Special Article

NUTRITION REVIEWS

Time-restricted feeding and risk of metabolic disease: a review of human and animal studies

Jeff Rothschild, Kristin K Hoddy, Pera Jambazian, and Krista A Varady

Time-restricted feeding (TRF), a key component of intermittent fasting regimens, has gained considerable attention in recent years. TRF allows ad libitum energy intake within controlled time frames, generally a 3–12 hour range each day. The impact of various TRF regimens on indicators of metabolic disease risk has yet to be investigated. Accordingly, the objective of this review was to summarize the current literature on the effects of TRF on body weight and markers of metabolic disease risk (i.e., lipid, glucoregulatory, and inflammatory factors) in animals and humans. Results from animal studies show TRF to be associated with reductions in body weight, total cholesterol, and concentrations of triglycerides, glucose, insulin, interleukin 6, and tumor necrosis factor-α as well as with improvements in insulin sensitivity. Human data support the findings of animal studies and demonstrate decreased body weight (though not consistently), lower concentrations of triglycerides, glucose, and low-density lipoprotein cholesterol, and increased concentrations of high-density lipoprotein cholesterol. These preliminary findings show promise for the use of TRF in modulating a variety of metabolic disease risk factors.

INTRODUCTION

It is estimated that 67% of the US population is now overweight or obese.[1] Carrying extra body weight is associated with several abnormalities, which are collectively referred to as the metabolic syndrome.[2] Insulin resistance appears to be the pathogenic factor central to this disorder.[2] Other features include elevated blood pressure, dyslipidemia, and an accumulation of adipose tissue in visceral depots.[2] Approximately 34% of US adults meet the criteria for the metabolic syndrome, and the risk of developing this metabolic disorder increases dramatically when the body mass index (BMI) exceeds 25 kg/m^2.[3]

Weight loss, by means of reducing daily energy intake, helps to improve each of these metabolic disease risk factors.[4] One diet that has gained considerable popularity in recent years is intermittent fasting (IF). IF involves a complete or partial restriction in energy intake (i.e., 50–100% restriction) on 1–3 days per week.[5] Recent reports indicate that IF produces substantial weight loss (5–10% of baseline body weight) in short durations (8–12 weeks).[5] Decreases in low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure, and visceral fat mass, along with increases in insulin sensitivity, have also been demonstrated.[6,7] Although IF is an effective means of lowering the risk of metabolic disease, approximately 20% of individuals cannot adhere to this form of dietary restriction.[6] As such, an alternative form of IF, termed "time-restricted feeding" (TRF), may be used to increase compliance. TRF allows individuals to consume ad libitum (AL) energy intake within a set window of time (3–4 h, 7–9 h, or 10–12 h), which induces a fasting window of 12–21 hours per day.

Affiliations: *J Rothschild* and *P Jambazian* are with the School of Kinesiology and Nutritional Science, California State University, Los Angeles, California, USA. *KK Hoddy* and *KA Varady* are with the Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, Illinois, USA.

Correspondence: *KA Varady*, Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 West Taylor Street, Room 506F, Chicago, IL 60612, USA. E-mail: varady@uic.edu. Phone: +1-312-996-7897. Fax: +1-312-413-0319.

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The purpose of this review was to summarize the relatively small but highly suggestive literature on TRF regimens. Although the effects of IF on metabolic disease prevention have been discussed in recent reviews,[8,9] the ability of TRF to alter these risk parameters has not yet been investigated. Accordingly, the objective of this review was to summarize the current literature on the effects of TRF on body weight and other markers of metabolic disease risk (i.e., lipid, glucoregulatory, and inflammatory factors) in animals and humans.

METHODS

A Medline search in PubMed was performed using the following keywords: "time-restricted feeding," "intermittent fasting," "feeding window," "food timing," "compressed feeding," "restricted food intake," and "Ramadan."

Inclusion criteria for animal studies were as follows: 1) randomized control trials, 2) total sample size ≥12 animals, 3) TRF windows of 3–12 hours, 4) primary endpoint of body weight, 5) minimum trial duration of 4 weeks, 6) male or female, and 7) mice or rats. The following exclusion criteria were applied: 1) nonrandomized trials with no control group, 2) total sample size <12 animals, 3) TRF window >12 hours, 4) body weight not the primary endpoint, 5) trial duration less than 4 weeks, and 6) animals other than mice or rats. Twelve animal studies[10–21] were retrieved that matched these criteria.

Inclusion criteria for human studies were as follows: 1) randomized control trials and nonrandomized trials, 2) total sample size ≥8 subjects, 3) TRF windows of 3–12 hours, 4) primary endpoints of body weight and two or more relevant metabolic disease risk parameters, 5) minimum trial duration of 2 weeks, 6) male or female subjects, 7) age between 16 and 80 years, 8) BMI between 18.5 and 40 kg/m^2, 9) nonsmokers, and 10) sedentary or moderately active individuals. The following exclusion criteria were applied: 1) cohort and observational studies, 2) total sample size <8 subjects, 3) TRF window >12 hours, 4) body weight not the primary endpoint, 5) less than two relevant metabolic disease risk parameters reported, 6) trial duration of <2 weeks, 7) BMI >40 kg/m^2, 8) diabetic subjects, and 9) very active individuals or athletes. These inclusion and exclusion criteria and levels of evidence were used for both Ramadan and non-Ramadan trials. Eleven human trials[22–32] were found that matched these criteria.

