Research Article

Effectiveness of six hours' time restricted feeding, in conjunction with calorie restriction, on risk of cardiometabolic diseases in a nonrandomized, controlled trial

Abstract

Background: Late professor Franz Halberg reported for the first time that eating breakfast causes a decrease in weight, while eating same amount of energy as dinner, was associated with lack of weight loss. There is a gap in the knowledge on epidemiological studies showing role of low caloric diet in decreasing cardio-metabolic risk. A pilot study, observed that restricted feeding in the evening, along with low calorie intake have independent effects on body weight. This study examines the effectiveness of circadian restricted feeding in conjunction with low calorie diet in patients with coronary risk factors.

Subjects and methods: After clearance from the review board of the spiritual health center, and verbal informed consent, 117 volunteers, aged 25-85 years, received low caloric diet with time restricted feeding in the evening. We randomly recruited age- and sex-matched urban subjects (n=150) as control group for comparison with volunteers on low caloric diets. All subjects were given a training for consuming low caloric, time restricted feeding in the evening at a spiritual health center, Meerut, India. Blood pressures were measured by sphygmomanometer and diet and physical activity were assessed by validated questionnaires, based on WHO guidelines.

Results: The findings revealed that some educated Indians of social class 1-3 may be motivated to follow a low caloric time restricted eating (TRE) in the evening for one year. After treatment with low caloric diet in the evening, mean body weight, body mass index, and systolic and diastolic blood pressure showed significant decline in the study group, compared to urban control group. Fasting blood glucose, triglycerides and total and LDL cholesterol, also showed significant decrease with mild increase in HDL cholesterol in the study group, compared to control subjects. Mean concentrations of immunoglobulins A, M and G showed significant increase in the intervention group without such changes in the control group. There was no decline in physical performance and there were no adverse effects on health except for temporary weakness in a few subjects in the study group.

Conclusions: It is possible that Indian subjects with stable cardio-metabolic risk factors can be motivated to consume low caloric diet with restriction of feeding in the evening. Regular intake of low caloric diet especially, in the evening, may be quite effective, with significant decline in fasting blood glucose and blood lipids as well as significant increase in immune-globulins and physical performance. Long term follow up studies would be necessary to draw final conclusion.

Keywords: restricted feeding, low energy diet, diabetes, hypertension, lifestyle, heart disease

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Introduction

Franz Halberg was the first investigator who demonstrated that eating in the morning may be associated with decrease in body weight, while eating same amount of energy as dinner causes no change in weight.[1] There is evidence that time restricted eating (TRE) and caloric restriction (CR) can independently reduce body weight, waist circumference, body mass index, and fat mass, in patients with cardio-metabolic risk[2–4] but there is a scarcity of such evidence among patients with cardiovascular disease (CVDs) and diabetes.

The findings from earlier and recent studies indicate that eating breakfast should be encouraged, because night time eating is associated with increased risk of cardio-metabolic diseases (CMDs).[1,5] Since Indians have been found to have increased susceptibility to cardio-metabolic diseases (CMDs), this hypothesis may be used for prevention of CVDs and diabetes among them.[6–8] Meal timing may influence tolerance substrate oxidation and circadian-related variables as well as weight gain or weight loss.[9,10] It is possible, that certain nutrients and the timing of food intake may play a significant role in the development of obesity and central obesity.[7,8,11,12]

Experimental studies link energy homeostasis to the circadian clock at the behavioral, physiological, and molecular levels. It is proposed that, resetting the circadian clock by circadian energy restriction and reduction in total calorie intake per day, may be used as a new approach for prevention of coronary risk factors and CAD.[12–14]

The effects of restricted feeding to a particular time of the day without calorie reduction or caloric restriction alone have independently variable effects on circadian physiology and metabolism as well as on weight gain or weight loss.[1,2, 9,10] This hypothesis of circadian dysfunction of metabolic factors in the morning has been proven in animal experiments.[11–16] The endogenous period of the SCN oscillation is approximately, but not exactly, 24 hours. It requires resetting each day to the external light-dark cycle to prevent drifting out of phase, because light is a strong synchronizer for the brain clock, perceived by the retina.[11–14] The SCN is responsible for transmission of the information to peripheral oscillators in various organs such as liver, pancreas, smooth muscles, heart, adipocyte and gut to prevent the dampening of circadian rhythms via neuronal connections or circulating factors.[17] Thus, feeding schedule can synchronize the peripheral clocks leading to resilience.

