the main transcriptional regulator of genes related to inflammation. Recent studies have indicated that the regulation of innate immunity and energy metabolism is connected through an antagonistic crosstalk between NF-κB and SIRT1 signalling pathways [11]. SIRT1 inhibits NF-κB signalling by deacetylation of the p65 subunit of the NF-κB complex. SIRT1 can also stimulate oxidative energy production, via the activation of AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor (PPAR)-ɣ and peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, which in

turn inhibits NF-κB signalling and suppresses inflammation [11]. On the other hand, NF-κB signalling and the inflammatory response can downregulate SIRT1 activity through the expression of micro RNA (miR)-34a [29], interferon-γ̍ [30] and reactive oxygen species [11]. Accordongly, it was recently reported that endocrine system dysfunction induced an increase in SIRT1 expression due to decreased SIRT1 activity, in an attempt of decreasing the effect of pro-inflammatory cytokines via anti-oxidative mechanisms [31]. The observed reduction in CRP may have downregulated NF-κB, subsequently restoring SIRT1 activity. In subjects affected by morbid obesity and related endocrine aberrations, an overexpression of SIRT1 as a compensatory or protective mechanism is a plausible explanation of high preoperative SIRT1 levels. As the health of the investigated subjects and their inflammatory status was improved postoperatively, SIRT mRNA expression might adaptively have been "normalized", explaining the following reduction in plasma SIRT1 levels.

Triglycerides, which also were significantly reduced postoperatively, showed a significant impact on SIRT1 plasma levels (Table 3). We have previously shown that triglycerides are strong predictors of SIRT1 mRNA expression in leukocytes [25]. The change in lipid metabolism after surgery might thus have influenced SIRT1 expression, or, vice versa; SIRT1 might have regulated physiological processes including fat metabolism via certain nuclear receptors, such as PPARα and PCG-1α [32]. Provided an initial overexpression of SIRT1 due to anti-inflammatory compensatory mechanisms, the cross−regulatory mechanisms and the subsequent fall in SIRT1 levels may have influenced and reduced triglycerides.

4.1. Limitations

The main limitation in our study is that measurements of body composition before and after surgery was not performed. Such analyses would probably have added more knowledge on potential sources of SIRT1 concentrations. Furthermore, as SIRT1 plasma levels were not measured before the dietetic and lifestyle counselling during the six months before surgery, we cannot exclude an initial rise in SIRT1 levels preoperatively, followed by a decrease during the year after surgery. A complete overview of medication status is lacking in our study. Both insulin and thyroxin have previously been shown to increase SIRT1 gene expression [33], in addition to certain food additives (resveratrol and betacyanins, among others). However, as only one patient in our sample used thyroxin and none used insulin, this has not influenced our results. As the use of blood-pressure medication was not recorded, any potential influence on SIRT1 levels of medicinal use cannot be excluded. MiRNAs, especially miR34a and miR 448 [29,34], seem to play an important role in weight reduction after bariatric surgery, thus, information on such regulation on SIRT1 might have strengthened our results. Likewise, the measurements of SIRT1 gene-expression, although the relationship between SIRT1 gene expression in different tissues and circulating SIRT1 are complex and poorly characterized. Direction of causality cannot be addressed from our study. Nevertheless, we presume that a primary drop in CRP and triglycerides after surgery has contributed to the reduced expression of SIRT1 and its plasma levels. Of note, a drop in plasma SIRT1 levels due to greater intracellular SIRT1 activity demands can be suggested as an additive or alternative mechanism. Finally, the effect of sex on the investigated markers after bariatric surgery needs further exploration.

5. Conclusion

In our population affected by morbid obesity, SIRT1 plasma levels were significantly reduced after bariatric surgery, suggesting a compensatory up-regulation of SIRT1 expression preoperatively due to the state of morbid obesity. The significant positive impact of postoperative reductions in CRP and triglycerides, but not of BMI, on SIRT1 plasma levels, implies that improvement in metaflammation might have stabilized SIRT1 gene expression through adaptive mechanisms. We suggest that loss of adipose tissue and/or potential changes in body composition, as well as reductions in CRP and triglycerides, might have contributed to the reduced SIRT1 concentrations after bariatric surgery.

Declaration of competing interest

The authors have no conflict of interest.

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