Levels of evidence for animal and human studies were as follows: level 1, systematic review of randomized trials; level 2, randomized trial; level 3, nonrandomized controlled cohort/follow-up study; level 4, case series, case-control, or historically controlled study; and level 5, mechanism-based reasoning.[33]

ANIMAL STUDIES

Body weight

Twelve studies[10–21] have implemented animal models to examine the effects of TRF on body weight (Table 1). Two studies used a 3–4 hour TRF,[10,11] four studies used an 8–9 hour TRF,[12–15] and six studies restricted feeding to one phase of 12 hours in the light phase or the dark phase.[16–21]

3–4 hour TRF window. Animal studies using a 3–4 hour TRF demonstrate decreases in body weight of 9–18%.[10,11] In an 18-week study by Sherman et al.,[11] mice were randomized into one of four groups: 1) 4-hour TRF with a high-fat diet, 2) 4-hour TRF with a low-fat diet, 3) AL feeding with a high-fat diet, or 4) AL feeding with a low-fat diet. Body weights of animals on low-fat (10% kcals from fat) and high-fat (60% kcals from fat) TRF diets were 17% and 18% lower than those of the respective AL-fed control animals.[11] Additionally, epididymal fat mass (visceral fat) was 41% and 48% lower in animals on low-fat and high-fat TRF diets, respectively, versus controls.[11] In another study by Sherman et al.,[10] mice were randomized to either a 3-hour TRF group or an AL control group and were fed a normal chow diet. After 16 weeks, mice in the 3-hour TRF group had 9% lower body weight than the AL controls, despite consuming 95% of the calories of the AL group.[10]

8–9 hour TRF window. Significant decreases in body weight of 12–28% have also been reported for 8–9 hour TRF protocols.[13,14] In a study by Hatori et al.,[13] mice were randomized into one of four groups: 1) 8-hour TRF with a high-fat diet, 2) 8-hour TRF with a normal chow diet, 3) AL feeding with a high-fat diet, or 4) AL feeding with a normal chow diet. After 16 weeks of treatment, mice on 8-hour TRF with a high-fat diet (60% kcals from fat) consumed calories equivalent to those consumed by AL-fed mice on a high-fat diet but weighed 28% less.[13] Mice on the TRF normal-chow diet weighed less than AL-fed mice on a normal-chow diet, though the difference did not reach statistical significance.[13] Contrary to these findings, Fonken et al.[12] demonstrated that male mice fed during an 8-hour TRF window in either the light phase or dark phase had no change in body weight versus controls. Two studies by Belkacemi et al.[14,15] implemented 9-hour TRF windows in rats. The first study[14] compared a 9-hour TRF window with AL feeding in diabetic versus nondiabetic sand rats. After 4 weeks, nondiabetic TRF rats had 12% lower body weight and diabetic TRF rats had 15% lower body weight relative to their respective controls.[14] The second study[15] found no significant differences in body weight between TRF groups and their

Table 1 **Animal studies: effect of time-restricted feeding on body weight and cardiometabolic risk factors.**