In all Indian religions, such as Hindus, Jains, Budhists, fasting, in particular at morning and eating before sun set, once or twice in a week is considered a protective behavior for health and wellbeing. Franz Halberg came to India to encourage us to study, the association of time of eating with CMDs.[2] However, he was surprised to discuss and see that in a spiritual health center (https://iass.info/), volunteers are invited to eat a low caloric diet, restricted to eat in the evening.[18] Eating only herbal tea as breakfast, fruits and salads in the lunch with normal dinner at sun set. It has been found beneficial against obesity, hypertension, diabetes mellitus and stable coronary artery disease (CAD).[18] All subjects are admitted in the center for 1-2 weeks for training on above dietary regimen, then they go home to practice similar diet and lifestyle in their home town to improve their health.[18] Experimental studies have also demonstrated extensive and divergent circadian gene expression in liver and heart, in relation to coordination in circadian timings and restricted food access during light or darkness.[13–17,19,20] It seems that energy metabolism is very complex, because restrictive food access during the light period and periodic fasting as well as, reduced caloric intake may have independent beneficial effects on energy metabolism and health.[20,21] This study aims to examine the effectiveness of LC diet, in conjunction with TRE in the evening, on cardio-metabolic risk factors among these subjects.

Subjects and methods

The ethical clearance was obtained from the Scientific Review board of spiritual health center; Badrinarayan Sevasram, and International Association for Scientific Spritualism; Baghpat, Meerut (UP), India and verbal informed consent, from all the volunteers, recruited for this study. Of 133 volunteers who came for recruitment to this study, 117, aged 25-85 years, were selected to receive intervention with low caloric diet with circadian restricted feeding in the evening. We randomly recruited age- and sex-matched urban subjects (n=150) as control group.

Inclusion criteria were; volunteers (n=117) interested in having training in taking low caloric diet with healthy spiritual lifestyle.

Exclusion criteria were, cancer (n=2), significant clinical manifestations of diseases such as angina or uncontrolled diabetes and hypertension (n=9), chronic diarrhea or dysentery (n=2) or tuberculosis (n=3).

All subjects in the intervention group were given a training for consuming low caloric, circadian restricted diet in the evening at Badrinarayan Sevagram and International Association for Scientific Spritualism; Meerut, India. Majority of the participants in both intervention and control groups had a known proven history of overweight (n=12 vs 14), obesity (n=5 vs 4), hypertension (n=22 vs 25), type 2 diabetes mellitus (n=29 vs 32) or angina pectoris (n=24 vs 26) respectively. In the control group, we selected age- and sex-matched urban patients from outside the clinic (n=150). All volunteers in the intervention group were admitted in the above center which aims to decrease the risk of CMDs by altering time of eating, along with total per day energy restriction.

Intervention group with circadian restricted, low caloric feeding: All the volunteers after admission to above center, were administered standard dietary regimen; herbal tea with milk and sugar at breakfast (80-100 Kcal), only salads, tomato, onion, cucumbers, radish, carrots, etc. at lunch (150-200 Kcal), evening tea with two whole-grain biscuits (80-100Kcal), and normal Indian dinner at sun set (wheat flour chapatti, vegetables, spices, pulses, salads, cottage cheese, and fruits, 850-1000 Kcal) with an aim to reduce the daily energy intake to 50-70%. The objective was to administer, a majority of the total daily energy intake in the evening, after sunset (1000 Kcal/day) with total energy intake of approximately 1200K Calories/day. All subjects were advised to continue standard diet given at the center, after they go back to their home town.

Control group: The control group was advised to consume low fat step 1, diet as per advise of National Cholesterol Education Program.[22]

The study participants and control subjects, were eating normally (breakfast, lunch, evening snack and dinner) before joining this study. The dietary patterns before entry to study in both the groups were similar; wheat flour chapatti, vegetables, spices, pulses, salads, cottage cheese, and fruits such as papaya, guava, and bananas. Salads included; tomato, onion, cucumbers, radish, carrots, etc.

Collection of data

Clinical data were recorded in both the groups. The health professionals recording the clinical data were blind to the groups. Regular detailed interviews were performed with the help of a pretested and validated questionnaire, prepared according to the guidelines of WHO and the International College of Nutrition. Tobacco and alcohol were not permitted in the above center but assessed by validated questionnaires in both groups. Dietary intakes and physical activity scores were assessed by a trained scientist or physician by validated questionnaires at entry to study, during admission in the training center and every 4 weekly for one year, among all the subjects in both groups.[23,24] Physical activity was estimated by considering both spare time and occupational activities. Cigarettes, beedies, Indian pipes, raw tobacco and chewing tobacco are all commonly consumed and tobacco is often used in more than one form. We therefore categorized users of any form of tobacco as smokers as was done in previous studies. Individuals who admitted to ingesting alcohol more than once a week were categorized as alcohol consumers. Dietary assessment was made by a 7-day food intake record by questionnaires, administered by a trained scientist. Food measures, food portions and food models were used to assess dietary intakes in both groups. Salt intake was estimated by considering salt administered in the food, and salt taken from the table to mix with food during eating. Energy and nutrient intake were calculated with the help of Indian food composition tables.[25]

