

EXERCISE AND INTERMITTENT FASTING AS PREVENTIVE MEASURES OF EARLY AGING THROUGH SIRT1: A NARRATIVE REVIEW

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ABSTRACT

Obesity accelerates biological aging, which showed in the low level of sirtuin 1 (SIRT1), an NAD⁺-dependent deacetylase that regulate inflammation, mitochondrial function, cellular senescence, and oxidative stress. This narrative review examined how aerobic exercise at different intensities and intermittent fasting (IF), especially time-restricted feeding (TRF), affect SIRT1 as a marker of early aging, and what is known about their combination. Human and animal studies reporting SIRT1 after exercise, fasting, or both were summarized narratively, and exercise intensity was classified with standard heart rate and oxygen-uptake cut-offs. Moderate-intensity aerobic exercise raised circulating or tissue SIRT1 in people and rodents with obesity, and high intensity did not clearly add to this. Fasting results were mixed: short-term TRF and Ramadan fasting raised SIRT1 expression in some human studies, whereas an 8-hour fast in healthy men did not, and Ramadan fasting in adults with overweight tended to lower it. Alternate-day fasting generally preserved SIRT1 in rodent brain. Combined fasting and exercise gave additive fat-mass reductions in randomized trials, but an additive effect on SIRT1 appeared in one rat study and not in a mouse study that tested the interaction. Human trials that combine TRF with aerobic exercise and measure serum SIRT1 alongside direct aging endpoints are needed.

Keywords: Aerobic Exercise; Early Aging; Healthy Lifestyle; Intermittent Fasting; Obesity; SIRT1

1 INTRODUCTION

Obesity is increasingly regarded as an accelerator of biological aging rather than only a metabolic risk factor. Excess adipose tissue sustains chronic low-grade inflammation, termed inflammaging [1, 2], and a higher body mass index is associated with accelerated epigenetic aging in twin pairs discordant for BMI [3]. In people with obesity, phenotypic age has also been linked to mortality risk [4]. Obesity may therefore hasten the aging process [5], which matters most in young adults, in whom it can set the pace of aging for decades.

Among the twelve hallmarks of aging, deregulated nutrient sensing, mitochondrial dysfunction, and chronic inflammation are directly tied to energy balance [6]. Sirtuins are NAD⁺-dependent deacetylases that connect cellular energy status to these processes [7, 8]. SIRT1 is the best characterized member. It regulates fat and glucose metabolism, mitochondrial quality control, fatty-acid oxidation and anti-inflammatory signalling, and disruption of these functions underlies aging [9]. Therefore, SIRT1 is used as an antiaging biomarker [10].

Obesity pushes SIRT1 in the wrong direction. Circulating SIRT1 is lower in people with obesity and rises with weight loss [11]. Hypertrophic adipocytes secrete pro-inflammatory cytokines and recruit M1 macrophages [2]. The resulting oxidative and carbonyl stress modifies SIRT1 after translation and lowers its level [12], while increased PARP-1 activity depletes NAD⁺ and reduces SIRT1 activity [13, 14]. Redox stress also links SIRT1 to cellular senescence [15]. SIRT1 is therefore a reasonable marker of obesity-related early aging and a candidate target for lifestyle prevention.

Two lifestyle strategies are widely studied. Intermittent fasting (IF) triggers adaptive stress responses [16, 17] and has been proposed to slow obesity-related aging through AMPK, SIRT1, PGC-1 α and FOXO signalling [18]. Time-restricted feeding (TRF) confines food intake to a fixed daily window, typically 8–10 hours [19]. Aerobic exercise is the other strategy, and its effect on SIRT1 appears to depend on intensity, tissue and the marker measured [20–22].

The evidence is scattered. Exercise and fasting studies differ in species, tissue, SIRT1 measure (mRNA, tissue protein, activity or serum) and sampling time, and few have tested the combination, particularly in humans. This review therefore (1) summarizes how aerobic exercise at different intensities affects SIRT1, (2) summarizes the effects of IF, particularly TRF, on SIRT1, (3) examines the evidence on their combination, and (4) discusses mechanisms, conflicting findings and research gaps relevant to preventing early aging.

2 MATERIALS AND METHODS

2.1 Study Design and Sources

This is a narrative literature review. It is not a systematic review: no protocol was registered and no formal risk-of-bias scoring was done. Sources were compiled from PubMed, ScienceDirect, Springer/Nature, ProQuest, and Google Scholar. Search terms combined “time-restricted eating”, “time-restricted feeding”, “intermittent fasting”, “aerobic exercise”, “exercise intensity”, “SIRT1”, “sirtuin”, “obesity” and “aging”.

