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Comparative Effects of Intermittent and Continuous Energy Restriction on Metabolic and Cognitive Functions in Menopausal Rodent Models

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KEYWORDS
Continuous energy restriction, Intermittent energy restriction,Menopause, Metabolic Function, Cognitive function

ABSTRACT:
Calorie restriction is an important strategy to reduce the metabolic risks associated with aging. Various calorie restriction regimens have proved to be beneficial in menopause, but their comparative effects still remain a matter of debate. Therefore, this study aimed to compare the effects of continuous and intermittent energy restriction regimens on metabolic and cognitive functions in a VCD-induced menopausal rodent model. Thirty-six female Wistar rats were randomized into six groups (n = 6), comprising three non-menopausal and three menopausal groups. Within each category, animals were sub grouped into control (no restriction), continuous energy restriction (CER), or intermittent energy restriction (IER) regimens for 12 weeks. Menopause was induced using 4-vinylcyclohexene diepoxide and confirmed by plasma estradiol levels, estrous cycle monitoring, and ovarian histology. Body weight was recorded every week, while plasma glucose, insulin, and lipid levels were measured both before and after the intervention. Cognitive performance was evaluated pre- and post-intervention using the Novel Object Recognition task. Paired t-tests and two-way ANOVA were used to compare the outcome parameters within and between groups. The non-menopausal IER group exhibited a marked reduction in body weight compared with the ad libitum group, improved fasting glucose levels, and enhanced insulin sensitivity. The IER group had higher HDL and, lower LDL levels than other groups. Despite these metabolic improvements, neither intervention conferred measurable gains in cognitive performance. These findings suggest that IER confers superior metabolic benefits over CER in the menopausal state and may represent a promising, practical dietary strategy for mitigating menopause-associated metabolic risks.

Introduction

Menopause is a physiological transition in women associated with a decline in estrogen levels, which results in metabolic and cognitive changes. As estrogen levels decline, women often develop insulin resistance together with disturbances in lipid metabolism [1]. These changes, in turn, predispose menopausal women to type 2 diabetes, metabolic syndrome, cardiovascular disease, and cognitive decline [2,3]

Various dietary strategies have proven to be of importance to maintain the metabolic parameters within normal limits during menopause[4]. Calorie Restriction (CR) is a non-pharmacological dietary intervention in which the average calorie intake is reduced without deprivation of essential nutrients[5]. Short-term calorie restriction has protective effects on cardiometabolic outcomes and mechanisms of cellular senescence [6,7]. Energy-restriction interventions in postmenopausal

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women have been shown to improve weight, visceral fat, lipid, and glucose measures[8,9]. There are two main types of CR: continuous energy restriction (CER), which involves a reduction in calorie intake by 20-40% daily, and intermittent energy restriction (IER), which alternates periods of normal eating with periods of 70%-80% calorie reduction. IER has shown a superior effect compared to CER on weight loss in younger women and post menopausal women [10,11].

Although both approaches have shown benefits, their comparative efficacy in the context of menopause remains unclear. Therefore, this study aims to compare the effects of intermittent and continuous energy restriction on metabolic outcomes (body weight, glucose-insulin homeostasis, lipid profile) and cognitive performance (novel object recognition task) using a validated menopausal rodent model.

Materials and Methods

This experimental protocol was designed, adhering to the guidelines established by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Ethical approval was obtained from the Institutional Animal Ethics Committee before study initiation.

Experimental Design (Figure 1): A total of 36 female Wistar rats, aged 3-4 months and weighing 150-175 g, were individually housed under standard laboratory conditions with a 12-hour light-dark cycle. During the acclimatization period, all animals were fed a normal chow diet. Following acclimatization, the experimental animals were randomly assigned to six groups: Menopause+Ad-libitum, Menopause+CER, Menopause+IER, Sham+Ad-libitum, Sham+CER, Sham+IER. Menopause was induced in 18 animals using intraperitoneal injections of VCD, while the remaining 18 non-menopausal animals received intraperitoneal injections of sesame oil as a vehicle control.