Reference	Animal model	Trial length	Intervention groups	Weight (% change)	Change in lipid factors	Change in glucoregulatory factors	Change in inflammatory factors
3–4 h feeding window							
Sherman et al. (2011)[10]	Mice *n* = 96, M 11 wk old	16 wk	1. 3-h TRF + NC 2. AL control + NC	1. ↓ 9%[a]	–	–	1. ↓ IL-6, ↓ TNF-α, ↓ CRP[a]
Sherman et al. (2012)[11]	Mice *n* = 96, M 6 wk old	18 wk	1. 4-h TRF + HF 2. 4-h TRF + LF 2. AL control + HF 2. AL control + LF	1. ↓ 18%[a] 2. ↓ 17%[a]	1. ↓ TC, ↓ HDL-C, Ø TG[a] 2. ↓ TC, ↓ HDL-C, ↓ TG[a]	1. Ø Glucose, ↓ insulin[a], ↓ insulin resistance[a] 2. Ø Glucose, ↓ insulin[a], ↓ insulin resistance[a]	1. Ø IL-6, ↓ TNF-α[a] 2. Ø IL-6, ↓ TNF-α[a]
8–9 h feeding window							
Fonken et al. (2010)[12]	Mice *n* = 50, M 8 wk old	8 wk	1. 8-h TRF dark-phase + NC 2. 8-h TRF light-phase + NC 3. AL control dark-phase + NC 4. AL control light-phase + NC	1. Ø 2. Ø	–	–	–
Hatori et al. (2012)[13]	Mice *n* = 128, M 12 wk old	16 wk	1. 8-h TRF + NC 2. 8-h TRF + HF 3. AL control + NC 4. AL control + HF	1. Ø 2. ↓28%[a]	1. Ø TC 2. ↓ TC[a]	1. ↑ Insulin sensitivity[a] 2. ↑ Insulin sensitivity[a]	1. ↓ IL-6, ↓ TNF-α[a] 2. ↓ IL-6, ↓ TNF-α[a]
Belkacemi et al. (2010)[14]	Rats *n* = 52, M Age not reported	4 wk	1. 9-h TRF, nondiabetic 2. 9-h TRF, diabetic 3. AL control, nondiabetic 4. AL control, diabetic	1. ↓12%[a] 2. ↓15%[a]	–	1. ↑ Insulin sensitivity[a] 2. ↑ Insulin sensitivity[a]	–
Belkacemi et al. (2012)[15]	Rats *n* = 15, F 8–10 wk old	4 wk	1. 9-h TRF, nondiabetic 2. 9-h TRF, diabetic 3. AL control, nondiabetic 4. AL control, diabetic	1. Ø 2. Ø	–	1. ↓ Glucose, ↓ insulin[a], ↓ insulin resistance[a] 2. ↓ Glucose, ↓ insulin[a], ↓ insulin resistance[a]	–
12 h feeding window							
Farooq et al. (2006)[16]	Rats *n* = 24, M Young adult rats	4 wk	1. 12-h TRF dark-phase + NC 2. 12-h TRF light-phase + NC 3. AL control dark-phase + NC 4. AL control light-phase + NC	1. Ø 2. Ø	1. ↓ TC[a] 2. ↓ TC[a]	1. ↓ Glucose[b] 2. Ø Glucose[a]	–
Salim et al. (2007)[17]	Rats *n* = 24, M Age not reported	4 wk	1. 12-h TRF dark-phase + NC 2. 12-h TRF light-phase + NC 3. AL control dark-phase + NC 4. AL control light-phase + NC	1. Ø 2. Ø	–	–	–
Salgado-Delgado et al. (2010)[18]	Rats *n* = 165, M 5–6 wk old	5 wk	1. 12-h TRF dark-phase + NC 2. 12-h TRF light-phase + NC 3. AL control dark-phase + NC 4. AL control light-phase + NC	1. Ø 2. ↑13%[a]	–	–	–
Arble et al. (2009)[19]	Mice *n* = 12, M 9 wk old	7 wk	1. 12-h TRF dark-phase + HF 2. 12-h TRF light-phase + HF 3. AL control dark-phase + HF 4. AL control light-phase + HF	1. ↓19%[b] 2. Ø	–	–	–
Bray et al. (2010)[20]	Mice *n* = 24, M Age not reported	12 wk	1. 12-h TRF dark-phase + HF 2. 12-h TRF dark-phase + LF 3. AL control dark-phase + HF 4. AL control dark-phase + LF	1. Ø 2. Ø	–	–	–
Tsai et al. (2013)[21]	Mice *n* = 24, M 12 wk old	16 wk	1. 12-h TRF dark-phase + HF 2. 12-h TRF dark-phase + LF 3. AL control dark-phase + HF 4. AL control dark-phase + LF	1. ↓18%[a] 2. Ø	1. Ø TC, ↓ TG[a] 2. ↓ TC, Ø TG[a]	1. ↓ Glucose, ↓ insulin[a] 2. ↓ Glucose, ↓ insulin[a]	–

Abbreviations and symbols: AL, ad libitum feeding (no time-restricted feeding); CRP, C-reactive protein; F, female; HDL-C, high-density lipoprotein cholesterol; HF, high-fat diet; IL-6, interleukin-6; LF, low-fat diet; M, male; NC, normal chow diet; TC, total cholesterol; TG, triglycerides; TNF-α, tumor-necrosis factor-alpha; TRF, time-restricted feeding; Ø, nonsignificant change; ↑, increased; ↓, decreased.

[a] Significantly different from the diet-matched control group ($P < 0.05$).

[b] Significantly different from the other TRF intervention group ($P < 0.05$).

respective AL control groups. The lack of effect in the second Belkacemi et al. study[15] is most likely due to very small sample size (n=15), which would limit the power to detect significant differences between groups.

12 hour TRF window. Studies implementing 12-hour TRF windows in animals demonstrate conflicting findings for body weight.[16–21] In two short-term studies (4 weeks),[16,17] mice fed during a 12-hour TRF window in either the light phase or dark phase demonstrated no change in body weight versus controls. Contrary to these findings, Salgado-Delgado et al.[18] reported increases in body weight (13%) when mice were fed during the light phase versus the dark phase. Increases in retroperitoneal and peritoneal fat mass were also reported in these TRF light-phase-fed mice.[18] Rats and mice are naturally nocturnal feeders that consume the vast majority of their energy intake during the dark phase. This initial study by Salgado-Delgado et al.[18] was one of the first to show that feeding during the light phase can lead to weight gain. In a study by Arble et al.,[19] the effects of a high-fat diet (60% kcals from fat) during either the light phase or the dark phase were tested. Results reveal that mice consuming a high-fat diet during the 12-hour dark phase weighed 19% less than mice fed a high-fat diet during the light phase.[19] Although not significant, there was a trend toward increased energy intake and decreased activity in the light-phase group compared with the dark-phase group, which may have contributed to the differences in body weight.[19] Two other studies by Bray et al.[20] and Tsai et al.[21] compared feeding a low-fat diet (10% kcals from fat) versus a high-fat diet (45% kcals from fat) during the 12-hour dark phase only. Bray et al.[20] demonstrated no effect on body weight or visceral fat mass after 12 weeks of treatment. In contrast, Tsai et al.[21] reported a decrease in body weight (18%) in the TRF high-fat diet group, but no change in the TRF low-fat diet group. The reason for these conflicting findings is not clear, but the longer study duration of Tsai et al.[21] (16 weeks) versus Bray et al.[20] (12 weeks) may have allowed the decreases in body weight by the high-fat group to become more pronounced and reach statistical significance.