Physical examination and sphygmomanometer readings were taken by a physician. Only three readings were recorded in sitting position and an average of last two readings was considered correct blood pressure of the subject. Body weight was recorded in underclothes to the nearest of 0.1 kg. Height was measured after removing shoes. Body mass index was calculated; obesity was defined as a body mass index > 30 kg/m^2 and overweight as a body mass index 25 kg/m^2 to 29.9Kg/M^2. Diabetes mellitus was diagnosed as fasting blood glucose >7.7 mmo1/1 (140 mg/dl) and postprandial 2 hours after 75 g of oral glucose > 11.2 m mol/1 (>200 mg/dl). Subjects having records of treatment for type 2 diabetes, hypertension and angina pectoris were also considered to have these risk factors. Blood pressure was measured on right arm (systolic and diastolic phase V of Korotkoff) after 5 min rest in the sitting position according to WHO guidelines by a single mercury manometer and by the same physician in all subjects. Hypertension was diagnosed when systolic blood pressure was 140 mmHg or higher and/or when diastolic blood pressure was 90 mmHg or higher. Heart rate was measured by auscultation for 5 minutes and expressed in beats/minute for each subject.

Majority of the subjects in both intervention and control group showed available record of diagnosis and treatment of CAD and other risk factors by a qualified physician. In others, the criteria for the diagnosis of CAD were: (a) history of angina or infarction and previously diagnosed disease, (b) affirmative response to the Rose questionnaire, and (c) electrocardiographic findings, namely Minnesota codes 1-1, 4-1, 5-9, 5-2 or 9-2. Presence of all of these three criteria was taken as confirmation of the diagnosis of CAD. Individual clinical criteria included known CAD, affirmative response to Rose questionnaire and electrocardiographic changes (Q wave change: codes 1-1 and 1-2; ST segment depression or elevation: codes 4-1, 4-2 and 9-2; and T wave inversions: codes 5-1 and 5-2). Prevalence of these electrocardiographic finding with and without clinical criteria for CAD is also given. 2D echocardiography was done by same cardiologist in all the subjects in both the groups.

Laboratory data

After an overnight fast of more than 10 hours, venous blood sample was obtained from all subjects. Laboratory technicians recording the data were blind to the groups. Each participant was asked to drink 75 g anhydrous glucose in 200 ml of water and a second blood sample was collected after 2 h for analysis of glucose. The blood was analyzed for blood counts and hemoglobin, urea, glucose, cardiac enzymes, total cholesterol, high- and low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations. High-density lipoprotein (HDL) cholesterol was measured by an enzymatic method. In all patients with higher blood lipid concentrations, measurements were repeated. Immunoglobulins (IMG) were measured in the fasting blood in a accredited laboratory.

Statistical analyses

We used Students t test for comparison of continuous variable and Chi square test for ordinal variables. The prevalence is given in percent and numerical variables as mean ±SD. Data were compared before and after the intervention in the group and final values at end of the study. Odds ratios and 95% confidence intervals were calculated by multivariate analysis after adjustment for age and body mass index, using overall mean values as the dependent variable. Only P-values with two-tailed test were considered significant.

Results

This controlled study compared 117 subjects receiving intervention with a circadian-restricted, low caloric diet, with 150 age and sex-matched control subjects. Mean age and gender were comparable between the two groups. Mean body weight, body mass index (BMI), systolic and diastolic blood pressure, and heart rate were comparable at baseline in the intervention and control groups as given in Table 1 and Table 2. Past history of taking low caloric diet was slightly more in the intervention group compared to control group (Table 1).

Table 1 Clinical data among subjects receiving low caloric diet and normal diet

Data	Volunteers on low caloric (1200 Kcal) diet (n=117)	High-risk urban control subjects (n=150)
Age groups, years, n(%)	n(%)	n(%)
20-40	33 (28.2)	41(27.3)
41-60	58(49.6)	76(50.7)
60-85	26((22.2)	33(22.0)
Mean (SD) age (years)	54.5 ±7.68	55.7± 8.89
Gender: males, n (%)		
Male	79 (67.5)	98(65.3)
Female	38(32.5)	52(34.6)
Low caloric diet	117(100)**	11(7.34)
Restricted feeding	117(100)**	11(7.34)
Past history of fasting	90(76.9)	98(65.3)
Active prayer/religious songs	117(100)**	72(48.0)
Sedentary	56(47.8)	78(52.0)
Moderate exercise	61(52.1)	72(48.0)

*=P<0.02,**=P<0.001

Table 2 Clinical characteristics of subjects at baseline and after follow up of 1 year