2.2 Eligibility Criteria and Data Extraction

Human or animal studies were included if they measured SIRT1 (serum or circulating level, tissue protein, mRNA or activity) after aerobic exercise, IF/TRF, or both. Systematic reviews and meta-analyses of combined TRE/IF and exercise were included for body-composition and metabolic outcomes, and mechanistic papers for pathway context. Studies reporting only other sirtuins were not included. Ongoing trials and unpublished work were not weighted as evidence. For each study the model, intervention, exercise intensity, marker, tissue and main result were extracted into tables.

2.3 Classification of exercise intensity

Exercise intensity was classified with the cut-offs in Table 1 [23, 24]. Animal studies were mapped to these bands by percentage of maximal oxygen uptake (%VO₂max) when the authors reported it; the authors’ own intensity labels are kept and flagged where they differ from the human bands.

Table 1: Classification of aerobic exercise intensity used in this review

Intensity	% HRmax	% HRR or VO ₂ R	% VO ₂ max	RPE (6–20)
Light	57–63	30–39	37–45	9–11
Moderate	64–76	40–59	46–63	12–13
Vigorous	77–95	60–89	64–90	14–17

HRmax, maximal heart rate; HRR, heart-rate reserve; VO₂R, oxygen-uptake reserve; RPE, rating of perceived exertion.

2.4 Ethics

Ethical approval was not required because no new data from human or animal participants were collected.

2.5 Limitations

This is a narrative review without a registered protocol or risk-of-bias scoring. Several entries were read at abstract level or from open summaries, and some come from regional journals with limited peer-review detail. The evidence is dominated by rodent studies and by single-site human studies in men. SIRT1 assays differ, and serum ELISA values are not comparable across studies.

3 RESULTS AND DISCUSSION

Aerobic exercise raised SIRT1 in most studies at both moderate and high intensity. Fasting studies gave mixed results that depended on fast length, population and tissue. Studies that measured SIRT1 after combining fasting with exercise are few, mostly in rodents, and do not yet show an advantage over TRF alone.

3.1 Aerobic exercise at different intensities

Moderate-intensity aerobic exercise raised SIRT1 in people and rodents with obesity, and no reviewed study showed a larger SIRT1 response at vigorous intensity (Table 2).

Table 2: Studies of aerobic exercise and SIRT1

Study	Model	Exercise protocol	SIRT1 measure	Main finding
Cho et al. [20]	Healthy male volunteers	Exercise at moderate and at high intensity	Circulating SIRT1 (with MDA, SOD, IL-6)	SIRT1 rose at both intensities; MDA, SOD and IL-6 also rose
Al Qorni et al. [25]	Women with obesity, 20–30 years	Moderate-intensity aerobic exercise	Circulating SIRT1	Significant increase
Kazemi and Heidarianpour [26]	Women with metabolic syndrome	8 weeks of moderate-intensity continuous training, 3 times per week	Serum SIRT1	SIRT1 and metabolic indices improved
Hejazi et al. [21]	Obese Wistar rats	8 weeks, 60 min, 5 days per week; authors' "moderate" 70–75% VO ₂ max vs "high" 80–85%	Soleus SIRT1 protein	Both raised SIRT1 vs control (0.82 and 0.86 vs 0.73 ng/mL); groups did not differ
Lang et al. [27]	Type 2 diabetic mice	8 weeks of moderate-intensity treadmill running	Hippocampal SIRT1 signalling	Less neuroinflammation and more BDNF; benefit blunted by the SIRT1 inhibitor nicotinamide
Gurd et al. [22]	Healthy humans	6 weeks of HIIT at about 90% VO ₂ peak	Muscle SIRT1 activity	Activity increased

Moderate-intensity aerobic exercise was enough to raise SIRT1. In women with obesity aged 20–30 years it raised circulating SIRT1 [25]. Eight weeks of moderate-intensity continuous training improved serum SIRT1 and metabolic indices in women with metabolic syndrome [26]. Long-term moderate treadmill exercise raised hippocampal SIRT1 signalling in diabetic mice, and the benefit was lost when SIRT1 was inhibited [27].

Higher intensity has not clearly added to this. In healthy male volunteers SIRT1 rose after both moderate- and high-intensity exercise [20]. In obese rats, moderate and high-intensity treadmill training raised soleus SIRT1 to a similar degree [21]. Intensity does shape other signals: AMPK signalling in human muscle varies with exercise intensity [28], and HIIT at about 90% VO₂peak increased SIRT1 activity in human muscle [22].

Two cautions apply. First, markers of oxidative stress and inflammation (MDA, SOD, IL-6) rose together with SIRT1 in the intensity study [20], so a SIRT1 rise is not a pure index of benefit. Second, rodent intensity labels do not map onto human categories: the rats' "moderate" intensity of 70–75% VO₂max falls in the vigorous band of Table 1.

