

Original Article

Effects of Intentional Weight Loss on Markers of Oxidative Stress, DNA Repair and Telomere Length – a Systematic Review

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Keywords

Oxidative stress · DNA repair · Obesity · Weight loss

Abstract

Background: Altered levels of markers of oxidative stress, DNA repair, and telomere integrity have been detected in obese individuals and may underlie the pathogenesis of obesity-related diseases. However, whether or not such effects are reversed by intentional weight loss has not been systematically reviewed. **Methods:** A literature search in PubMed/Medline identified 2,388 articles of which 21 studies (randomized controlled trial (RCT) (n = 10) and non-randomized intervention studies (n = 11)) were classified as testing the effects of intentional weight loss on i) oxidative stress (n = 15), ii) DNA repair (n = 2), and iii) telomere length (n = 4). **Results:** Across a broad range of intervention designs, diet-, exercise-, surgery-, balloon-induced weight loss regimens decreased oxidative stress measures. Studies investigating DNA repair capacity or telomere length as endpoints after weight loss were less common in number and yielded null or inconsistent results, respectively. **Conclusion:** While this systematic review supports a role for intentional weight loss in reducing obesity-associated oxidative stress, it is not clear whether the effects are primary outcomes or secondary to improvement in obesity-associated insulin resistance and/or chronic inflammation. Although the lack of effect of intentional weight loss on DNA repair capacity might be anticipated given that oxidative stress is reduced, additional studies are needed. The inconsistent effects of weight loss on telomere length or DNA repair suggest the need for a re-assessment of intervention designs and assay methodology to definitively address this topic.

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Published by S. Karger GmbH, Freiburg

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Introduction

Obesity is a major public health problem in the Western world, and the obesity pandemic is expected to persist over the next several decades [1]. 20% of the general population in the US are obese (BMI ≥ 30 kg/m²) [2]. Dyslipidemia, insulin resistance, and chronic inflammation are associated with obesity, and increased risk has been reported for type 2 diabetes, cardiovascular disease, and stroke. In addition, obesity results in an increased risk for multiple cancer types including cancers of the colon and rectum, endometrium, liver as well as esophagus [3, 4]. Obesity is characterized by chronic, low-grade inflammation in adipose tissue; this can directly enhance oxidative stress [5]. Further, obesity has been associated with decreased DNA repair processes that are essential cell responses to DNA damage [6, 7], and shorter telomere length [8, 9].

Dietary caloric restriction (while maintaining adequate nutrition) is the only behavioral intervention able to extend lifespan in model organisms – ranging from yeast to mammals – while concurrently protecting against the decline of biological function and reducing the risk of several age-related diseases [10]. The biological mechanisms underlying the beneficial effects of caloric restriction on health outcomes have been intensively investigated and include alterations in energy metabolism, insulin sensitivity, oxidative stress/DNA repair, inflammation, and neuroendocrine processes [10].

Exercise is an important intervention to support and accelerate the process of weight loss in addition to an effective diet plan. Being physical active stimulates metabolism in a human's organism, including oxidative, inflammatory and neuroendocrinological systems [11]. Intensive physical exercise may adversely influence the balance between oxidative and anti-oxidative factors and, thus, cause increased levels of oxidative stress [11]. Nevertheless, several exercise-only interventions have reported a reduction of biomarkers of oxidative stress [12–15]. Thus, the evidence is not entirely consistent and suggests that there may be differences attributable to varying types of exercise interventions (e.g., duration, intensity, aerobic, anaerobic). Little is known about the differences of oxidative stress-related processes between obese and non-obese individuals.

Bariatric surgery is the most effective treatment for morbid obesity [16]. The treatment reverses obesity-associated diseases such as type 2 diabetes, hypertension, dyslipidemias, and polycystic ovary syndrome [17]. Bariatric surgery has been shown to affect biological mechanisms like inflammation and oxidative stress in adipose tissue [18–20].

Bioenteric intragastric balloon (BOP) is an alternative to the pharmacological treatment of obesity. While the endoscopic procedure is associated with less risks compared to surgery, the treatment is only temporary and the balloon needs to be removed after 6 months [21]. There are not many studies investigating the effect of BOP on biological mechanisms.

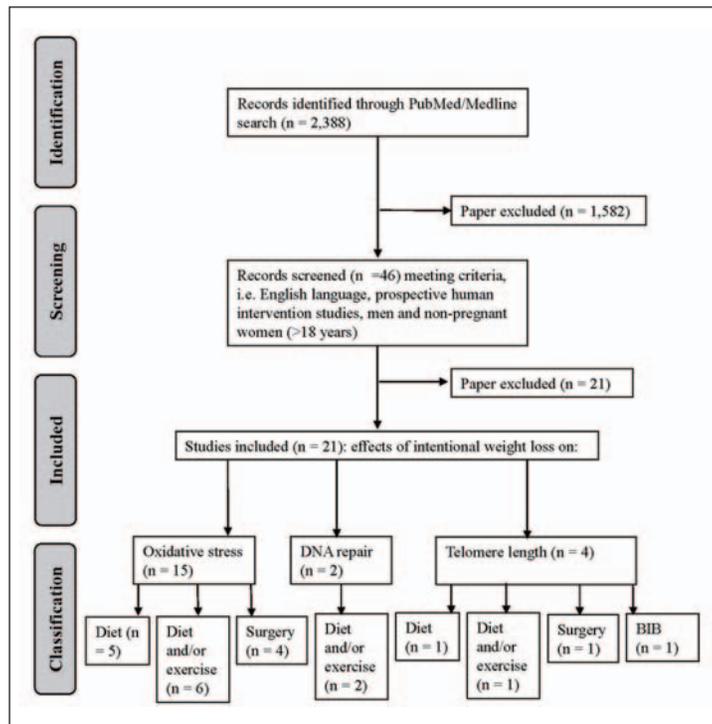
Little attention has been given to whether or not weight loss induced by either of these interventions leads to changes in markers of oxidative stress, repair of DNA damage, and telomere integrity.