Variable	Low caloric diet, (n=117)		Control group, (n=150)	
	Baseline	After 1 year	Baseline	After 1 year
Mean body weight, Kg	54.5± 7.68	52.0± 7.72*	55.7± 8.89	55.2±8.85
Body mass index, Kg/M2	22.7±3.4	21.4±3.1*	22.8±3.7	22.6±3.4
Blood pressures, mm Hg Systolic	124±12.5	116±9.8*	126.5±13.7	125.6±12.7
Diastolic	84±7.8	78±6.6*	86.5±9.2	85.5±8.8
Echocardiographic ejection fraction,%	66.4 ± 8.23	72.2 ± 9.81	69.7± 9.87	68.5± 8.89
200 meter running time. Seconds	50.75± 7.11	41.1± 4.13*	53.21 ± 8.44	52.35± 8.11
Total caloric intake, K Cal/day	2127 ± 347	1207 ± 213*	2213 ± 374	2203 ± 362
Daily physical activity scores.	3.91±0.31	3.97±0.34	3.86±0.42	3.81±0.45

*=P<0.01, P values were obtained by Student's t test

The consumption of total per day dietary energy was significantly greater among study subjects on a low-caloric diet compared to control group (Table 2). Mean body weight, BMI and mean systolic and diastolic blood pressures were significantly decreased in the study group compared to control group. There was a marginal decline in echocardiographic ejection fraction in the study group compared with control subjects. Assessment of efficiency examined via 200 meter running, revealed that running time was significantly lower in the study group compared to control group (Table 2). Total energy intake, kilo calories /day was significantly lower in the study group, compared to control subjects, whereas, daily physical activity scores were similar in the two groups (Table 2).

Table 3 shows that fasting blood glucose, total and LDL cholesterol and triglycerides showed significant decline in the study group with an increase in HDL cholesterol in the study group, whereas the changes were non-significant in the control group. Urinary ketones excretions were significantly higher in the study group, however, no such finding in the control group (Table 3).

Table 3 Cardio-metabolic risk factors at baseline and after follow up of 1 year

Variable	Low caloric diet, (n=117)		Control group, (n=150)	
	Baseline	After 1 year	Baseline	After 1 year
Fasting blood glucose, mg/dl	104.3±9.76	98.7±10.93*	105.4±12.31	107±13.65
Blood urea, mg/dl	27.8±4.31	25.3±4.11	26.71±5.77	27.32±7.23
Total Cholesterol, mg/dl	201.6±21.14	162.4±20.05**	207.7±26.53	204.55±22.8
LDL Cholesterol, mg/dl	118.7±7.93	104.3±8.01*	121.5±10.65	119.3±9.77
VLDL Cholesterol, mg/dl	36.4±4.31	36.2±4.05	39.6±6.77	37.5±6.34
HDL Cholesterol, mg/dl	54.5±5.13	64.5±6.02*	52.4±6.77	53.6±7.02
Triglycerides, mg/dl	201.6±26.71	165.5±23.33**	195.2±27.4	193.6±26.5
Urinary ketones	nil	++	nil	nil

*= P <0.05, ** = P <0.01

Table 4 shows the mean concentrations of IMGs and lymphocyte counts in the two groups. The concentrations of IMG, A, G, and M, showed significant increase from baseline and were significantly greater in the study group compared to control group (Table 4). Total lymphocyte count also revealed significant increase in the study group, and the increase was significantly greater compared to control group.

Table 4 Immunological risk factors at baseline and after follow up in the two groups, after 1 year

Variable	Low caloric diet, (n=117)		Control group, (n=150)	
	Baseline	After 1 year	Baseline	After 1 year
Immunoglobulin A, mg/dl	153.4±17.37	158.5±7.93**	113.4±17.93	112.6±16.27
Immunoglobulin G, mg/dl	1276.1±169.63	1314.3±82.38*	1006.1±183.38	988.4±174.73
Immunoglobulin M, mg/dl	153.6±18.36	167.3±6.2**	143.8±16.21	132.6±21.04
Lymphocyte count, n/µL	3567±410	4208±455*	3634±432	3706±459

*= P < 05%, **= P< 0.01

Discussion

This study shows that time restricted feeding at sun set, in conjunction with low calorie diet, administered for one year among patients with CMDs, were associated with significant decline in total and LDL cholesterol and triglycerides with significant increase in HDL cholesterol. The study group also shows significant reduction in blood glucose. The interesting points are that low-caloric diet (approximately 1202 Kcal/day) was also time restricted at sun set, and consumed as substitute for dinner with no breakfast and only salads and fruits for lunch. The results also indicate that study group had significant decrease in body weight, body mass index, systolic and diastolic blood pressures, with improvement in the physical performance. Total dietary energy intake per day were significantly lower in the study group compared to control group, although physical activity scores showed no significant differences. In an earlier study, Halberg et al observed in a series of studies and experiments, that eating a single daily 2000 Kcal meal either in the morning or evening, had weight loss in association with breakfast but not with dinner.[1]