Figure 1

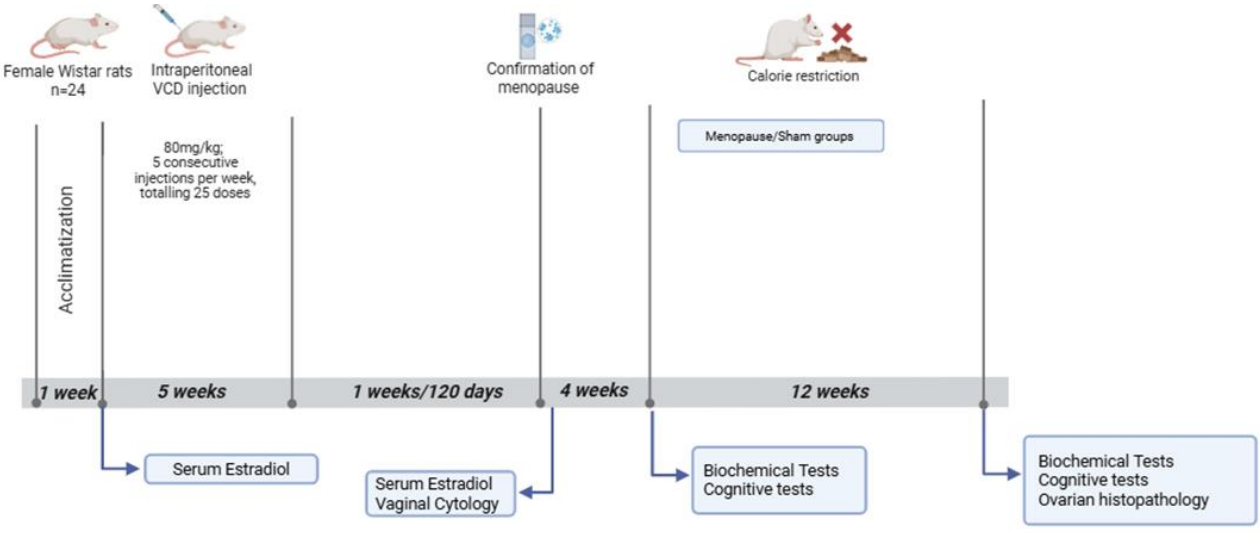

Figure 1: Experimental Design. VCD: 4-vinylcyclohexene dipoxide; CER: Continuous Energy Restriction; IER: Intermittent Energy Restriction.

Menopause induction

Menopause was induced by intraperitoneal administration of VCD (Sigma-Aldrich, St. Louis, MO, USA) intraperitoneally at a dosage of 80 mg/kg) dissolved in sesame oil. The treatment protocol involved five injections each week, for a total of twenty-five doses [12]. Induction of menopause was

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confirmed by tracking the estrous cycle using vaginal cytology, along with measuring plasma estradiol concentrations. The presence of a persistent diestrus phase for a minimum of 10 consecutive days as considered the successful induction of menopause, which was assessed 120 days after the last dose of VCD administration.

Calorie Restriction

Following a one-week recovery period post-induction, Calorie consumption wasestimated based on the daily food intake using equation (1):

$$\text{Energy intake (kJ/day)} = \frac{(\text{Weight of food given} - \text{Weight of food remaining}) \times \text{Energy density of food}}{\text{Number of rats per cage} \times \text{Number of days}}$$

The CER groups received a restricted diet that constituted a 25% reduction in the daily caloric intake throughout the 12-week study period. The IER groups underwent alternating periods of 75% restriction for 12 h followed by ad libitum feeding for another 12 h. The control groups were fed a standard rodent chow diet ad libitum throughout the study. All dietary formulations were designed to ensure adequate nutrition while conforming to specified calorie restriction protocols.

Measurement of outcome parameters

Body weight was measured weekly. Blood samples were collected from lightly anesthetised animals (isoflurane) pre-intervention (baseline) and post-intervention (after 12 weeks) via the retro-orbital route [13] to assess metabolic parameters, including fasting glucose, insulin, total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, using enzyme-linked immunosorbent assay (ELISA) kits. For each collection, approximately 0.5-0.7 mL of blood was obtained. Animals were monitored during recovery from anesthesia until fully ambulatory. Insulin resistance was estimated using the homeostasis model assessment-insulin resistance (HOMA-IR) calculated with equation (2)[12].

$$\text{HOMA-IR} = \frac{\text{Fasting insulin (}\mu\text{U/ml)} \times \text{Fasting}}{405} \quad (2)$$

Cognitive function was assessed before and after 12 weeks of energy restriction. Recognition memory was evaluated using the Novel Object Recognition task, according to previously published protocols [14].