Material and Methods

We conducted a systematic literature search covering literature from January 1946 to April 2017. We reviewed the existing literature of the effects of intentional weight loss interventions on markers of oxidative stress, DNA repair, and telomere length. One researcher (CH) searched the database PubMed/Medline, using keywords: (obesity OR weight loss OR weight control OR caloric restriction) AND (oxidative stress OR DNA repair OR telomere).

At identification stage, papers were selected by reading the abstract according to the following inclusion criteria: articles written in English, prospective human weight loss intervention studies, men and non-

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) flow diagram [17].



pregnant women (>18 years). At the screening stage, papers were selected using the following criteria: studies focused on the effect of diet- and/or exercise-, and surgery-induced weight loss on markers of oxidative stress, DNA repair, or telomere length.

21 out of 2,388 papers were included in this review and classified into three groups testing the effects of intentional weight loss on i) oxidative stress (n = 15), ii) DNA repair (n = 2), and iii) telomere length (n = 4). Data were extracted by two authors (CH and CMU) in an MS Excel spreadsheet based on details on study population, BMI, intervention, randomized controlled trial (RCT, yes or no), measurement, and results. Disagreements relating to data extraction were discussed between authors and resolved. The overall process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) flow diagram (fig. 1) [22].

Results and Discussion

Oxidative Stress

An imbalance between the generation of reactive oxygen species and antioxidant defenses in favor of reactive species is referred to as oxidative stress, and this phenomenon can be observed either intracellularly or systemically [23]. Reactive species are byproducts of the normal cellular metabolism of oxygen and can directly influence cell signaling and homeostasis [14]. Moreover, deregulated oxidative stress can induce toxic effects via damage of cellular structures, including proteins, lipids, and nucleic acids [24]. Damage of this type can impair cell function by affecting enzyme activities, e.g. via the inhibition of protein phosphatases and by increasing mutation rates via formation of adducts such as 8-hydroxy-2-deoxyguanosine [25]. Oxidative stress has been associated with aging and multiple age-related diseases, including cancer [26, 27], neurodegeneration [28, 29], cardiovascular disease [30, 31], and diabetes [32]. Commonly assessed markers for oxidative stress are lipid oxidation products such as 8-isoprostane and malondialdehyde, and DNA oxidation products such as

8-hydroxy-2-deoxyguanosine (8-oxo-dG) which can be measured in blood and/or urine [33]. The activity of antioxidant enzymes, e.g., glutathione peroxidase or catalase, can also provide information regarding oxidative stress [34]. While multiple biomarkers have been developed that measure various types of oxidative stress, there are unresolved challenges in devising accurate and reproducible assays that can be applied to human studies [24, 25].

We identified 15 studies investigating the effect of weight loss interventions (diet- and/or exercise-, and surgery-induced) on individuals' oxidative stress level (table 1): 6 RCTs and 9 non-randomized intervention studies (n = 5 diet, n = 6 diet and/or exercise interventions, and n = 3 bariatric surgery interventions) [35–48]. All studies measured oxidative stress markers in blood samples (plasma or serum, e.g., enzyme activities, 8-isoprostane, 8-oxo-dG; for details see table 1) [35–48].

Diet-Induced Weight Loss

A double-crossover, double-blind RCT of intermittent fasting was recently conducted among 24 healthy individuals (BMI 20–30 kg/m²) [39]. Study participants were subject to two 3-week treatment periods, separated into intermittent fasting and intermittent fasting with anti-oxidant supplementation (vitamins C and E) [39]. Although the study participants showed excellent adherence to the study-provided diets, only a marginal increase (2.7%) in SIRT3 expression was observed, with no change in the expression of other genes or biomarkers of oxidative stress [39].

Another study recruited 122 overweight/obese participants (25 ≤ BMI < 34 kg/m², 30–59 years) into a 3-year-long study, testing the effects of a clinical intervention with daily 100-kcal calorie deficits [36]. They distinguished the participants as 'successful mild weight loss group' (SWL), with an average body weight reduction of 5.4% (−4.16 ± 0.31 kg), n = 50, compared to an 'unsuccessful group' (0.05 ± 0.14 kg), n = 49 [36]. The SWL group showed significant decreases in insulin, triglycerides, total and low-density lipoprotein cholesterol, free fatty acids, and leukocyte count (p = 0.030) [36]. Further, SWL participants experienced reduced serum interleukin(IL)-1β, IL-6, and urinary 8-isoprostane (45%, 30%, and 14%, respectively) [36]. Statistically significant group differences were seen for percentage of body fat, waist circumference, leukocyte count (p = 0.018), insulin, IL-6 (p = 0.031), IL-1β (p < 0.001), tumor necrosis factor-α (p < 0.001), and urinary 8-isoprostane (p = 0.036) [36]. A positive association was observed between IL-1β and urinary 8-isoprostane (r = 0.44, p < 0.001) as well as between changes in IL-6 and urinary 8-isoprostane (r = 0.39, p < 0.001) [36].