TRE is an increasingly popular dietary strategy for weight loss. Recent studies suggest that combining TRE with CR may have more favorable effects on both physical and biochemical aspects when compared with CR alone.[2] A meta-analysis was conducted to compare the effects of TRE with CR (n=231) vs. CR alone (n=227) on anthropometric and biochemical measures in adults with higher body weight.[2] After follow-up, TRE with CR compared to CR alone was associated with a significantly greater decline in body weight (mean difference (MD): −2.11 kg, 95% CI: −2.68 kg to −1.54 kg, p = < 0.00001, I^2 = 42%), body fat mass (MD: −0.75 kg, 95% CI: −1.35 kg to −0.16 kg, p = 0.01; I^2 = 0%), and waist circumference (MD: −1.27 cm, 95% CI: −2.36 cm to −0.19 cm, p = 0.02, I^2 = 0%), while no additional impact of TRE in combination with CR in comparison to CR on serum biochemical parameters were found. These results indicated that the improvement in biochemical parameters are mainly caused by CR. The improvements in anthropometric parameters showed more benefit by TRE.

In another meta-analysis,[3] including 8 randomized trials, involving 579 subjects, the aim was to evaluate the efficacy of TRE with CR on weight loss and cardio-metabolic risk. The findings revealed that TRE with CR reduced the body weight, BMI fat mass, and waist circumference significantly (WMD: −1.40, 95% CI: −1.81 to −1.00, and I^2: 0%; WMD: −0.73, 95% CI: −1.39 to −0.07, and I^2: 0%; WMD: −1.87, 95% CI: −3.47 to −0.26, and I^2: 67.25%, respectively). Interestingly, TRE plus CR exhibited no significant benefit on the blood pressure, glucose profile, and lipid profile, compared with CR only. A subgroup analysis found that early TRE is more effective in weight loss (WMD: −1.42, 95% CI: −1.84 to −1.01, and I^2: 0%) and improving fat mass (WMD: −1.06, 95% CI: −1.91 to −0.22, and I^2: 0%) than delayed or broader TRE when combined with CR. In a randomized trial including 139 subjects, after 12 month follow up, the mean weight loss from baseline at 12 months was −8.0 kg in the time-restriction group and −6.3 kg in the daily-calorie-restriction group.[4] Changes in weight were not significantly different in the two groups at the 12-month assessment (net difference, −1.8 kg. Results of analyses of waist circumferences, BMI, body fat, body lean mass, blood pressure, and metabolic risk factors were consistent with the results of the primary outcome. It is clear that in obese subjects, a combination of TRE and CR had no more beneficial effects compared with daily calorie restriction.

In a randomized, controlled trial among 20 infants with under nutrition, infant milk or dairy milk (800 ml/day) were administered for 4 weeks.[27] The findings showed that restricted feeding in the morning or evening revealed circadian stage dependent effects of milk at 4 weeks. In a case study among 15 subjects, meals were taken either as usual (breakfast, lunch and dinner) or as a single daily meal taken in the early evening for 8 weeks.[28] Systolic and diastolic blood pressure were significantly lowered by about 6% more during the span when subjects were consuming 3 meals/day than when they consumed a single daily meal in the early evening. However, body weight, fat mass and total body water were significantly decreased in association with a single daily meal, compared to 3 meals/day, after 8 weeks of follow-up.[28]

Our study is different from above studies, because intervention subjects were taking time restricted feeding at sun set, along with calorie restricted diet. Our study provides a proof, for the first time that a significant numbers of Indian subjects suffering from stable CMDs may be motivated to consume low caloric diet at sun set for a follow up period of 1 year. We cannot compare our study with others, because there is no study comparing the effects of caloric restriction along with time restricted feeding at sun set, in patients with CMDs. In a pilot study, 32 volunteers with CMDs, aged 25-67 years, were advised low caloric diet with circadian restricted feeding at sun set, compared to 500 age and sex matched control subjects.[14] Fasting blood glucose, triglycerides and total cholesterol were significantly lower in the study group, compared to high-risk urban subjects. Multivariate logistic regression analysis after adjustment of age and body mass index showed that the relative risk (RR) and confidence interval of difference (CI) for restricted feeding ($P<0.001$) and low-calorie intake ($P < 0.001$) were inversely associated with the risk of CVDs and type 2 diabetes.[14] The findings revealed that time restricted feeding at sun set and low caloric diet may be important protective factors against CMDs, despite no breakfast and nominal lunch, which may be associated with improved health.[14]