Lipid factors

Dyslipidemia is characterized by high circulating levels of LDL cholesterol and triglycerides accompanied by low levels of high-density lipoprotein (HDL) cholesterol. Prospective cohort studies suggest that lipid abnormalities are associated with an increased risk of cardiovascular events.[34,35] Weight loss has been shown to lower LDL cholesterol and triglyceride concentrations in both humans and animals.[36] The effects of TRF on plasma lipids have been evaluated in four animal studies to date (Table 1): one study using a 3-hour TRF,[11] one study using an 8-hour TRF,[13] and two studies using a 12-hour TRF.[16,21] Thus, findings in animals are very limited.

3–4 hour TRF window. In the study by Sherman et al.,[11] mice were fed either a high-fat (60% kcals from fat) or a low-fat (10% kcals from fat) diet during a 4-hour TRF window. After 18 weeks of treatment, total cholesterol concentrations were approximately 20% lower in both TRF groups versus their respective AL-fed controls.[11] HDL cholesterol concentrations were also reduced by approximately 30% in both TRF groups versus controls.[11] Triglyceride levels were decreased by 20% only in the TRF low-fat diet group versus controls.[11] It is unclear why triglycerides were not also lowered in the high-fat group, as both groups lost similar amounts of weight.

8–9 hour TRF window. The effect of 8-hour TRF on plasma lipids was investigated by Hatori et al.[13] In this study,[13] mice consumed either a high-fat diet or a normal-chow diet during an 8-hour TRF window. After 16 weeks, total cholesterol concentrations decreased by 49% in the high-fat TRF diet group versus controls.[13] No changes in total cholesterol were noted for mice fed the TRF normal-chow diet, however.[13] The decrease in total cholesterol in the TRF high-fat group is most likely due to the reduction in body weight (28%) observed. Since no changed in body weight was observed in the TRF normal-chow group versus AL-fed controls, this could explain why total cholesterol levels remained unchanged.

12-hour TRF window. In the study by Farooq et al.,[16] the effect of 12-hour TRF in the light phase was compared with 12-hour TRF in the dark phase. After 4 weeks of diet, total cholesterol levels decreased in both the TRF light phase group (by 29%) and the TRF dark phase group (by 36%).[16] Surprisingly, these substantial reductions in total cholesterol occurred in the absence of weight loss in both groups.[16] Tsai et al.[21] also examined the effect of 12-hour TRF on plasma lipids. In this study,[21] mice were fed a high-fat or low-fat diet only in the dark phase. Circulating triglycerides were decreased only in the TRF high-fat group, while total cholesterol concentrations were reduced only in the TRF low-fat group.[21]

Glucoregulatory factors

Insulin resistance plays a major pathophysiological role in type 2 diabetes and is strongly associated with obesity, coronary heart disease, and dyslipidemia.[37] Reductions in body weight have been shown to decrease insulin resistance and increase glucose uptake, thereby lowering circulating glucose levels.[38] The effect of TRF interventions

on glucoregulatory factors has been reported in six recent animal studies (Table 1).[11,13–16,21]

3–4 hour TRF window. The impact of a 4-hour TRF on glucose, insulin, and insulin resistance was tested by Sherman et al.[11] After 18 weeks of a high-fat or low-fat 4-hour TRF diet, glucose levels remained unchanged in both diet groups.[11] Insulin, on the other hand, decreased substantially (60%) in both TRF groups.[11] Insulin resistance, measured by the homeostatic model assessment of insulin resistance (HOMA-IR), also declined by a similar extent in both groups (70%).[11] These beneficial modulations in glucoregulatory factors may be similar in both groups, as both lost similar amounts of weight.

8–9 hour TRF window. In the study by Belkacemi et al.,[14] nondiabetic and diabetic rats were fed a normal-chow diet in a 9-hour TRF feeding window. After 4 weeks of diet, insulin sensitivity was improved in both nondiabetic and diabetic TRF animals versus AL-fed controls.[14] In another study by Belkacemi et al.,[15] which implemented a similar study design, fasting glucose and insulin decreased in both nondiabetic rats and diabetic rats after 4 weeks of 9-hour TRF. Decreases in insulin resistance, measured by HOMA-IR, were also reported in both TRF groups versus controls.[15] The effects of 8-hour TRF on glucoregulatory parameters have also been evaluated by Hatori et al.[13] Mice consumed either a high-fat or a normal-chow diet during 8-hour TRF daily. Insulin sensitivity was shown to increase in both TRF groups versus the AL-fed controls.[13] Accumulating evidence suggests that high-fat diets may negatively affect insulin sensitivity.[39,40] In view of this, implementing TRF for individuals who consume a high-fat diet may protect against these negative effects.