Animals were monitored daily for general health, behaviour, and body weight throughout the 12-week intervention period. Any animal showing signs of distress or pain was evaluated by a veterinarian and, if necessary, removed from the study.

After the entire protocol, as per CPCSEA guidelines, the rats were anesthetised and euthanised. Ovaries were harvested from the rats for histological examination. Ovarian tissues were fixed in formalin, embedded in paraffin, and sectioned for hematoxylin and eosin (H&E) staining. Histological analysis focused on assessing follicular atresia by counting the number of primordial and primary follicles in the ovaries. A complete absence or significant reduction in these follicles was considered successful induction of menopause.

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Data were tested for normality using the Shapiro–Wilk test. Parametric or non-parametric tests were applied accordingly. To compare outcomes before and after energy restriction within groups, paired t-tests were used for normally distributed data, while the Wilcoxon signed-rank test was applied for non-normally distributed variables. Two-way ANOVA and post hoc tests were employed to assess the interaction effects of group and time on metabolic and lipid parameters. A significance level of $p < 0.05$ was considered statistically significant for all tests.

Results and Discussion

This study investigated the effects of continuous and intermittent energy restrictions on metabolic and cognitive parameters in a VCD-induced menopausal rat model. Menopause was successfully induced by VCD administration, as confirmed by hormonal, cytological, and histological analyses. Plasma estradiol levels decreased significantly after VCD treatment (pre: 653.14 ± 237.24 pg/mL; post: 370.32 ± 226.81 pg/mL, $p = 0.021$). Vaginal cytology showed a persistent diestrus phase in 66.7% of CER and 83.3% of IER animals. Histopathological examination revealed

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reduced follicular structures and fibrotic changes in atretic follicles, consistent with ovarian failure (Figure 2).

Figure 2

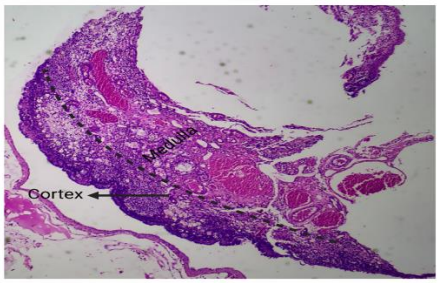

Figure 2: Ovarian Histopathology showing atretic follicles in cortex and congested blood vessels in medulla

Body weight Changes:

Weekly monitoring revealed no significant group differences in body weight during the first five weeks (Week 1: $F(5,30) = 1.12$, $p = 0.37$; Week 5: $F(5,30) = 1.56$, $p = 0.21$). From Week 6 onwards, the differences became statistically significant (Week 6: $F(5,30) = 3.42$, $p = 0.012$). By Week 6, group-wise differences became significant ($F(5,30) = 3.42$, $p = 0.012$), with the Sham + IER group showing attenuated weight gain (200.5 ± 8.6 g) compared to Sham + Ad-libitum (235.2 ± 10.1 g; $p = 0.01$). No consistent differences were observed in weights among the CER and Menopause groups.(Figure 3).

Figure 3

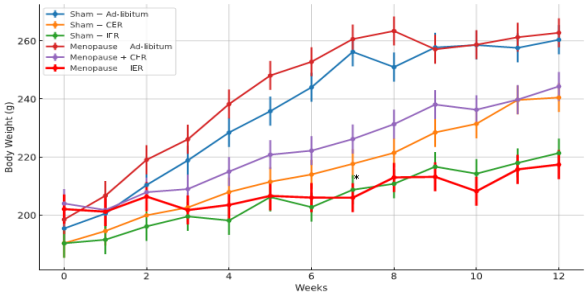

Figure 3: Effect of calorie restriction regimens on body weight over 12 weeks.Values are presented as mean ± SD (n=6 per group). Sham + ad-libitum and menopause + ad-libitum animals showed progressive weight gain. In contrast, IER groups, particularly menopause + IER (red line), maintained stable body weights with only minimal increases, reflecting effective weight control. One-way ANOVA confirmed group differences from* Week 6 onward ($p < 0.05$), post-hoc Tukey's analysis identifying significant weight reduction in the Sham + IER group compared to Sham+adlib group

Metabolic changes: (Table 1)