Recent studies indicate that a modest caloric restriction in daily calorie intake, may improve a range of cardio-metabolic risk factors in healthy young and middle-aged adults.[29–31] In all of the CMDs, values considered within normal range are also linked with an increased risk of morbidity and mortality. Cohort studies have shown that incidence and mortality due to CMDs continue to decline even when cardio-metabolic risk factor levels decline below what guidelines consider to be normal, suggesting that even healthy individuals can benefit from modest restriction in calories.[29–31]There is paucity of knowledge regarding the long-term effectiveness of caloric restriction on the risk for atherosclerosis. In a clinical study among 18 subjects on calorie restricted diet for an average of 6 years were compared with 18 age-matched healthy individuals on typical American diets.[29] Serum total cholesterol, LDL cholesterol, ratio of TC to HDL-C, triglycerides, fasting glucose, fasting insulin, CRP, PDFG-AB, and systolic and diastolic BP were all markedly lower, whereas HDL-C was higher, in the calorie restricted group compared to the American diet group. Carotid artery intima-media thickness was ≈40% less in the calorie restricted group compared to control group.[29] In view of these results and the findings of our study, it is possible that calorie restriction can cause significant decline in the risk of CMDs. In a phase 2 trial, 218 healthy, non-obese adults were randomly assigned to a calorie-cutting group, by 25%, or control group, instructed to eat what they liked.[30] Calorie restriction was associated with a persistent and significant reduction from baseline to 2 years of all measured conventional cardio-metabolic risk factors, including change scores for LDL-cholesterol ($p<0{\cdot}0001$), total cholesterol to HDL-cholesterol ratio ($p<0{\cdot}0001$), and systolic ($p<0{\cdot}0011$) and diastolic ($p<0{\cdot}0001$) blood pressure. In addition, calorie restriction resulted in a significant improvement at 2 years in C-reactive protein ($p=0{\cdot}012$), insulin sensitivity index ($p<0{\cdot}0001$), and metabolic syndrome score ($p<0{\cdot}0001$) relative to control. It is possible that a moderate restriction of calorie for 2 years, can significantly lower multiple cardio-metabolic risk factors in young, non-obese adults.[30]

In our study, the decline in calories intake in the study group was approximately 45.3% more, compared to control group, showing no decline in energy intake (Table 2). A marked reduction in calorie in the intervention group, indicate that the majority of the beneficial effect stems from, calorie restriction rather than time restricted feeding. However, restriction of majority of the calorie intake (>80%) has been made at a time window of sun set, between 18.00 to 19.00 hours depending on sun set in various seasons, which may have provided some of the benefits. Apart from these factors, fasting interval from 18.00 hours to next day 12.00 hours (18.00 hours) may also have provided some of the benefits.[32] Recently, these approaches; caloric restriction with time restricted feeding and fasting have also been used in other studies.[32–35] A meta-analysis has demonstrated that intermittent fasting and time-restricted feeding as well as continuous energy restriction are effective strategies for weight loss.[32] The findings in 9 out of 11 studies revealed that intermittent energy restriction paradigms produce equivalent weight loss, compared to continuous energy restriction. In a randomized, controlled, cross-over trial among 15 subjects, time restricted feeding in early period, was associated with lower mean fasting blood glucose.[33] Time restricted feeding improved glycemic responses to a test meal in men at risk of diabetes, regardless of clock time[33] as well as it reduced body weight in older adults in a pilot.[34] It seems that time restricted feeding is some form of intermittent fasting that contains, a long daily fasting period, like in our study. In a pilot study, comprising of 11 overweight subjects, early time restricted feeding was associated with significant decline in mean 24-hour blood glucose levels and glycemic excursions.[35] There was a significant increase in ketones, cholesterol and in the expression of response to stress and aging gene SIRT1 as well as autophagy gene; LC3A in the morning. However, in the evening, there was a trend of increase in BDNF with increased expression of MTOR, which is a major sensing protein of the nutrients, responsible for regulation of cell growth. It is possible that apart from benefits in 24-hour blood glucose levels, early time restricted feeding can influence several circadian clock genes, modulate circadian rhythm of cortisol, along with anti-aging effects in humans.[35] Our study also shows that this joint approach of targeting energy and time, with longer fasting interval was associated with significant increase in immunoglobulins in the study group without such benefits in the control group (Table 4). Previous studies also support that circadian restriction of feeding modulate autonomic nervous system dysfunction and cardio-metabolic risk.[36–39] Apart from time restricted and calorie restricted feeding, ketogenic diets have been demonstrated to influence circadian signatures in liver and gut clocks.[38] Therefore, it seems that resetting the circadian clock by multiple approaches can boost metabolic health.[39]