12-hour TRF window. Two studies conducted by Farooq et al.[16] and Tsai et al.[21] have investigated the effect of 12-hour TRF on glucoregulatory factors in rodents. In the first study, by Farooq et al.,[16] rats were fed a normal-chow diet during either a 12-hour TRF dark phase or a 12-hour TRF light phase. Fasting glucose concentrations were shown to be lower in rats fed during the dark phase compared with rats fed during the light phase.[16] These findings are not surprising, as rodents generally exhibit impaired insulin sensitivity and increased fasting glucose during their inactive (daytime) phase, and increased insulin sensitivity and lower glucose levels during their active (night-time) phase.[41] In the second study, by Tsai et al.,[21] mice were fed either a high-fat diet or a low-fat diet during a 12-hour TRF in the dark phase. After 16 weeks of treatment, glucose and insulin levels decreased similarly in both TRF groups.[21] Thus, 12-hour TRF may help lower glucose and insulin, independent of the background composition of the diet.

Inflammatory factors

Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are markers of inflammation that may play a role in the progression of atherosclerosis and type 2 diabetes.[42,43] Recent evidence also suggests that circulating levels of these factors are reduced with weight loss.[44] Three animal studies have examined the impact of TRF on these inflammatory markers (Table 1).[10,11,13]

3–4 hour TRF window. In the study by Sherman et al.,[10] mice consumed all of their energy needs within a 3-hour TRF window. By the end of the 16-week study, circulating levels of IL-6, TNF-α, and CRP had decreased in these mice versus controls.[10] Reductions in mRNA levels of IL-6 and TNF-α in white adipose tissue were also observed and were correlated with threefold decreases in plasma protein levels.[10] No changes in CRP mRNA levels were observed.[10] A subsequent study by Sherman et al.[11] implemented a 4-hour TRF with a either a high-fat diet or low-fat diet. After 18 weeks, IL-6 remained unchanged, but TNF-α was reduced in both groups versus controls.[11] Thus, it is possible that improvements in inflammatory markers may occur with either a high-fat diet or a low-fat diet during TRF.

8–9 hour TRF window. Inflammatory markers were also measured in the study by Hatori et al.,[13] who implemented 8-hour TRF with either a high-fat diet or a normal-chow diet. Similar to findings of the 3–4 hour TRF studies,[10,11] IL-6 and TNF-α plasma levels decreased in both TRF groups versus their respective control groups.[13] The expression of IL-6 and TNF-α mRNA in white adipose tissue was also reduced with both TRF diets and was correlated with reductions in protein levels.[13]

HUMAN TRIALS

Body weight

To date, 11 trials have been conducted to evaluate the effects of TRF on body weight in humans (Table 2).[22–32] Of these, two have examined the effects of 4-hour TRF,[22,23] three have tested 7–8 hour TRF,[24–26] while six others have investigated 10–12 hour TRF.[27–32]

4-hour TRF window. In a trial conducted by Halberg et al.,[22] overweight male subjects underwent 4-hour TRF every other day for 2 weeks. Subjects were instructed to

Table 2 **Human trials: effect of time-restricted feeding on body weight and cardiometabolic risk factors.**

Reference	Subjects	Trial length	Intervention	Weight (% change)	Lipid factors (% change)				Change in glucoregulatory factors	Change in inflammatory factors
4 h feeding window					TC	LDL-C	HDL-C	TG		
Halberg et al. (2005)[22]	$n = 8$, M 25 ± 1 y Overweight	2 wk	4-h TRF Every other day	Ø	–	–	–	–	↑ Glucose uptake* ↑ Insulin suppression of lipolysis*	Ø IL-6 Ø TNF-α
Soeters et al. (2009)[23]	$n = 8$, M 20–30 y Normal weight	2 wk	4-h TRF Every other day	Ø	–	–	–	–	Ø Insulin sensitivity Ø Insulin suppression of lipolysis	–
7–8 h feeding window										
Ravanshad et al. (1999)[24]	$n = 91$, M 16–76 y Normal weight	4 wk	7-h TRF	Ø	Ø	–	–	Ø	↓27% Glucose*	–
Aksungar et al. (2007)[25]	$n = 40$, M & F 20–39 y Normal weight	4 wk	8-h TRF	Ø	Ø	Ø	Ø	Ø	–	–
Temizhan et al. (2000)[26]	$n = 52$, M & F 33 ± 10 y Normal weight	4 wk	8-h TRF	↓5% M* ↓5% F*	↓8% M* ↓10% F*	↓11% M* ↓12% F*	↑3% M* ↑2% F*	↓19 M* ↓29% F*	↑18% Glucose M* ↑22% Glucose F*	–
10–12 h feeding window										
Nematy et al. (2012)[27]	$n = 82$, M & F 29–70 y Overweight	4 wk	10-h TRF	↓2%*	↓5%*	↓12%*	↑11%*	↓19%*	Ø Glucose	–
LeCheminant et al. (2013)[28]	$n = 29$, M 23 ± 1 y Normal weight	2 wk	12-h TRF	↓1%*	–	–	–	–	–	–
Adlouni et al. (1997)[29]	$n = 32$, M 25–50 y Normal weight	4 wk	12-h TRF	↓3%*	↓8%*	↓12%*	↑14%*	↓30%*	↓14% Glucose*	–
Fakhrzadeh et al. (2003)[30]	$n = 91$, M & F 30 ± 4 y Normal weight	4 wk	12-h TRF	↓2% M* ↓2% F*	↓24% M* ↓29% F*	↓37% M* ↓35% M*	↑21% M* ↑31% F*	↓37% M* ↓19% F*	↓31% Glucose M* ↓27% Glucose F*	–
Zare et al. (2011)[31]	$n = 32$, M 23–37 y Healthy	4 wk	12-h TRF	↓2%*	↓6%*	↓9%*	↑15%*	↓4%*	–	–
Ziaee et al. (2006)[32]	$n = 81$, M & F 20–35 y Normal weight	4 wk	12-h TRF	↓2%*	Ø	↑4%*	↓9%*	Ø	↓10% Glucose*	–