Buchowski et al. [35] initiated a RCT testing the effects of 25% caloric restriction or control diet on oxidative stress markers in 40 overweight or obese women, with direct observation for 28 days and follow-up for the next 90 days. At study outset, the median 8-isoprostane concentration (57.0 pg/ml, interquartile range (IQR) = 40.5–79.5 pg/ml) in the caloric restriction group was 1.75-fold times that of the concentration observed in normal-weight women (32.5 pg/ml) [35]. During caloric restriction, 8-isoprostane levels were reduced, resulting in statistically significant differences from the control group by day 5 (median 33.5 pg/ml, IQR = 26.0–48.0 pg/ml; p < 0.001) [35]. While the women continued on the caloric restriction diet, concentrations remained low [35]. However, after 3 months on their habitual diet, they returned to baseline levels in about 80% of the women. The authors concluded that oxidative stress levels may be rapidly decreased and maintained through a modest reduction in caloric intake [35].

Meydani et al. [38] conducted a controlled feeding study among 46 moderately overweight volunteers (BMI 25–30 kg/m², age 20–42 years). They were randomized to a 6-month high-glycemic (HG) or low-glycemic (LG) dietary load caloric restriction regimen at either 10% (n = 12) or 30% (n = 34) of basal caloric intake. Independent of the intervention arm, plasma glutathione peroxidase activity increased (p = 0.04) and plasma protein carbonyl

Table 1. Effects of intentional weight loss on oxidative stress

Reference	Study population	BMI, kg/m ²	Intervention	RCT (y/n)	Measurement	Results
<i>Diet-induced weight loss</i> Wegman et al. [39]	n = 24 women or men	20 to 30	2 × 3 weeks treatment periods (preceded by a 1-week pre-conditioning period, and separated by a 2-week washout) intermittent fasting and antioxidant supplementation (vitamins C and E) participants maintain overall energy balance by alternating between days of fasting (25% of normal caloric intake) and feasting (175% of normal) 10 weeks follow-up	y	oxidative stress (8-oxo-G, 8-oxo-DG) and genes related to aging (SOD2, TFAM, SIRT1, SIRT3) in peripheral blood mononuclear cells	marginal increase (2.7%) in SIRT3 expression no change in expression of other genes or oxidative stress markers no adverse weight change
Chae et al [36]	n = 122 women or men	25 to 34	3 years clinical intervention involving daily 100-kcal caloric deficits successful mild weight loss group (SWL): >2 kg unsuccessful mild weight loss group (UWL): <2 kg	n	inflammatory cytokines (IL-1β, IL-6, TNFα, CRP) in EDTA blood, leukocyte count and oxidative stress (LDL in EDTA blood, 8-isoprostane in urine samples)	numbers of circulating leukocytes (p = 0.030) were significantly reduced in the SWL group (-0.60 ± 0.28 × 10 ⁹ /l) serum IL-1β and IL-6 levels and urinary 8-isoprostane excretion decreased by 45% (p < 0.001), 30% (p = 0.037), and 14% (p = 0.049), respectively, following successful weight loss after the 3-year intervention, the SWL group had lower IL-1β (p < 0.001) and TNF-α (p = 0.015) levels compared with the UWL group changes in IL-1β levels also positively correlated with changes in leukocyte count, urinary excretion of 8-isoprostane, and plasma ox-LDL. In addition, changes in serum levels of TNF-α positively correlated with changes in both urinary 8-epi-PGF _{2α} and plasma ox-LDL. Changes in serum IL-6 levels positively correlated with changes in leukocyte count and urinary 8-epi-PGF _{2α}

Table 1 continued on next page

Table 1. Continued

Reference	Study population	BMI, kg/m ²	Intervention	RCT (y/n)	Measurement	Results
Buchowski et al. [35]	n = 40 overweight or obese women	25.4 to 43	28 days 25% caloric restriction control diet 3 months follow-up	y	oxidative stress markers (8-isoprostane) in urine and serum	8-isoprostane levels fell rapidly in the caloric restriction group reaching statistical difference from the control group by day 5 (median 33.5, IQR = 26.0–48.0, p < 0.001) and remained suppressed while continuing on the caloric restriction diet.
Meydani et al. [38]	n = 46 overweight women or men	25 to 30	6 months high glycemic (HG) low glycemic (LG) dietary load caloric restriction at either 10% (n = 12) or 30% (n = 34) of basal caloric intake	y	oxidative stress and antioxidants (enzyme activity: glutathione peroxidase, catalase, 8-epi-PGF _{2α} protein carbonyl, 8-hydroxy-deoxyguanosine) in plasma	after controlling for caloric restriction levels and dietary regimen for 6 months, plasma glutathione peroxidase activity increased (p = 0.04) and plasma protein carbonyl levels decreased (p = 0.02) and a non-significant decrease in plasma 8-epi-prostaglandin F2 alpha level was observed (p = 0.09) no significant change in other markers (e.g., catalase, and superoxide dismutase) caloric restriction decreased the body weight, however, there was no significant difference between the HG and LG diets or between 10% and 30% caloric restriction regimens in changes of body weight over time
Skrha et al. [62]	n = 18 obese women or men with type 2 diabetes and obese women or men non-diabetic	35 ± 1.9 and 37.3 ± 2.1	8 days very low-calorie diet (600 kcal/day)	n	beta-hydroxybutyrate, malondialdehyde levels in plasma, and activity of superoxide dismutase in erythrocytes	significant decrease of plasma malondialdehyde with an increase of superoxide dismutase activity (p < 0.001) in non-diabetic participants one week after the very low calorie diet, an increase of superoxide dismutase activity was found in diabetic patients (p < 0.01) there was a significant correlation between non-esterified fatty acids or beta-hydroxybutyrate and superoxide dismutase activity (p < 0.01)