In a recent randomized, controlled, crossover trial among 22 subjects, feeding in the night was associated with wait gain with increase in waist circumference, fasting blood glucose and Hb1c that are indicators of the metabolic syndrome.[36] However, eating in the morning decreased, the body weight, Hb1c and systolic BP, indicating that it may be protective against the metabolic syndrome. Our study also shows, that calorie restriction along with time restricted feeding allows us to skip breakfast without any adverse effects. Time restricted feeding at sun set, also decreases the need for dinner and late night eating as well as provides a long interval of fasting, which are known to influence the risk of CMDs.[36–39] Skipping breakfast concomitant with late-night dinner eating is associated with worse outcomes in relation to CMDs and following ST-segment elevation myocardial infarction.[5,40–42] Our study also emphasizes that time restricted eating at sun set, with 6 hours restricted eating time between 1.00 PM to 7.00PM, with 18 hours of fasting, was associated with significant benefit, which is similar to other recent studies.[43–45] It has been observed that eating and drinking everything within a consistent 8 or 10-hour window allows our body to rest and restore for 14 hours at night.[43,44] Eating patterns are increasingly varied; skipping breakfast, intermittent fasting, meal frequency and timing of eating occasions and irregular eating patterns appear less favorable for achieving a healthy cardio-metabolic profile.[43–45] Skipping of breakfast has been found to cause unhealthy eating and unhealthy snacking.[46] However, reduction in caloric intake and periodic fasting have been demonstrated, to contribute independent benefits to metabolic effects of caloric restriction,[21] Intentional eating with mindful attention to the timing and frequency of eating frequency and period of fasting may lead to healthier lifestyle with improved cardio-metabolic risk which is also advised by the American Heart Association.[14,21,37,39–47]

Further evidence indicate that the reduction in total calories by reduced intake of macronutrients, such as protein may extend life span, which may provide improved cardio-metabolic risk.[21,48,49] In experimental studies, a dietary intake of carbohydrate and fat reduced by 50%, and proteins, vitamins and minerals, amplifies at least one gauge of adrenocortical function as a putative mechanism of decreased risk and life prolongation.[21,22,27–30] A lower heart rate was also observed in the present study which is a indicator of greater heart rate variability, a manifestation of autonomic nervous system activity.[21,22,26] Alterations in circadian rhythms induced by diet might complicate the interpretation of results, especially if the effect of the intervention is assayed at only one time of the day,[49] Thus, dietary restriction can significantly influence the circadian rhythm. It seems that several metabolic benefits of caloric restriction, including effects on lifespan, are impaired in circadian clock mutants indicating an interaction between caloric restriction and the circadian clock

Long-term daytime restricted feeding may have epigenetic effects indicating increase in catabolism, alteration in physiological functions leading to decrease in the risk of obesity, metabolic syndrome and CVDs.[20–25] In earlier studies, Halberg demonstrated for the first time that eating breakfast-only was associated with weight loss, whereas this was not the case when eating the same amount of calories as dinner-only in humans; in animal experimental, restricted feeding during the rest span was associated with mortality in singly-housed animals.[26–28] Moreover, Halberg observed that configuration of the circadian system differed greatly depending on whether feeding took place in the morning or evening under identical lighting (rest/activity) conditions.[28–31] Clinical studies on the role of restricted feeding and/or low-calorie diet/fasting on cardio-metabolic risk are scarce. In the present study, we examine the effects of restricted feeding at dinner in conjunction with reduced energy at breakfast and lunch, among known patients with obesity, cardiovascular diseases (CVDs), hypertension, coronary artery disease (CAD), and type 2 diabetes, compared to such patients consuming meals as usual.

Caloric restriction has beneficial effects on health and longevity.[21] Calorie restriction may implements time-restricted feeding, a short period of feeding followed by prolonged fasting. Periodic fasting, in the form of time restriction or mealtime, improves metabolism without reduction in caloric intake. In experiments, calorie restriction significantly reduces blood glucose and insulin around the clock, improve glucose tolerance, and increased insulin sensitivity.[50] Time restriction reduces blood insulin and increases insulin sensitivity, but in contrast to calorie restriction, time restriction may not improve glucose homeostasis. The expression of circadian clock genes in liver was affected by both diets while the mRNA expression of glucose metabolism genes was significantly induced by calorie restriction, but not by time restriction.[50] It is clear that periodic fasting contributes to some metabolic benefits of calorie restriction, but time restriction is metabolically different from calorie restriction.[49,50]