Abbreviations and symbols: F, female; HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; M, male; TC, total cholesterol; TG, triglycerides; TNF-α, tumor-necrosis factor-alpha; TRF, time-restricted feeding; Ø, nonsignificant change;↑, increased; ↓, decreased.
* Post-treatment value significantly different from baseline ($P < 0.05$).

eat sufficient quantities of food during the 4-hour TRF window to maintain their body weight.[22] Thus, no changes in weight were noted.[22] A study by Soeters et al.[23] implemented the same 4-hour TRF protocol (every other day) in normal-weight males. Subjects in this study were also encouraged to consume all of their daily energy needs during the 4-hour TRF window, which resulted in no change in body weight.[23]

7–8 hour TRF window. Three studies[24–26] have examined the effects of 7–8 hour TRF on body weight in normal-weight adult males and females. Two studies[24,25] showed no effect, while one study by Temizhan et al.[26] demonstrated a 5% weight loss after 4 weeks of intervention. It is unclear why the Temizhan et al.[26] study showed weight loss, while the others did not,[24,25] given that the intervention, trial duration, and study populations were very similar. Nevertheless, it is possible that energy intake in the Temizhan et al.[26] was lower than that in the other studies.[24,25] However, this cannot be established with certainty because energy intake was measured in only one of the trials.[24] Although the subjects lost no weight in this trial,[24] a 10% reduction in energy intake was reported (using a 24-h recall). It is important to note, however, that this reduction in energy intake may be the result of under-reporting,[45] and thus energy intake may not have actually been reduced. Future studies in this area should implement more robust measures, such as the doubly labeled water technique,[46] to assess energy intake. Assessments of energy expenditure would also be highly beneficial.

10–12 hour TRF window. Remarkably, trials that implemented longer feeding windows (10–12 h) demonstrated consistent reductions in body weight of 1–3%.[27–32] These results are surprising, as it would be assumed that expanding the feeding window would make it easier for an individual to consume all of his or her energy needs for the day. It should be noted, however, that the majority of these 10–12 hour TRF studies were Ramadan trials,[27–32] and as such, the TRF window occurred during the night. Thus, hours of feeding would be limited, as 7–8 hours of the TRF window would be used for sleeping. The relationship between energy intake and weight loss was assessed in a few of these studies.[27,29] Adlouni et al.[29] demonstrated a 3% weight loss despite a 20% increase in daily energy intake as reported by a 3-day food record. Weight loss (2%) was also observed in the study by Nematy et al.,[27] but no change in energy intake was identified via a food frequency questionnaire. Once again, these energy intake values should be interpreted with caution, as food records and food frequency questionnaires are limited in their accuracy and reliability.[45] Thus, it is unknown how 10–12 hour TRF affects energy intake and energy expenditure and, thus, body weight.

Lipid factors

Changes in cholesterol and triglyceride levels in humans were only evaluated in the 7–8 hour and 10–12 hour TRF trials (Table 2). To date, no trial has evaluated the impact of smaller TRF windows (4 h) on circulating lipids levels.

7–8 hour TRF window. Plasma lipids were beneficially modulated in the trial by Temizhan et al.[26] but remained unchanged in the other two studies.[24,25] Temizhan et al.[26] implemented an 8-hour TRF diet for 4 weeks in adult subjects. Total and LDL cholesterol levels decreased similarly in males (8%, 11%) and females (10%, 12%).[26] Likewise, triglyceride levels were lowered by a similar extent in men (19%) and women (29%), and HDL cholesterol levels were augmented by 2–3% from baseline.[26] Favorable changes in plasma lipids most likely occurred only in the study by Temizhan et al.[26] because this was the only trial to demonstrate weight loss. LDL cholesterol has been estimated to be reduced by 2.0 mg/dL per kilogram of weight loss.[36] Thus, the reduction in body weight most likely played a role in these lipid improvements.[26] These data also suggest that 7–8 hour TRF may not impact lipid levels in the absence of weight loss, but further research is required before conclusions can be reached.