3.2 Intermittent fasting and time-restricted feeding

Fasting results were mixed and depended on fast length, population and tissue (Table 3).

Table 3: Studies of fasting and SIRT1

Study	Model	Fasting protocol	SIRT1 measure	Main finding
Jamshed et al. [29]	Humans	Short-term early TRF	SIRT1 gene expression	SIRT1 and the autophagy gene LC3A rose ($p < 0.04$)
Haji Molahoseini et al. [30]	43 men	30 days of Ramadan fasting	SIRT1 mRNA, blood mononuclear cells	4.63-fold higher during fasting
Madkour et al. [31]	56 adults with overweight or obesity; 6 normal-weight controls	Ramadan intermittent fasting	SIRT1 gene expression	Fell 10.4% (trend); antioxidant genes rose
Islam et al. [32]	10 healthy men	8-hour fast, with or without 2 h low-intensity arm ergometry	Muscle SIRT1 phosphorylation	No activation; trended lower ($p < 0.06$)
Rubovitch et al. [33]	Mice with mild traumatic brain injury	Alternate-day energy restriction	Cortex and hippocampus SIRT1	Prevented the injury-related fall in SIRT1
Badreh et al. [34]	Wistar rats	Alternate-day fasting	SIRT1 and other longevity proteins	Prevented the age-related fall; earlier start worked better
Zhang et al. [35]	High-fat-diet obese mice	8 weeks of intermittent fasting, aerobic exercise, HIIT or regular diet	Hippocampal AMPK/SIRT1 signalling	Each intervention activated AMPK/SIRT1 and reduced apoptosis
Wilson et al. [36]	Obese male and female mice	12 weeks of intermittent fasting (2 fasting days per 8-day cycle)	Muscle SIRT1 expression	Lower than obese controls in males and/or females; sex- and tissue-specific

In humans, short-term early TRF raised SIRT1 gene expression together with ketones, stress-response genes and the autophagy gene LC3A [29], and 30 days of Ramadan fasting raised SIRT1 mRNA 4.63-fold in blood mononuclear cells of 43 men [30]. Other human data do not agree. In adults with overweight or obesity, SIRT1 expression tended to fall by 10.4% at the end of Ramadan while antioxidant genes rose [31]. In healthy men, an 8-hour fast with or without 2 hours of low-intensity arm exercise did not activate SIRT1 signalling in muscle [32].

Animal studies, mostly with alternate-day fasting (ADF), show preserved or restored SIRT1 in brain. ADF prevented the SIRT1 fall in cortex and hippocampus after mild traumatic brain injury in mice [33] and the age-related fall in rats, with earlier initiation more effective [34]. In obese mice, IF and exercise each activated hippocampal AMPK/SIRT1 signalling [35]. Peripheral tissue can respond differently: after IF, muscle SIRT1 was lower than in obese controls in male and/or female mice, and responses differed by sex and tissue [36].

3.3 Combined fasting and exercise

Few studies have measured SIRT1 after combining fasting with exercise. They are in rodents, and the combination has not clearly outperformed TRF alone (Table 4).

In mice, TRF plus running and TRF alone each raised liver SIRT1 versus controls, with no significant interaction between the two factors. TRF-based groups outperformed ADF, and the combination exceeded exercise alone [37]. In rats fed a high-fat, high-fructose diet, which lowered hepatic SIRT1 and PGC-1 α , 12 weeks of HIIT plus ADF raised both proteins, and SIRT1 was higher than with ADF or HIIT alone [38]. In humans, adding 2 hours of low-intensity arm exercise to an 8-hour fast did not change fasting responses in muscle [32]. In young women with obesity, a two-week program of

combined aerobic exercise and IF was reported to reduce mTOR, a nutrient-sensing kinase involved in aging, and Bcl-2 [39]. A pilot mouse study of 8-hour TRF with or without treadmill training suggested slightly less weight gain and possibly additive benefits for insulin sensitivity and liver metabolism with the combination, though it was not powered to confirm this [19, 40].