Glucose homeostasis: Fasting plasma glucose increased significantly from pre-intervention to post-intervention in both the sham + ad-libitum group ($p = 0.033$) and the menopause + ad-libitum group ($p = 0.04$). In contrast, menopause + IER animals exhibited a significant reduction in glucose ($p = 0.01$), while CER groups showed no significant changes. Changes in glucose were significantly different across groups ($F(5,84) = 3.64$, $p = 0.005$, $\eta^2 = 0.18$). Post-hoc pairwise comparisons (Bonferroni-adjusted) revealed that the menopause + IER group had significantly lower fasting glucose levels compared to menopause + ad-libitum ($p < 0.01$) and Sham animals ($p < 0.05$) after the intervention (Figure 4a).A significant reduction in fasting insulin in menopause + IER animals ($p = 0.01$), with no changes in other groups,was observed. Two-way ANOVA did not identify significant main effects, consistent with the paired analyses (Figure 4b). Analysis revealed that HOMA-IR increased significantly in menopause + ad-libitum animals ($p = 0.001$), while it decreased significantly in menopause + IER rats ($p = 0.004$). A borderline reduction was noted in sham + IER ($p = 0.057$). The two-way repeated-measures ANOVA showed the HOMA_IR changes varied among groups over time ($F(5,84) = 5.55$, $p < 0.001$, $\eta^2 = 0.25$). Post-hoc pairwise comparisons revealed that menopause + IER animals exhibited a significant reduction in HOMA-IR compared with menopause + ad-libitum ($p < 0.01$) and Sham groups ($p < 0.05$) following the intervention (Figure 4c).

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Figure 4

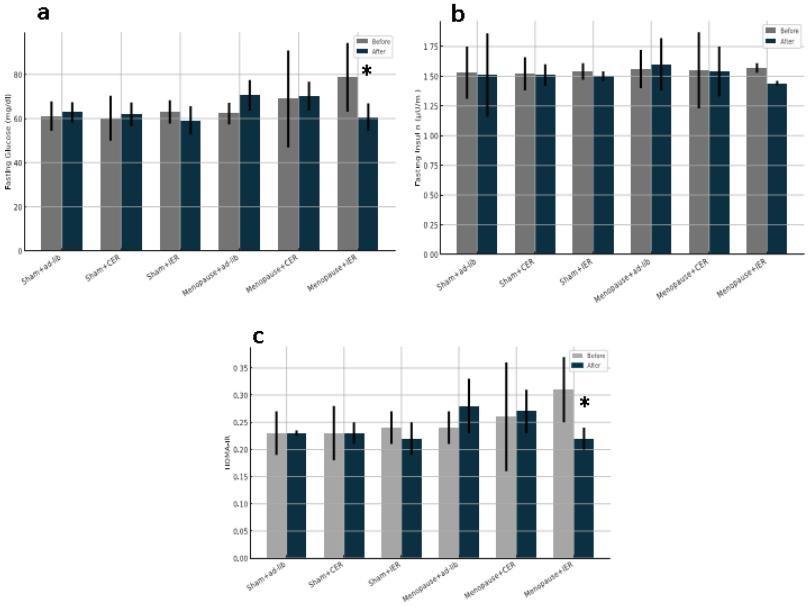

Figure 4. Effect of calorie restriction regimens on glycemic outcomes. (a) Fasting glucose (mg/dl); (b) Fasting insulin (µU/ml); (c) HOMA-IR index. Data are shown as mean ± SD (n-6 animals/group. CER: Continuous Energy Restriction; IER:IntermittentEnergy Restriction. Statistical analysis was performed using Two-Way Mixed ANOVA (Time × Group), followed by Tukey's post-hoc test. Significant within-group changes are indicated by *p < 0.05. Menopause + IER animals demonstrated significant reductions in fasting glucose and HOMA-IR compared with menopause + ad-libitum and Sham groups, while fasting insulin showed minimal change across groups

Lipid Parameters: Paired t-tests demonstrated significant decreases in HDL levels in sham + ad-libitum ($p = 0.045$) and menopause + ad-libitum ($p = 0.036$) groups, and a significant increase in menopause + IER animals ($p = 0.01$) (Table 1). The two-way ANOVA revealed a significant difference between the change in HDL levels among the groups over time ($F(5,84) \approx 3.8$, $p = 0.004$). Post-hoc analysis confirmed that menopause + IER rats had significantly higher HDL compared with both Sham and menopause + ad-libitum animals ($p < 0.01$) (Figure 5a). LDL levels were found to be significantly lower in (menopause IER) and (sham +IER) groups (Figure 5b), while no significant changes were detected in the other groups. The two-way ANOVA showed that changes in LDL levels across groups varied over time ($F(5,84) \approx 2.9$, $p = 0.02$ with post hoc analysis showing a significant reduction in the Menopause + IER group compared to other groups. Triglycerides and total cholesterol did not show any significant changes before and after intervention.