10–12 hour TRF window. Improvements in circulating lipids were noted in the majority of the 10–12 hour TRF trials reviewed here.[27,29–31] Total cholesterol decreased by 5% to 29%, LDL cholesterol was reduced by 9% to 37%, and triglycerides decreased by 4% to 37% from baseline.[27,29–31] The most impressive alterations in plasma lipids were seen in the study by Fakhrzadeh et al.[30] It is unclear, however, why the alterations in lipids in that study were so much more pronounced, as the intervention and subject populations employed were very similar to those of the other studies.[27,29,31] Weight loss was also similar between trials,[27,29–31] so this may not have played a significant role. It is possible that the subjects in the study by Fakhrzadeh et al.[30] were consuming a macronutrient profile that favored lipid reductions, such as a diet high in polyunsaturated fatty acids.[47,48] However, since no dietary records were collected, the role of macronutrients in these lipid changes remains unknown. As for HDL cholesterol, sizeable increases ranging from 11% to 31% were also noted.[27,29–31] These large elevations are somewhat surprising, as HDL cholesterol levels are generally only raised by endurance exercise training.[49] To this end, a key limitation of these trials[27,29–31] is the lack of energy expenditure assessment. Thus, it is not possible to elucidate whether these increases in HDL cholesterol occurred due to the diet intervention or to a confounder, such as increased exercise. Contrary to the other four studies in this category, the study by Ziaee et al.[32] noted no change

or slightly deleterious changes in lipids. For instance, total cholesterol and triglycerides remained unchanged, while LDL cholesterol levels were increased (4%) and HDL cholesterol levels were decreased (9%).[32] Due to the lack of data collected on diet or physical activity, it remains unclear why the findings in this study[32] deviated from other findings.[27,29–31] Nevertheless, the majority of trials suggest that 10–12 hour TRF windows may be cardioprotective by improving all four plasma lipid parameters.[27,29–31]

Glucoregulatory factors

Fasting glucose and insulin or insulin sensitivity were measured in two trials of 4-hour TRF,[22,23] two studies of 7–8 hour TRF,[24,26] and four trials of 10–12 hour TRF.[27,29,30,32] Findings from these trials are reported in Table 2.

4-hour TRF window. In a study by Halberg et al.,[22] insulin-mediated whole-body glucose uptake rates increased by 16% in healthy men undergoing 4-hour TRF for 2 weeks. Higher rates of insulin-induced inhibition of adipose tissue lipolysis were also observed.[22] In contrast to these findings, Soeters et al.[23] saw no improvements in peripheral or hepatic insulin sensitivity and no changes in insulin-induced suppression of lipolysis with 4-hour TRF. It should be noted, however, that the Soeters et al.[23] participants consumed 40% of their daily energy intake from liquid meals, while the Halberg et al.[22] subjects ate solid meals. Since liquid meals may cause different responses in insulin sensitivity than solid meals,[50] this may explain the difference in findings between studies.

7–8 hour TRF window. The effects of 7–8 hour TRF on glucose levels are unclear, as one study observed 27% decreases,[24] while another study observed 20% increases.[26] These alterations in glucose were not related to decreased body weight, as the study that observed 5% weight loss demonstrated increases in fasting glucose,[26] while the study that observed no weight loss observed decreases.[24] It can be speculated, however, that the increases in glucose noted by Temizhan et al.[26] may be due to increased gluconeogenesis or altered circadian rhythms of growth hormone and cortisol that occur during short-term fasting.[51] In view of this, it will be of interest in future studies of TRF to measure growth hormone and cortisol concentrations.

10–12 hour TRF window. In contrast to the other two TRF time windows, 10–12 hour TRF windows demonstrate fairly consistent decreases in fasting glucose concentrations.[29,30,32] Reductions ranged from 10% to 30% after 4 weeks of treatment in normal-weight middle-aged males and females.[29,30,32] Interestingly, in the study by Nematy et al.,[27] no reductions in glucose concentrations were observed, despite 2% decreases in body weight. It should be noted, however, that the subjects in the Nematy et al.[27] study reported alterations in sleep patterns during the trial. Inconsistent sleep patterns can have negative effects on blood glucose levels[52] and may explain why these subjects showed no change in circulating glucose with TRF.

Inflammatory factors

Data on the impact of TRF on inflammatory cytokines, such as IL-6, TNF-α, and CRP, in humans are extremely limited, as these endpoints have been evaluated in only one 4-hour TRF trial (Table 2).[22]

4-hour TRF window. Halberg et al.[22] saw no changes in IL-6 or TNF-α in healthy men undergoing 4-hour TRF every other day for 2 weeks. These results are not surprising, as IL-6 and TNF-α generally only decrease with at least a 5% weight loss.[44] Since no weight loss was reported in this trial, this is likely why these inflammatory factors were not altered.

DISCUSSION

Findings from the present review indicate that the effect of TRF on body weight differs between animals and humans, while the effect of TRF on metabolic disease risk factors is similar. For instance, 3–4 hour and 8–9 hour TRF windows are fairly consistently associated with decreases in body weight in animals but are rarely associated with weight loss in humans. On the other hand, a 12-hour TRF window produces inconsistent body weight reductions in rodents but produces sizeable and consistent weight loss in humans. The reason the animal and human literature differed so vastly for body weight remains unknown. A comparison between findings is difficult because the majority of studies in both categories failed to report energy intake or energy expenditure. Thus, it remains uncertain how TRF affects these two crucial parameters and how changes in these variables translate into modulations in body weight. These points should be considered when designing future trials of TRF.

As for plasma lipids, improvements were noted in both animal and human studies. Total cholesterol and triglycerides appear to decrease fairly consistently in both animals and humans across almost all TRF windows. Reductions in LDL cholesterol and increases in HDL cholesterol levels, however, were generally demonstrated only in humans following a 10–12 hour TRF regimen. It is still unclear why HDL increased in these 10–12 hour TRF

human trials, as no exercise training protocol was implemented. This highlights the need for accurate reporting of alterations in physical activity during periods of TRF.