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Table 1. Continued

Reference	Study population BMI, kg/m ²	Intervention	RCT (y/n)	Measurement	Results
<i>Diet- and/or exercise-induced weight loss</i> Duggan et al. [46]	n = 439 postmenopausal women	>25 12 months dietary weight loss (n = 118) aerobic exercise (n = 117) diet + exercise (n = 117) control (n = 87)	y	oxidative stress (ox-LDL, plasma F ₂ -isoprostane, and FOP) in venous blood sample	F ₂ isoprostane were significantly reduced in diet (p = 0.0002) and diet+exercise (p < 0.0001) arms Diet and diet+exercise participants had significant increases in FOP levels (p = 0.0001)
Abd El-Kader et al. [47]	n = 109 women or men	30-35 12 weeks weight reduction group (diet + exercise) (n = 59) control (n = 50)	y	oxidative stress markers (malondialdehyde, conjugated dienes), and anti-oxidant status (e.g. glutathione peroxidase, superoxide dismutase) in peripheral blood	oxidative stress and anti-oxidant status markers were significantly increased in the weight reduction group after 12 weeks (p < 0.005) control group presented no significant changes (p>0.005)
Gutierrez-Lopez et al. [37]	n = 48 obese women or men (n = 32) normal-weight women or men (n = 16)	30 to 34.9 hypocaloric diet (20% caloric restriction) (HD) hypocaloric diet + regular moderate aerobic exercise (HDMAE)	n	oxidative stress damage (thiobarbituric acid-reacting products (TBARS), carbonyl, dityrosine (DT/URF)) in plasma	the treatment with hypocaloric diet decreased the anthropometric parameters as well as oxidative stress and molecular damage, which was more effectively prevented by the treatment with aerobic exercise subjects in HD treatment showed a decrease in TBARS values (3.42 ± 0.5 μmol/l). The values of this marker decreased to values lower than that in normal-weight subjects (4.82 ± 0.6 μmol/l). Similar effect in the exercise group. weight change in HD group: 87.44 ± 16.30 to 80.83 ± 12.36 kg weight change in HDMAE group: 80.46 ± 8.55 to 77.41 ± 8.6 kg

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Table 1. Continued

Reference	Study population BMI, kg/m ²	Intervention	RCT (y/n)	Measurement	Results
Wycherley et al. [45]	n = 29 34.2 ± 0.9 overweight or obese women or men with type 2 diabetes	12 week moderate energy-restricted diet (~5,000 kJ/day and approximately 30% energy deficit) with aerobic exercise training (n = 13) without aerobic exercise training (n = 16)	y	malondialdehyde in plasma	significant reduction in malondialdehyde, no difference between both groups
Rector et al. [43]	n = 25 26–43 overweight or obese women or men	4- to 7-month (mean 6 months) weight loss program that consisted of energy restriction (reduced by approximately 500 kcal/day) and supervised aerobic exercise (5 days/week, 45 min/day at 60% Vo(2 max); approximately 375 kcal/day)	n	oxidized LDL (oxLDL), myeloperoxidase (MPO), and low- and high-density lipoprotein (LDL and HDL) lipid hydroperoxide concentrations in serum	Exercise- and diet-induced weight loss (approximately 10%) significantly (p < 0.05) increased insulin sensitivity and reduced IR, oxLDL, and LDL lipid hydroperoxides but did not alter HDL lipid hydroperoxides or MPO concentrations. Changes in oxidative stress were not associated with alterations in homeostasis model assessment and quantitative insulin sensitivity check index
Roberts et al. [44]	n = 31 33 ± 1.5 obese men with metabolic syndrome	21-day diet and exercise intervention 12–15% of calories from fat (polyunsaturated-to-saturated fatty acid ratio 2.4:1), 15–20% of calories from protein, and 65–70% of calories from primarily unrefined carbohydrate, high in dietary fiber (>40 g per/day)	n	myeloperoxidase and marker 8-isoprostane in fastin blood, and superoxide in serum via fluorometric detection	After 3 weeks, significant reductions (p < 0.05) in BMI, myeloperoxidase, 8-isoprostane In vitro, fluorometric detection of superoxide and hydrogen peroxide production decreased (p < 0.01). Nine of 15 were no longer positive for metabolic syndrome post-intervention
<i>Surgery-induced weight loss</i>					
Martinez de las Escalera et al. [50]	n = 39 >35 obese and type-2 diabetic women	6 months biliopancreatic diversion (n = 12) laparoscopic greater curvature plication (n = 15) laparoscopic adjustable gastric banding (n = 12)	n	gene expression in white adipose tissue of UCP2, superoxide dismutase 1 and 2	patients undergoing biliopancreatic diversion showed significantly improvement in mitochondrial antioxidant activity (p < 0.01)