Figure 5

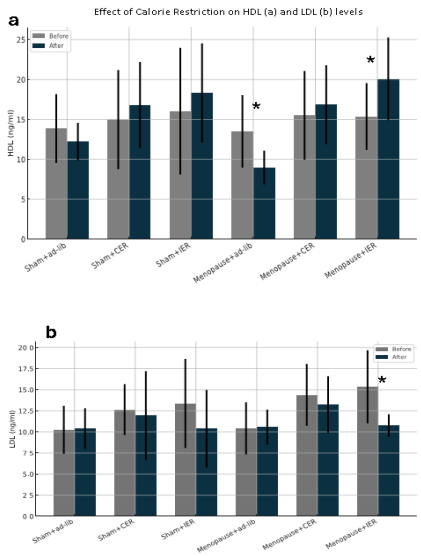

Figure 4: Effect of calorie restriction regimens on lipid profile. (a) HDL cholesterol (ng/ml); (b) LDL cholesterol (ng/ml); Data are expressed as mean ± SD

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(n =6 animals/group). CER = Continuous Energy Restriction; IER = Intermittent Energy Restriction. Two-Way Mixed ANOVA (Time × Group) was used, followed by Tukey's post-hoc test. Significant within-group differences are marked (*p < 0.05). Menopause + IER animals exhibited a significant increase in HDL, while menopause + ad-libitum rats showed significant HDL decline and reduction in LDL compared with menopause + ad-libitum and Sham groups,

Table 1: Comparison of Metabolic Parameters Pre- and Post-Intervention Across Study Groups (Mean ± SD)

Parameter	Group	Before energy restriction	After energy restriction	p-value
Fasting Glucose (mg/dl)	Sham+ad-libitum	61.20 ± 6.70	62.85 ± 4.65	0.033*
	Sham+CER	60.15 ±10.2	61.98± 5.27	0.289
	Sham+IER	63.09±5.32	59.20±6.43	0.969
	Menopause+adlibitum	62.33±4.91	70.55±5.90	0.04*
	Menopause +CER	68.93±21.94	70.24±6.54	0.89
	Menopause + IER	78.73±15.59	60.69±6.28	0.01*
Fasting Insulin (µU/ml)	Sham+ad-libitum	1.53±0.22	1.51 ± 0.35	0.80
	Sham+CER	1.52 ± 0.14	1.51±0.09	0.67
	Sham+IER	1.54 ± 0.07	1.50± 0.04	0.56
	Menopause+adlibitum	1.56±0.16	1.60±0.22	0.48
	Menopause +CER	1.55±0.32	1.54 ± 0.21	0.23
	Menopause + IER	1.57±0.04	1.44±0.02	0.01*
HOMA-IR	Sham+ad-libitum	0.23 ± 0.04	0.23 0.005	0.87
	Sham+CER	0.23 ±0.05	0.23± 0.02	0.18
	Sham+IER	0.24 ±0.03	0.22± 0.03	0.057
	Menopause+adlibitum	0.24 ± 0.03	0.28 ± 0.05	0.001*
	Menopause +CER	0.26 ± 0.10	0.27 ± 0.04	0.34
	Menopause + IER	0.31 ± 0.06	0.22 ± 0.02	0.004*
HDL(ng/ml)	Sham+ad-libitum	13.85 ± 4.32	12.21 ± 2.36	0.045*
	Sham+CER	14.98 ± 6.21	16.81 ±5.39	0.26
	Sham+IER	16.03 ± 7.94	18.31± 6.20	0.18
	Menopause+adlibitum	13.50±4.55	8.96±2.11	0.036*
	Menopause +CER	15.50±5.55	16.84±4.94	0.27
	Menopause + IER	15.36±4.18	20.08±5.19	0.01*
LDL (ng/ml)	Sham+ad-libitum	10.25 ± 2.85	10.41 ± 2.38	0.88

