Research article

Metabolic and functional factors associated with a change in resting metabolic rate among older adults with type 2 diabetes–results from the CEV-65 randomized trial

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ABSTRACT

Aims: This study evaluated the effects of circuit resistance training (CRT), a vegetarian/Mediterranean diet (VegMedD), and empagliflozin on Resting Metabolic Rate (RMR) in older adults with Type 2 Diabetes (T2DM).

Methods: 67 participants from CEV-65 trial ($\geq$65 years, 61 % female) were randomly assigned to CRT, VegMedD, or empagliflozin for 10 weeks. Assessments included RMR, medical, metabolic, nutritional, anthropometric and functional measurements. RMR changes were analyzed using paired t-tests, effect sizes, and repeated analysis of variance.

Results: No significant RMR differences were found between groups at baseline and post-intervention with minor RMR increases in 16 (CRT) to 25 % (VegMeD/empagliflozin). Factors correlating with RMR changes included sleep hours (r = 0.25), fat percentage (r = −0.27), leg strength (r = 0.29), and systolic blood pressure (r = 0.24). Except for blood pressure, all the other variables predicted RMR changes (R^2 = 0.22).

Conclusions: CRT, VegMedD, and empagliflozin showed similar effects on RMR in elderly with T2DM. Factors predicting changes in RMR are sleep hours, fat percentage, and leg strength, with those who increased/did not change their RMR presenting greater improvement in the aforementioned variables. These findings highlight the potential of these factors as therapeutic targets for improving metabolic health and warrant further investigation.

1. Introduction

Resting metabolic rate (RMR) is defined as the minimal rate of metabolism necessary to maintain life and accounts for 60–70 % of total energy expenditure in most individuals [1]. Increasing age causes a decrease in RMR, mainly due to changes in body composition (such as a decrease in lean mass) [2]. More specifically, from the age of 20, several studies have reported a progressive decline in RMR of approximately 1–2% per decade [3].

In older adults with type 2 diabetes (T2DM), who represent a significantly growing population, RMR may be higher than in older adults without diabetes [4,5] due to the endogenous increase in glucose production [6] or the increased energy costs brought about by the inflammatory status associated with T2DM [7]. Nevertheless, any decrease in RMR due to reduced caloric intake may have significant consequences for older adults with T2DM, as it makes it difficult to achieve weight loss [8] - one of the leading but challenging therapeutic goals in this population. A previous analysis from our group highlighted discrepancies in RMR estimation formulas for older adults with T2DM, underscoring the need for tailored metabolic interventions [9].

A diet based on caloric deficit, which is a common therapy for T2DM and aims to cause weight loss, comes with a "metabolic cost" (metabolic adaptation) - a decrease in RMR in older adults [8,10]. On the other hand, weight loss generally promotes better glycemic control [11]. These two facts pose a therapeutic dilemma: does a hypocaloric diet constitute a leading strategy for weight loss in diabetics, especially since a decrease in RMR causes an even greater decrease in caloric demand [12] and activates compensatory mechanisms of increased hunger [13]? However, diets can be based on a qualitative and less quantitative principle; that is, not on less caloric intake (if any) but on changing the composition of the diet while aiming for a beneficial glycemic effect and lowering the risk of diabetes complications. *The Mediterranean diet* has been described as having such potential and has been shown to be efficient for glycemic control [14] and, more importantly, lowering the risk of cardiovascular disease [15]. This diet emphasizes quality over quantity and is considered to be based on eating patterns rather than macronutrient or energy-based [16]. Such a diet pattern and its components may be beneficial for promoting satiety [17], which may minimize the effects of metabolic adaptation. The Mediterranean diet is rich in unsaturated fats, fiber, and antioxidants which offer metabolic benefits, including improved glycemic control and reduced inflammation [18], which as mentioned may modulate RMR changes among patients with T2DM [6,7]. Moreover, studies examining its effect on the change in RMR are scarce [19,20] and, to the best of our knowledge, have not been conducted on elderly individuals with diabetes.