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Table 1. Continued

Reference	Study population	BMI, kg/m ²	Intervention	RCT (y/n)	Measurement	Results
Schmatz et al. [48]	n = 60 obese women or men	46.25 ± 7.3	Roux-en-Y bypass surgery patients with diabetes and without diabetes (n = 20 each) clinical treatment patients with diabetes	n	lipid peroxidation, carbonyl protein, nonprotein sulfhydryl (NPSH), superoxide dismutase and catalase activity in serum samples	significant decrease in BMI, body weight, waist circumference, lipid profile, glucose, and glycated hemoglobin concentrations in the bariatric group. lipid peroxidation, carbonyl protein, NPSH, superoxide dismutase and catalase activity were significantly decreased in the bariatric surgery group compared to the control group.
Boesing et al. [40]	n = 40 obese women or men (37.8 ± 11.2 years) and normal-weight women or men	48.1 ± 8.7 and 22.4 ± 2.4	Roux-en-Y-bypass surgery (n = 20) normal weight control (n = 20)	n	reduced glutathione, and catalase, and myeloperoxidase activity in whole blood	BMI decreased at 3 (38.3 ± 1.7, p = 0.018) and 6 months after surgery (34.9 ± 1.7, p < 0.001) reduced glutathione was higher in controls (p < 0.001) catalase was higher in the bariatric group (p < 0.01) myeloperoxidase decreased in bariatric group after 3 (p = 0.028) and 6 months (p < 0.001)
Joao-Cabrera et al. [42]	n = 40 obese women or men and normal-weight women or men	46.7 ± 3.0 and 21.7 ± 3.2	Roux-en-Y-bypass surgery (n = 25) normal weight control group (n = 20)	n	malondialdehyde, superoxide dismutase, catalase, glutathione, glutathione disulfide, and total radical antioxidant parameter levels in plasma	significant reduction (p < 0.01) of plasma levels of malondialdehyde (16.70/9.11 nmol/g prot), superoxide dismutase (10.70/9.24 U/mg Hb), glutathione disulfide (210.80/148.20 mmol/l/g) significant increase (p < 0.01) of plasma levels of glutathione (2.002/2.823 mmol/l/g of Hb) and total radical antioxidant parameter (585.40/815.48 microg Trolox), p < 0.01, and of catalase (12.06/13.22 Deltat/mg Hb/min), p < 0.05
Elizondo et al. [41]	n = 14 obese women or men with fatty liver disease and non-obese women or men	45.4 ± 2.2 and 22.4 ± 0.6	Roux-en-Y-bypass surgery (n = 7) non-obese patients who underwent anti-reflux surgery (control) (n = 7)	n	8-isoprostane levels in serum	3 months after surgery, 8-isoprostane decrease by 76% in bariatric surgery group

RCT = Randomized controlled trial; 8-oxo-G/8-oxo-DG = 8-oxoguanin/8-oxodiguanin; SOD2 = superoxide dismutase 2; TFAM = mitochondrial transcription factor A; SIRT1/2 = sirtuin 1/2; SWL/UWL = successful/unsuccessful mild weight loss group; IL-1β = interleukin 1 beta; IL-6 = interleukin 6; TNF-α = tumor necrosis factor alpha; CRP = C-reactive protein; LDL = low density lipoprotein; (ox) HDL = (oxidized) high density lipoprotein; MPO = myeloperoxidase; DT/URF = carbonyl diytrosine; TBARS = thiobarbituric acid reacting products; FOP = fluorescent oxidation products.

levels declined ($p = 0.02$) [38]. Concomitantly, plasma 8-isoprostane levels decreased non-significantly ($p = 0.09$), and no changes in superoxide dismutase and catalase activity were observed [38].

Diet- and/or Exercise-Induced Weight Loss

The Nutrition and Exercise in Women (NEW) study, recruited 439 postmenopausal women with BMI over 25 kg/m^2 who were randomized into four groups: i) dietary weight loss, ii) aerobic exercise, iii) diet + exercise, or iv) control [46]. The diet intervention was a group-based program aiming for a 10% weight loss [46]. The exercise intervention consisted of 45 min/day, 5 days/week moderate-to-vigorous aerobic activity [46]. Fasting blood samples were obtained at baseline and after 12 months [46]. Markers of oxidative stress were analyzed including oxidized low-density lipoprotein (oxLDL), plasma F2-isoprostane, and fluorescent oxidation products (FOP) [46]. Diet, either with or without exercise intervention, resulted in a significant increase of LDL and F2-isoprostane ($p = 0.0002$, $p < 0.0001$) and a decrease of FOP ($p = 0.0001$) [46] while the exercise group showed no statistically significant effects ($p = 0.01$) [46]. However, the exercise group did not experience as much weight loss (-2.4% ; $p < 0.03$) as the diet (-8.5%) and the diet + exercise group (-10.8%), which may be one explanation for the different results.

Another recent study focused on obese type 2 diabetes patients, given that type 2 diabetes is associated with irregular inflammatory or oxidative stress-related biomarkers [47]. 80 patients were randomized into either weight reduction (low-calorie diet and aerobic exercise training) or control group [47]. After 12 weeks the weight reduction group showed significantly reduced levels of oxidative stress-related markers ($p < 0.005$; e.g., malondialdehyde, glutathione peroxidase, superoxide dismutase, glutathione), while levels of the control group did not change [47].

Gutierrez-Lopez et al. [37] recruited 16 normal-weight and 32 obese subjects (BMI $30\text{--}34.9 \text{ kg/m}^2$) into a non-randomized intervention study testing the effects of a hypocaloric diet and hypocaloric diet plus regular moderate aerobic exercise intervention on oxidative stress. At baseline, obese study participants had greater oxidative stress markers as well as increased molecular damage and polymerization of insulin. The hypocaloric diet intervention resulted in reduced oxidative stress and decreased molecular damage. The oxidative stress levels improved even more with the combined diet and exercise intervention [37].