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	Sham+CER	12.63 ± 3.02	11.92 ±5.26	0.73
	Sham+IER	13.37 ± 5.27	10.37 ± 4.59	0.04*
	Menopause+adlibitum	10.42±3.09	10.57±2.06	0.91
	Menopause +CER	14.38±3.66	13.25±3.35	0.58
	Menopause + IER	15.34±4.33	10.77±1.33	0.02*
Triglycerides (ng/ml)	Sham+ad-libitum	24.52±1.81	23.09±1.87	0.43
	Sham+CER	22.98 ± 4.65	23.98 ± 6.02	0.67
	Sham+IER	23.98 ± 3.92	22.27 ± 8.57	0.11
	Menopause+adlibitum	25.21±1.68	25.56±2.54	0.64
	Menopause +CER	21.00±4.43	24.10±1.27	0.09
	Menopause + IER	22.35±2.79	26.09±10.77	0.35
Total cholesterol (ng/ml)	Sham+ad-libitum	29.99 ± 4.96	27.20 ± 4.47	0.73
	Sham+CER	32.16 ± 7.78	33.62 ± 6.94	0.47
	Sham+IER	33.19 ± 9.02	32.17 ± 7.84	0.21
	Menopause+adlibitum	28.97 ± 6.06	23.65 ± 3.55	0.058
	Menopause +CER	33.08 ± 7.91	34.92 ± 5.95	0.15
	Menopause + IER	34.15 ± 6.58	36.00 ± 7.02	0.18

CER: Continuous energy restriction, IER: Intermittent energy restriction; *significant difference at $p<0.05$

Cognitive test:

Novel Object Recognition testing revealed no significant differences in the discrimination index before and after intervention across any group (Table 2).

Table 2: Comparison of Differentiation Index following Novel Object Recognition Pre- and Post-Intervention Across Study Groups (Mean ± SD)

Group	ET Familiar Object (s) (Before CR) (Mean ± SD)	ET Novel Object (s) (Before CR) (Mean ± SD)	DI (Before CR) (Mean ± SD)	ET Familiar Object (s) (After CR) (Mean ± SD)	ET Novel Object (s) (After CR) (Mean ± SD)	DI (After CR) (Mean ± SD)	p-value
Sham+ad-libitum	13.4±3.5	14.7±2.3	0.46 ±0.10	10.7 ± 5.2	13.5 ± 4.5	0.3±0.19	0.3

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Sham+CER	15.25 ± 5.14	13.9 ±7.6	0.046±0.12	16.2 ± 3.7	17.6± 8.5	0.041±0.20	0.52
Sham+IER	13.6± 6.5	15.8±5.2	0.075±0.18	12.3 ± 4.7	15.3 ± 6.2	0.106±0.21	0.63
Menopause+ad-lib	12.6 ± 2.3	14.3 ± 2.6	1.7 ± 0.3	12.32 ± 2.28	13.49 ± 1.61	1.17 ± 2.17	0.77
Menopause + CER	12.0 ± 2.5	13.59 ± 2.38	1.59 ± 0.09	11.96 ± 2.26	13.60 ± 2.60	1.64 ± 0.66	0.43
Menopause +IER	12.11 ± 2.4	13.98 ± 2.08	1.87 ± 0.67	12.18 ± 2.45	14.16 ± 2.12	1.99 ± 0.91	0.65

ET: Exploration time, CR: Calorie restriction, DI: Discrimination index; CER: Continuous energy restriction, IER: Intermittent energy restriction; No significant difference

Discussion:

This study compared the effects of continuous and intermittent energy restriction in a VCD-induced menopausal rat model. The VCD-induced menopause model is a well-established method to study these changes, as it mimics the gradual onset of menopause and its metabolic consequences in rodents.

Menopause induction was confirmed by hormonal, cytological, and histological analyses. The hormonal confirmation of menopause via the decrease in estradiol levels supports the validity of our VCD-induced model, aligning with the existing literature that posits a similar profile of hormonal changes in menopausal women. The observed persistent diestrus phase in most rats and structural ovarian changes confirmed the induction of menopause in experimental animals.

The significant weight loss observed in the non-menopausal IER group compared with the non-menopausal ad libitum group is an important finding. This is consistent with previous studies [15], which suggested that IER may be superior to CER in terms of weight loss. However, in the menopausal group, though IER showed reduced weight gain compared to the menopausal adlibitum group, the effect was not significant. It is demonstrated that the loss of ovarian function promotes a diet-independent increase in adipose tissue mass and associated metabolic pathologies in mice [16]. The lack of significant differences among menopausal groups mostly reflects the estrogen-deficient state, characterized by reduced metabolic rate and increased adiposity. Intermittent energy restriction, however, attenuated this effect, as indicated by the absence of weight gain in the menopause + IER group. The differential weight responses may suggest the potential role of estrogen in modulating energy homeostasis, with distinct pathways engaged under estrogen-deficient conditions.