Empagliflozin is an oral glucose-lowering drug that was approved for clinical use in 2014 [21]. It belongs to the sodium-glucose cotransporter 2 (SGLT2) inhibitor group. Empagliflozin causes increased urinary glucose excretion, improved glycemic control, reduced glucotoxicity and insulin resistance as well as small weight loss ($\approx$1–2 kg) and decrease in waist circumference (WC) [22]. In light of the evidence regarding its effect on various morbid outcomes and reducing the risk of mortality, the prescription of this drug and other SGLT2 inhibitors is increasing, with this therapeutic drug family established as a first or second line of treatment for T2DM [23]. Empagliflozin affects metabolism by promoting the above-mentioned changes which may contribute to changes in RMR as recently described, although direct effects on RMR remain inconclusive and require further investigation [24]. Also, effects on RMR following this treatment have not been described in older adults with T2DM, the population that constitutes most diabetic patients.

Resistance training is the best strategy for maintaining muscle mass and thus slowing the decline in RMR over time [25]. Therefore, this form of training is part of weight loss recommendations for older adults who are overweight or obese [26]. Resistance training was effective at increasing muscle mass and improving insulin sensitivity in older adults with T2DM [27]. However, such improvements in adults and young older adults with T2DM do not necessarily translate into an increase in RMR following six months of exercise (resistance, aerobic or combined) [28]. The effect of resistance training compared to a diet that is not hypocaloric centered, such as the Mediterranean diet or to the commonly prescribed empagliflozin, has not yet been tested in older adults with T2DM.

The goals of the current study are to describe, for the first time to the best of our knowledge, the effects of circuit resistance training (CRT), drug therapy with empagliflozin and a Mediterranean-vegetarian diet on RMR over 10 weeks in an independent community of older adults with T2DM - as part of the randomized clinical CEV-65 trial [29]. These treatments share some similarities in terms of their efficacy and mechanism, as they all reduce insulin resistance and lower circulating insulin levels. In addition, the study goals were to identify factors associated with a change in RMR in this population within the three treatments described – all significantly representing primary treatments for diabetes.

2. Subjects, materials and methods

2.1. Sample and procedure

This secondary analysis is part of the CEV-65 randomized (1:1:1) parallel clinical trial (Buch et al., 2019) at Tel-Aviv Medical Center, which focused on older adults with T2DM [29]. The present study evaluated home-based CRT, empagliflozin, and a vegetarian/Mediterranean diet (VegMedD) for 10 weeks. The initial participants were analyzed within the first 10 weeks after the minimal number of dropouts was reached (n = 67). The study was approved by the Tel-Aviv Sourasky Medical Center Institutional Review Board and registered at clinicaltrials.gov (NCT03560375). Informed consent was obtained from all participants.

2.2. Eligibility criteria

Participants were older than 65 years, engaged in limited aerobic activity, and had hemoglobin A1C between 6.5 % and 8 %.

Exclusion criteria included recent resistance training, steroid use, severe health conditions, and SGLT-2 inhibitor treatment (for detailed information [29]). Out of 150 candidates, 100 were recruited based on American Diabetes Association guidelines. The first phase concluded with 83 completions. Sixteen participants were excluded due to high variance in RMR measurements (n = 9) [30] or missing tests (n = 7), focusing on the most accurate and consistent data.

2.3. Interventions of CEV-65 (CRT, empagliflozin, VegMedD)

The CRT group was developed after a systematic review and meta-analysis [31], and the CRT was home-based with minimal supervision (two sessions [<15 % of sessions] based on our previous report [32]). It involved 10 resistance exercises, each with 12–15 repetitions at moderate intensity, forming a circuit. Participants progressed from one to three circuits per session, each lasting approximately 30 min. Compliance was tracked through participant reports and a dedicated booklet, with good adherence defined as completing at least two-thirds of planned workouts. A detailed training program can be found in Ref. [29].

Empagliflozin: Participants were administered 10 mg of empagliflozin daily, preferably in the morning, by the study physician (R. E.). Compliance was determined by tablet recall after 10 weeks, with good compliance being the consumption of at least 80 % of the medication.