In terms of glucoregulatory factors, evidence from both animal and human studies demonstrates fairly consistent decreases in glucose and insulin levels across all TRF windows. Insulin resistance was also shown to decrease in 3–4 hour and 8–9 hour TRF animal studies. Although the data are extremely limited, 3–4 hour and 8–9 hour TRF windows may decrease circulating inflammatory factors, such as IL-6 and TNF-α, in animals. It should also be noted that these reductions in inflammatory factors appear to occur only in the presence of weight loss. As for humans, the evidence on inflammatory factors is far too sparse to generate meaningful conclusions at present.

In interpreting these data, it is important to consider the strength of the evidence. The animals studies included in this review were generally of a higher level of evidence than the human trials. For example, all of the rodent studies included here were randomized control trials (level 2), while the human studies were cohort or case-control trials with no control group (level 4). The lack of a control group may lead to a higher false-positive or false-negative rate because it cannot be assumed that the significant differences are due to the intervention rather than to another factor in the environment. These factors are very important to consider when interpreting these data. All in all, the findings from animal studies are stronger when compared with those from human studies.

How TRF compares with IF also merits some discussion. In terms of body weight, the majority of IF studies (which do not include Ramadan trials) report a 5–10% weight loss after 8–12 weeks of treatment.[5] As for TRF, a 2–5% weight loss is generally reported after 4 weeks of treatment. Thus, it can be speculated that extending the TRF treatment period to 8 weeks would yield a 4–10% weight loss, which is similar to that observed with IF. On the other hand, decreases in LDL cholesterol, triglycerides, and glucose may be more pronounced with TRF versus IF regimens.[6,7] For instance, after 4 weeks of TRF, LDL cholesterol, triglyceride, and glucose levels decrease by 9–37%, 4–37%, and 10–27%, respectively. Decreases in these parameters after longer periods of IF (8–12 weeks) are generally less pronounced (LDL cholesterol, 5–15%; triglycerides, 10–25%; and glucose, 10–15%).[6,7] Thus, compared with IF, TRF may yield greater improvements in these metabolic disease risk parameters in a shorter period of time. It is unclear why TRF regimens may produce greater reductions in disease risk factors. A major difference between TRF and IF protocols is the frequency of fasting. TRF regimens require individuals to fast for a certain duration of time every day. In contrast, IF regimens generally only require subjects to fast for 1–3 days per week. Thus, it is possible that the greater frequency of fasting with TRF versus IF may contribute to the superior improvements in metabolic disease risk. Interestingly, dropout rates in TRF studies (~10%) are also lower than those reported in IF studies (~20%).[5–7] This finding suggests that TRF regimens may be more tolerable than IF regimens. Nevertheless, in order to truly delineate how TRF compares with IF, a large-scale, longer-term (16–24 week) human trial that directly compares TRF with IF is necessary. This type of trial is surely warranted, particularly when the mounting popularity of TRF diets is considered.

This review has several limitations. First and foremost, the animal studies included in this review were generally of a higher level of evidence than the human studies. Since the human trials lacked a control group and did not randomize subjects by condition, the validity of the human data is questionable. A second limitation of this review was the small number of animal and human studies that met the inclusion and exclusion criteria. As such, it is difficult to draw meaningful conclusions for the varying TRF windows (i.e., 3–4 h, 7–9 h, and 10–12 h) because only a few studies have been performed for each of these interventions. Third, this review may be misclassifying the Ramadan studies as having used 10–12 hour feeding windows when in actuality they may have used 3–4 hour feeding windows. To elaborate, the TRF window during Ramadan occurs during the night, generally from sunset to sunrise. Since the majority of these feeding hours would be used for sleeping, these subjects would only have a 3–4 hour period of time to "feed." Thus, it is conceivable that the 10–12 hour TRF human trials should be grouped with the 3–4 hour TRF trials. However, since the duration of sleep was not reported in any of the Ramadan studies, it is impossible to know with certainty the true duration of the nightly feeding period. For this reason, these Ramadan studies were grouped separately. Fourth, a large age range (16–84 years) was included for human trials. Although this allows maximum generalizability, it is also a limitation because younger individuals may respond differently to TRF than older individuals. Unfortunately, it is difficult to identify a relationship between age and treatment outcome in this review, since there were no studies conducted solely on very young individuals or on older individuals. Further investigation to determine whether the effect of TRF on disease risk varies according to age group is warranted.

CONCLUSION

In summary, evidence from animal and human studies suggests that TRF may be an effective dietary intervention to improve a variety of metabolic risk factors, including plasma lipids, fasting glucose and insulin levels, insulin

sensitivity, and certain inflammatory cytokines. The effect of TRF on body weight, however, as well as how changes in body weight influence changes in metabolic disease risk, remains unclear. Nevertheless, these preliminary findings show promise for the use of TRF in modulating a variety of metabolic disease risk factors. Whether TRF regimens result in increased adherence versus IF regimens, warrants investigation in a human randomized control trial.

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Declaration of interest. The authors have no relevant interests to declare.

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