Wycherley et al. [45] conducted another study that compared a diet intervention with and without aerobic exercise training in overweight and obese subjects with type 2 diabetes. The 12-week intervention led to a significant reduction of malondialdehyde ($p \leq 0.05$) and an increase of urinary nitrite/nitrate ($p < 0.01$) in both groups [45]. The total antioxidant capacity slightly increased with both interventions ($p < 0.08$) [45]. Both interventions induced a comparable weight reduction of 8.5–8.9%. If weight loss enhances effects on oxidative stress, this may explain the lack of a difference.

Surgery-Induced Weight Loss

As the most effective treatment, bariatric surgery is the gold standard for the treatment of severe obesity [16]. Since the first steps in the 1950s, the number of patients undergoing bariatric surgery have followed similar trends as the incidence of obesity [49], and the research on post-surgery outcomes and complications has increased. Even prior to significant weight loss, the surgical treatment reverses metabolic syndrome-related diseases, such as type 2 diabetes, hypertension, dyslipidemias, polycystic ovary syndrome, and non-alcoholic steatosis hepatitis [17]. While insulin levels return back to normal rates within days after bariatric surgery, it takes many months to recover insulin resistance as well as inflammation

and oxidative stress in adipose tissue [18–20]. Five studies have focused on the effect of bariatric surgery on oxidative stress [40–42, 48, 50].

One recent study was conducted in 60 obese women and men [48]. 40 patients (n = 20 diabetic, n = 20 non-diabetic) underwent bariatric surgery, and 20 patients received clinical treatment [48]. Compared to pre-surgery, the bariatric surgery group showed a significant reduction in levels of lipid peroxidation, carbonyl protein, and non-protein sulfhydryl, as well as in superoxide dismutase and catalase activity [48]. Further, they observed a significant decrease of inflammatory biomarkers including IL-6, IL-1, and tumor necrosis factor-alpha [48].

In another study in 20 obese women or men undergoing bariatric surgery were compared with 20 normal-weight controls [40]. Reduced glutathione and activity of catalase and myeloperoxidase were measured in blood samples [40]. At 6 months, the bariatric groups showed higher catalase activity ($p < 0.01$) compared to controls [40]. In addition, myeloperoxidase decreased in the bariatric group after 3 ($p = 0.028$) and 6 months post-surgery ($p < 0.001$) [40].

Following the same study design, Joao-Cabrera et al. [42], measured in addition different markers of oxidative stress in plasma (e.g. malondialdehyde, superoxide dismutase, catalase, and total radical antioxidant parameter). A significant reduction 12 months post-surgery ($p < 0.01$) could be detected in malondialdehyde, superoxide dismutase as well as in glutathione disulfide [42]. In contrast, plasma levels of glutathione and total radical antioxidant parameters showed a significant increase ($p < 0.01$) [42]. In a smaller population of 14 participants, including an intervention (n = 7) and a control (n = 7) group, a decrease of 8-isoprostane by 75% was reported 3 months post-surgery [41].

Only one study investigated the effects of different bariatric surgical procedures on oxidative stress [50]. Using quantitative real-time polymerase chain reaction (PCR), they analyzed the expression of various genes in mitochondria of white adipose tissue samples of 39 obese and diabetic women [50]. Their results showed a significant improvement of antioxidant-related gene expression (e.g., UCP2, SOD1 and SOD2) in patients undergoing the malabsorptive procedure of the biliopancreatic diversion compared to the restrictive procedure (laparoscopic adjustable gastric banding and laparoscopic greater curvature plication) [50].

DNA Repair

Repair mechanisms are essential cell responses to DNA damage, and defects can accelerate aging processes and aggravate chronic diseases [51]. In experimental models, DNA repair deficiency has been linked to central characteristics of the metabolic syndrome: severe obesity, fatty liver disease, dyslipidemia, and insulin resistance [6, 7].

At least four types of DNA repair mechanisms need to be considered: i) base-excision repair, ii) nucleotide-excision repair, iii) mismatch repair, and iv) double-strand-break repair [52]. Dysfunction of DNA repair mechanisms can be assessed by measuring DNA damage using, e.g., PCR or fluorescence in situ hybridization (FISH), and by directly measuring DNA repair capacity, e.g., by single cell gel electrophoresis (COMET) assay [52]. In addition, genomic instability, which may be caused by DNA repair defects, is considered an evolving hallmark of cancer [53]. Our systematic literature search identified only two RCTs focusing on the effect of diet- and/or exercise-induced intentional weight loss on DNA repair capacity (table 2) [54, 55]. No parallel study was identified evaluating the effects of surgery-induced weight loss.

Habermann et al. [54] evaluated the effects of the independent and combined weight loss interventions on DNA repair capacity analyzing data from the NEW study (study design see above). They applied a modified COMET assay using cryopreserved lymphocytes from the