In a recent review, physiological responses to food intake throughout the day have been nicely described.[8] Among 32 women, compared to eating at 13.00 hours, eating later in the day (16.30 hours) was associated with decreased resting energy expenditure, decreased fasting carbohydrate oxidation, decreased glucose tolerance, blunted daily profile in free cortisol concentrations, and reduced thermal effects of food on wrist temperature, indicating differential effects of meal timing on metabolic health.[5] In a weight loss study, 420 subjects undergoing a 20-week weight loss program were categorized according to the time at which they ate their main daily meal as lunch. Those subjects who were eating late, lost less weight and at a slower rate than those eating early in the day, while energy intake, energy expenditure, dietary composition and sleep duration were similar in both groups.[6] In a further study, obese or overweight females consumed energy-restricted diets differing in the proportion of energy distributed at breakfast and dinner.[18] Those female subjects eating more energy at breakfast than dinner lost more weight and exhibited an improved metabolic profile in triacylglycerol and insulin concentrations. In a further study, eating after 20:00 and protein intake within 4 hours of sleep have been positively associated with body mass index, independent of age, sleep timing and sleep duration.[20] Several studies have been published indicating that regular cereal consumption at breakfast helps children and adolescents stay slimmer, which has also been confirmed in a meta- analysis.[19] Our study is unique because no other study to our knowledge has examined the effects on coronary risk factors and type 2 diabetes of no breakfast, salads and fruits for lunch and dinner as usual (total=1200 Kcal/day) taken in the evening at 18:00 hours.

Experimental studies indicate that rodents on restricted feeding can adapt to adjust to the diurnal feeding span within a few days and learn to eat their daily food intake during that limited time.[10,21–23] Restricted feeding may be associated with alteration in physiological activities normally coordinated by the SCN, such as body temperature, locomotor activity, and heart rate.[21,22] Another study revealed that long-term day-time restricted feeding can increase the amplitude of clock gene expression, increase expression of catabolic factors, and reduce the levels of disease markers leading to better health.[24] However, a timed high-fat diet led to reduced body weight and improved metabolism compared to consumption of the same caloric intake spread out throughout the day.[25]

It is clear from our study, that eating normal dinner at sun set, with intake of lower total calories per day, can cause significant benefit in cardio-metabolic risk and immunological factors, despite no breakfast. Apart from calorie restriction and time restriction, our study laso gives the opportunity of 18 hours of fasting from 18.00 hours to 12.00 hours. In an experimental study daily fasting improved health and survival in male mice, independent of diet composition and calorie.[50] Previous studies also reported beneficial effects of alternate day and intermittent fasting on risk factors of CMDs.[51,52] In a previous experiment in drosophila, dietary restriction of amino-acid imbalance explained extension of lifespan.[53] Since current therapeutics for obesity are limited and only offer modest improvements, novel interventions, such as energy restriction are needed for weight loss.[10] Preventing obesity with time-restricted feeding, 8-9 hours food access in the active phase is promising, yet its therapeutic applicability against preexisting obesity, diverse dietary conditions, and less stringent eating patterns needs exploration. Our study and other experiments show that time-restricted feeding attenuated metabolic diseases arising from a variety of obesogenic diets, and that benefits were proportional to the fasting duration. Interestingly, time-restricted feeding stabilized and reversed the progression of metabolic diseases in mice with preexisting obesity and type 2 diabetes. The circadian clock, at the molecular, physiological, and behavioral levels, raises the possibility that the timing of food intake itself plays a significant role in weight gain or weight loss. A further study provides evidence that nocturnal mice fed a high-fat diet only during the 12-hour light phase gain significantly more weight than mice fed only during the 12-hour dark phase.[10]

In a previous experiment, caloric restriction delayed disease onset and mortality in Rhesus Monkeys.[55] It is known that circadian disruption of sleep and night shift work can disrupt central circadian clock and peripheral clocks that are important in the pathogenesis of obesity, metabolic syndrome, CVDs, type 2 diabetes and cancer.[33,34,56–58] After the Second World War, the shortage of food in some North European countries led to a sharp fall in mortality from coronary artery disease. However, when the war ended, mortality rose sharply. Our study is unique, because no information regarding the long-term effects of calorie restriction in humans eating a good quality diet is available. In a cohort study, involving 19,831 subjects, follow up after 8.1 years revealed that eating duration of less than 8 hours, was associated with significant increase in cardiovascular mortality.[49] In Ramadan fasting, majority of the Muslim friends eat between 7.30PM to 4.30 AM, in a eating period of about 9 hours which is associated with decreased cardio-metabolic risk, despite night eating, without any increase death rate in a meta-analysis of 15 studies.[59] The lack of adverse effects may be because fasting is absolute in the day time, under the shadow of all the planets in a line causing reduced magnetic storms by the sun and moon.

Conclusion

In brief, our results showed a significant decline in blood lipids and blood glucose with significant increase in HDL cholesterol. These findings indicate that the potential for a substantial advantage for cardio-metabolic health of practicing moderate calorie restriction with TRE before sunset, offer promise for pronounced long-term population health benefits. CR has already been observed to slow the process of aging in rats, mice, fish, worms, and various insects. There are a small number of subjects who have been practicing CR for a number of years in the belief that it may extend their lifespan beyond the usual range. The availability of these individuals is making it possible for us to investigate the effects of long-term CR and TRE in humans.

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Conflicts of interest

The authors declare that there are not conflict of interest.

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