Table 4: Studies of combined fasting and exercise

Study	Model	Intervention	Outcome	Main finding
Wang et al. [37]	Mice	ADF or TRF, with or without running	Liver SIRT1	TRF and TRF plus running raised SIRT1 vs control; no significant interaction; TRF groups beat ADF
Hosseinkhah et al. [38]	Rats on a high-fat, high-fructose diet	12 weeks of HIIT and/or ADF	Liver SIRT1 and PGC-1 α	Diet lowered both; HIIT plus ADF raised both, SIRT1 higher than with ADF or HIIT alone
Islam et al. [32]	10 healthy men	8-hour fast plus 2 h low-intensity arm ergometry	Muscle signalling	Exercise did not augment fasting responses
Rejeki et al. [39]	Young women with obesity	Combined aerobic exercise and IF for 2 weeks	mTOR, Bcl-2	Reported as effective for reducing mTOR and Bcl-2
Vieira et al. [40], [19]	High-fat-diet mice	10 weeks of 8-hour TRF with or without treadmill training	Weight gain, insulin sensitivity, liver metabolism (SIRT1 not reported)	Slightly less weight gain and possibly additive benefit; pilot-sized

Randomized trials support additive effects on body composition. A meta-analysis of 19 trials (568 participants) found that TRE plus exercise, compared with exercise on a control diet, reduced body mass (mean difference -1.86 kg), fat mass (-1.52 kg), triglycerides, LDL cholesterol and leptin, but added nothing for fasting glucose, insulin, total cholesterol or HDL [41]. A second meta-analysis of 15 studies (338 participants) found small reductions in fat mass and body-fat percentage with fat-free mass preserved, regardless of exercise type [42]. In a 12-week trial of 104 women aged 40–60 years, flexible TRE with aerobic exercise reduced fat mass by 10.2%, against 4.6% for TRE and 3.5% for exercise alone [43]. A smaller trial of 5:2 fasting plus HIIT in 36 women with obesity found a significant fall in body weight only in the combined group, but between-group differences were not significant and dropout was 25–50% [44].

3.4 Mechanisms

Exercise and fasting converge on AMPK and NAD $^{+}$. AMPK and SIRT1 depend on each other for metabolic adaptation to fasting and exercise in skeletal muscle [45]. During exercise, ATP turnover raises AMPK, which activates NAMPT and raises NAD $^{+}$, increasing SIRT1 activity [20]. Aerobic exercise may also counter the obesity-related fall in SIRT1 by raising antioxidant defense through SOD [20]. During fasting, lower insulin/Akt signalling lets FOXO1 enter the nucleus and activate the SIRT1 promoter. Rising glucagon and cAMP engage the CREB/CRTC2 complex at the same promoter, which can overcome the repression of SIRT1 transcription by ChREBP in obesity [46].

3.5 Differ in Findings

Five factors explain most of the disagreement. First, marker and compartment: serum protein, muscle mRNA, phosphorylation and enzyme activity are different readouts of SIRT1 and need not move together [20, 22, 32]. Second, timing: acute bouts and chronic training produce different signals, and sampling times vary between studies. Third, fast length, population and body status: an 8-hour fast in healthy men showed no activation [32], Ramadan raised SIRT1 mRNA in men [30] but tended to lower it in adults with overweight or obesity [31]. Fourth, model: rodent work uses mostly ADF and diet-induced obesity, tissue and sex matter [36], and background diet shapes exercise-induced sirtuin responses [47]. Fifth, weight loss itself raises circulating SIRT1 [11], so a rise after a combined program may partly reflect fat loss rather than direct pathway activation.

For SIRT1 specifically, whether the combination beats either strategy alone is not yet clear. The only study that tested an interaction found none between TRF and running [37], one rat study found a larger SIRT1 rise with HIIT plus ADF

[38], and human data on fasting plus exercise are lacking. Body-composition trials show additive fat loss [41–43] but not additive glucose effects [41]. Overall, the combination is biologically plausible and clinically useful for body composition, whereas additive effects on SIRT1 remain unproven.

3.6 Relevance to early aging

SIRT1 is a mechanistic surrogate. None of the reviewed studies measured aging endpoints such as epigenetic clocks, senescence markers or telomere length, so claims that exercise or fasting prevent early aging remain inferential.

3.7 Directions for future research

Four designs would settle the question: (1) human randomized trials with TRF-only, exercise-only, combined and control arms that measure serum and tissue SIRT1; (2) chronic moderate-versus-vigorous comparisons, with oxidative-stress and inflammatory markers alongside; (3) analyses that adjust for weight loss and energy intake and use standard sampling times, for example 24–48 hours after the last session; and (4) functional aging outcomes in the same trials, and tests of early versus late eating windows and fed versus fasted exercise.

4 CONCLUSIONS

Moderate-intensity aerobic exercise reliably raises SIRT1 in people with obesity, and vigorous intensity has not been shown to add to this. Evidence for intermittent fasting and TRF is mixed and depends on fast length, tissue and population. Combined fasting and exercise gives additive fat-mass benefits in clinical trials, but an added effect on SIRT1 is plausible rather than proven, and human data are almost absent. For young women with obesity, moderate-intensity aerobic exercise combined with TRF is a reasonable strategy to test for preventing early aging, provided future trials measure SIRT1 alongside direct aging endpoints.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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