The present study showed that intermittent energy restriction (IER) improved metabolic outcomes more consistently than continuous restriction (CER) or ad-libitum feeding in the menopausal group. Specifically, IER lowered fasting glucose and improved insulin sensitivity when compared to the Menopause CER group. This aligns with previous research demonstrating the beneficial effects of intermittent fasting on glucose metabolism and insulin resistance[17]. Impaired glucose tolerance due to estrogen deficiency is mitigated by IER. The improvement in insulin sensitivity may prove beneficial in menopausal women who are predisposed to increased insulin resistance due to estrogen depletion [1]. Previous studies in menopausal rodent models with CER showed significant improvement in glucose homeostasis[18,19]. This finding is not seen in the present study. This can be explained as in the study calorie restriction was

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accounted for only 25% whereas as previous studies it was 30-40%.

The study showed IER increased HDL, while also decreasing LDL. CER did not produce significant improvements in lipid parameters. The greater improvements in HDL level observed in the IER group are consistent with recent research, suggesting that intermittent fasting may have beneficial effects on metabolic health [20,21]. These benefits could be explained by metabolic adaptations that occur during fasting, such as improved insulin signaling and more efficient lipid handling [22]. On the other hand, the relatively short duration of the intervention might account for the lack of significant changes observed in triglycerides and total cholesterol across the groups.

The absence of group-level cognitive benefits may be due to the relatively short intervention period, as twelve weeks may not have been sufficient to induce structural or synaptic changes detectable in behavioural tasks. Chronic stress from repeated handling and diet transitions may have attenuated potential cognitive gains.

This study has used a validated menopausal model, confirmed by estradiol levels, vaginal cytology, and histopathology. The inclusion of both menopausal and sham groups, combined with both CER and IER regimens, allowed comprehensive comparisons. These results highlight the potential of IER as a metabolic intervention in the menopausal state. If translated into clinical settings, IER could represent a simple, low-cost dietary strategy to reduce the risk of type 2 diabetes and cardiovascular disease in postmenopausal women.

Limitations of the study: Calorie intake was not measured, which restricts the interpretation of the observed body weight changes. In addition, the 12-week intervention period may have been too short to elicit measurable cognitive improvements.

Future studies should include biomarkers such as inflammatory cytokines and oxidative stress markers, to better explain how energy restriction affects metabolism and cognition. Translational studies in postmenopausal women are necessary, with clinical trials evaluating different IER regimens along with their safety and adherence.

Conclusions

This study demonstrated that intermittent energy restriction offers distinct metabolic benefits compared with continuous energy restriction in a VCD-induced menopausal rat model. IER enhances insulin sensitivity and improves lipid profiles, suggesting IER may help counter the metabolic challenges associated with menopause. Although cognitive performance remained unchanged, the significant metabolic improvements observed with IER suggest that it is a promising dietary intervention for managing the specific health risks associated with menopause. Future research should focus on elucidating the underlying mechanisms and translating these findings into clinical trials in menopausal women to optimize the dietary strategies for this population.

Ethics approval and consent to participate

Ethical clearance obtained from the Institutional Animal Ethics Committee IAEC approval number: (FFMC/ CPCSEA January 2021/2029)

List of abbreviations

CR: Calorie Restriction

CER: ContinuousEnergy Restriction

IER: Intermittent Energy Restriction

VCD: Vinylcyclohexenediepoxide

HDL: High-Density Lipoprotein

LDL: Low-Density Lipoprotein

ELISA: Enzyme-Linked Immunosorbent Assay

HOMA-IR: Homeostasis model assessment-insulin resistance.

Data Availability

The data underlying this study are not available in a public repository; however, they may be obtained from the corresponding author upon reasonable request.

Conflicts of Interest

The authors state no conflict of interest

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Authors' contributions

1. Neetha Shastry: Conceptualization, Investigation, Formal analysis, Writing-original draft preparation

2. Nicole Periera: Conceptualization, Data collection, cognitive test analysis

3. Cleeta Rebeiro: Biochemical parameter analysis

4. Hemalatha Bangera: Investigation, Histopathology

6. PraseenaKallingal: Data management and statistical analysis

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Supplementary Materials- Not applicable

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