Table 2. Effects of intentional weight loss on DNA repair

Reference	Study population	BMI, kg/m ²	Intervention	RCT (y/n)	Measurement	Results
Habermann et al. [54]	<i>Diet- and/or exercise-induced weight loss</i> n = 439 overweight and obese women	≥25	12 months reduced calorie weight loss diet (n = 118) moderate- to vigorous-intensity aerobic exercise (n = 117) diet + exercise (n = 117) control (n = 117)	y	DNA repair capacity cell exposed to 1.23 Gy of gamma-irradiation	DNA repair capacity did not change significantly after 12 months in interventions compared to controls no significant changes when stratified by changes in body composition or aerobic fitness at baseline, positive correlation of DNA repair capacity with weight, BMI, and fat mass and inversely with lean body mass
Heilbronn et al. [55]	n = 46 overweight, non-obese women or men	25–30	6 months control (weight maintenance diet) (n = 12) calorie restriction (25% calorie restriction of baseline energy requirements) (n = 12) calorie restriction with exercise (12.5% calorie restriction plus 12.5% increase in energy expenditure by structured exercise) (n = 12) very low-calorie diet (890 kcal/d until 15% weight reduction, followed by a weight maintenance diet) (n = 12)	y	dehydroepiandrosterone sulfate and tri-iodothyroine in serum, DNA damage via DNA fragmentation in whole blood cells using comet assay	DNA damage was significantly reduced from baseline to in all intervention groups (p < 0.005) dehydroepiandrosterone sulfate levels were unchanged in all groups

RCT = Randomized controlled trial.

pre- and post-intervention time points that were analyzed within the same batch [54]. DNA repair capacity did not change significantly as a result of any of the diet or exercise interventions compared to control; further, there were no significant changes when results were stratified by changes in body composition or aerobic fitness (VO₂max) [54].

In 2006, an RCT investigated whether a calorie restriction alone or in combination with an increased energy expenditure affects DNA damage [55]. Participants were randomly assigned to one out of four groups including control, calorie restriction (25% diet restriction), calorie restriction and exercise (12.5% diet restriction, 12.5% increase in energy expenditure), and low-calorie diet until 15% weight reduction followed by weight maintenance [55]. DNA damage was measured via COMET assay using whole blood cells [55]. After the 6-month intervention, DNA damage was significantly reduced in all three weight loss intervention groups compared to the control group [55].

Telomere Length

Telomeres are the specific DNA-protein structures that are found at both ends of each chromosome and protect the genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion [56]. The enzyme telomerase, which elongates telomeres and thus ensures telomere integrity, is central for a cell's ability to replicate without limit, a hallmark of carcinogenesis [57]. Telomeres shorten with age or with replicative cycles, and shortening has been associated with inflammatory processes [58]. Increased shortening leads to senescence, apoptosis, or oncogenic transformation of somatic cells, affecting the health and aging of an individual [56]. Changes in telomere length are generally assessed in blood samples by extracting cellular DNA.

A number of investigations have reported that obesity is associated with shorter telomere length in varying cell types [8, 9]. A recent meta-analysis and systematic review comprising 119,439 individuals reported that 39 studies presented weak to moderate correlations between obesity and telomere length [59]. However, they also saw significant methodological, clinical, and statistical heterogeneity between studies, which suggests that this association needs to be better defined and additional causative factors must be taken into account [59]. The effect of intentional weight loss on telomere length has been studied in two RCTs and two non-randomized intervention studies (table 3) [8, 9, 60, 61].

Diet-Induced Weight Loss

Garcia-Calzon et al. [9] reported in 2014 that a 2-month energy-restricted diet (30% of energy from fat, 15% energy from proteins, and 55% energy from carbohydrates) based on their glycemic index resulted in increased telomere length among 12- to 16-year-old obese adolescents, with a greater effect in overweight/obese adolescents who had the shortest telomeres at baseline ($r = 0.96$; $p < 0.001$) [9].

Diet- and/or Exercise-Induced Weight Loss

The NEW study (study design see above), also tested the effects of the diet/exercise interventions on leukocyte telomere length [8]. DNA was extracted from isolated leukocytes, and quantitative PCR) was used to measure telomere length. Baseline telomere length was moderately inversely associated with age ($r = -0.12$; $p < 0.01$) and moderately positively with maximal oxygen uptake, a measure of fitness, ($r = 0.11$; $p = 0.03$), but not with BMI or percent body fat [8]. After the interventions, change in telomere length was inversely associated with telomere length at baseline ($r = -0.47$; $p < 0.0001$) [8]. The independent and combined diet/exercise interventions did not result in any significant group differences in leukocyte telomere length compared to controls. Further, the authors observed no differences in telomere length by the degree of weight loss [8].

Table 3. Effects of intentional weight loss on telomere length

Reference	Study population	BMI, kg/m ²	Intervention	RCT (y/n)	Measurements	Results
<i>Diet-induced weight loss</i>						
Garcia-Calzon et al. [9]	n = 74 overweight or obese girls or boys (12-16y)	≥25	2 months energy-restricted diet (30% of energy (E) from fat, 15% E from proteins, and 55% E from carbohydrates) 6 months follow-up	n	telomere length of genomic DNA extracted from leukocytes from peripheral blood sample, using RT-PCR	telomere length lengthened in participants during the intensive period (+1.9 ± 1.0, p < 0.001) being greater in overweight/obese adolescents with the shortest telomeres at baseline (r = -0.96, p < 0.001)
<i>Diet- and/or exercise-induced weight loss</i>						
Mason et al. [8]	n = 439 obese women	≥25 or ≥23 if Asian-American	12 months dietary weight loss (n = 118) aerobic exercise (n = 117) diet + exercise (n = 117) control (n = 87)	y	leukocyte telomere length extracted from isolated leukocytes from venous blood sample	no significant difference in leukocyte telomere length was detected in any intervention group compared to controls, nor was the magnitude of weight loss associated with telomere length at 12 months mean weight changes were -2.4% (p = 0.03) in the exercise group, -8.5% (p < 0.001) in the diet group, and -10.8% (p < 0.001) in the diet + exercise group, compared to -0.8% among controls
<i>Surgery-induced weight loss</i>						
Formichi et al. [60]	n = 237 obese women or men (19-66y) and non-obese women or men	≥25 or ≥23 if Asian-American	12 months obese individuals with bariatric surgery (n = 93 total, n = 39 sleeve gastrectomies, n = 22 gastric bandings, n = 25 gastric bypasses, n = 5 biliopancreatic diversions, n = 2 gastric plications) obese individuals without surgery (n = 14) non-obese controls (n = 130)	y	leukocyte telomere length extracted from isolated leukocytes from peripheral blood samples	relative telomere length of obese subjects was significantly shorter (p < 0.0001) than non-obese individuals; but no difference between obese individuals with (n = 62) and without (n = 45) metabolic syndrome relative telomere length was significantly shorter at 12 months after surgery compared to baseline measurements (p < 0.0001)
<i>Bioenteric intragastric balloon</i>						
Carulli et al. [59]	n = 37 obese women or men	>30	6 months bioenteric intragastric balloon implantation	n	leukocyte telomere length extracted from isolated leukocytes from peripheral blood	telomere length was significantly increased (p < 0.001) telomere lengthening was positive associated with weight loss (p = 0.007) there was an inverse correlation between telomere length at baseline and after the telomere length lengthening (p = 0.03)

RCT = Randomized controlled trial.

Surgery-Induced Weight Loss

Formichi et al. [60] have conducted the only surgery-induced non-randomized intervention study focusing on the patients' telomere length up to 12 months post-surgery. 237 individuals were recruited (130 non-obese individuals 107 obese individuals). 93 of the 107 obese participants underwent bariatric surgery treatment [60]. Findings support the results of diet-induced interventions, reporting that the telomere length of obese participants was significantly shorter ($p < 0.0001$) [60]. Moreover, the obese group has been divided into individuals with ($n = 62$) and without ($n = 45$) metabolic syndrome, and measurements showed that there was no difference in the telomere length between both groups [60]. 12 months post-surgery, the 93 individuals in the bariatric surgery group had significantly shorter telomere length compared to baseline ($p < 0.0001$) [60].

Bioenteric Intra-gastric Balloon (BOP)

To date, Carulli et al. [59] performed the only study that has investigated the effect of the BOP procedure on telomere length. Blood samples from 37 obese individuals undergoing BOP as weight loss intervention were analyzed [59]. All participants showed a significant increase in telomere length ($p < 0.001$) [59]. Telomere lengthening was positively associated with weight loss ($p = 0.007$), and an inverse association was observed between telomere length at baseline and lengthening ($p = 0.003$) [59].

Conclusions

Oxidative stress, DNA repair, and telomere maintenance are processes that have been linked to aging as well as to multiple chronic diseases. Their association with obesity is strong to moderate [5–9]. In animal studies, caloric restriction has been shown to be effective in reducing oxidative stress and increasing DNA repair capacity. Thus, a key question is whether intentional weight loss among the obese or overweight (either through dietary restriction, dietary restriction and exercise, bariatric surgery or BOP) may have similar effects and positively impact these biologic mechanisms or associated biomarkers.

Intentional weight loss, either through diet, exercise or bariatric surgery, reduced oxidative stress in obese individuals as evidenced by decreased levels of 8-isoprostane and malondialdehyde and increased activity of anti-oxidant enzymes, whereas contrary effects on DNA repair capacity were observed. In some respect, the lack of impact on DNA repair is anticipated since the level of oxidative stress was decreased by intentional weight loss. However, given that assay limitations were reported in one of the two RCTs addressing this question in obese subjects, further investigation is required.

Telomere maintenance is directly linked to aging and immortalization, a hallmark of cancer. Obesity has been quite consistently linked to shorter telomere length. However, the evidence in support of improvement with intentional weight loss through diet, surgery, or BOP was inconsistent and highlights the need for a re-assessment of the intervention designs and assay methodology required to definitively address this topic.

A limited number of studies compared the effects of diet-, exercise-, and combined diet-exercise interventions. Only one study included an exercise-only group in their study design, which seemed to have no effects on levels of oxidative stress, in contrast to prior reports on exercise-only interventions [12–15]. Combined diet- and exercise-induced weight loss interventions may achieve an additional benefit with respect to oxidative stress, DNA repair, and telomere length. Further studies, however, are needed to investigate whether the type of intervention (diet, exercise, or combined) is critical to affect a significant change of levels of oxidative stress, DNA repair, and telomere length and to what extent weight loss is central.

Different bariatric surgery procedures can have differential impact on a human's metabolism, which may affect malabsorption of various important metabolites. One study reported that the improvement in oxidative stress and, thus, the mitochondrial health of white adipose tissue may differ between surgical procedures [50], suggesting that malabsorptive procedures (e.g., biliopancreatic diversion) are associated with better metabolic outcomes than restrictive bariatric surgery (e.g., sleeve gastrectomy). Formichi et al. [60], however, did not observe any differences between surgery procedures regarding effects on telomere length. Because of the recognition that malabsorptive and restrictive procedures have a significantly different impact on metabolism, future studies should explore their different effects on oxidative stress, DNA repair, and telomere length.

Acknowledgments

C. Himbert is sponsored by the Stiftung LebensBlicke and Claussen-Simon-Stiftung, Germany.

C. Himbert and C. Ulrich are funded by the Huntsman Cancer Foundation, and C. Ulrich also by R01CA189184 and U01CA2061.

Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

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