VegMedD: This modified Mediterranean diet was ad libitum and fat-based (mainly from plants such as nuts or seeds or from their spreads and from avocado), aiming for a minimum protein intake of 1 gr/kg/day. It promoted legumes (1–2 servings/d), dairy (yogurt, ricotta cheese), eggs, and fish, while meat and poultry were recommended to be avoided. Carbohydrate intake was restricted to 3 servings per main meal for men and 2 for women, plus 1 serving per intermediate meal. Participants used checklists for 15-g carbohydrate and 10-g protein portions, with adherence assessed by a questionnaire based on the PREDIMED study; a score ≥9 indicated good compliance [15,33].

General Compliance: Participants were instructed not to initiate other lifestyle or medical changes during the trial. Adherence to this request was monitored bimonthly via phone calls. Protocol deviation was comparable across groups (participants evaluated the protocol: n = 4, n = 3 and n = 3 for the CRT, empagliflozin and VegMedD groups, respectively, at week 10; data not shown).

2.4. Main outcome - RMR measurement

RMR was measured via indirect calorimetry (considered the gold standard [34]) using an open-circuit ventilated canopy measurement device (Quark RMR; COSMED Srl, Rome, Italy). The Quark RMR calculates RMR through the measurement of the volume of oxygen inhaled (VO_2) and the volume of carbon dioxide exhaled (VCO_2), together with other ventilatory parameters. These values were also used to calculate the respiratory quotient ($RQ = VCO_2/VO_2$). A standardized protocol was implemented with a warmup and calibration prior to each test session by using a gas mixture of 16 % oxygen and 5 % carbon dioxide balanced with nitrogen.

Tests were performed with the participants in a supine position after a 5-min rest period in a dimly lit room at a temperature of 21–22 °C. All measurements were conducted in the morning (08.30–10.00 a.m.) after a 12-h fast and 12-h restriction of any strenuous exercise. The participants were instructed to avoid speaking and to relax without falling asleep. Data were collected over a 10–15 min interval, where the first 5 min were used for familiarization and not counted.

According to current recommendations, RMR was considered valid if a steady state was achieved, defined as a 5-min period with less than 10 % coefficient of variation [(CV; standard deviation x (mean of individual replicate measures) × 100] for VO_2 and VCO_2 [30]. After reaching a steady state, the measurements were stopped. If a steady state was not reached, the test was aborted after 15 min to keep the subject burden as low as possible.

2.5. Other measurements

The CEV-65 study protocol [29] details the measurements used. The study evaluated participants' lifestyle habits, diabetes complications, and medication history. BMI, body composition (including fat percentage), and waist circumference were measured using standardized methods and bioelectrical impedance analysis (BIA). Glycemic control was assessed through hemoglobin A1C and insulin levels, while blood pressure was monitored using an automated device. Functional characteristics were examined via the Comprehensive Functional Assessment Questionnaire, dynamometer measurements of hand grip and knee extension strength. Nutritional intake was analyzed through a 24-h recall, focusing on energy, carbohydrate, protein, and fat intake.

2.6. Statistical analysis

For detailed statistical methodologies please refer to the supplementary file. Statistical analyses were conducted using IBM SPSS Statistics version 29, with a significance threshold of $p < 0.05$. To assess the assumption of normality, we applied the Shapiro-Wilk test. A non-significant result in this test indicates that the assumption of normality is met. The analyses showed that the study variables were normally distributed, allowing to use parametric statistical methods. We reported continuous variables as mean ± SD and categorical variables as percentages, focusing on participants with valid RMR measurements who completed the 10-week intervention across the CRT, empagliflozin, and VegMedD groups.

We assessed baseline characteristics and intervention compliance using one-way ANOVA or chi-square tests. Changes in RMR were visualized using box and whisker plots and analyzed with paired t-tests, including effect size evaluation. Group comparisons of RMR changes utilized one-way ANOVA, and we categorized RMR change status for further analyses.

Correlations between RMR changes and potential predictors were analyzed, with significant factors entered into a multiple linear regression model to identify predictors of RMR changes. We addressed multicollinearity and compared predictor variables between groups with different RMR change statuses.

3. Results

3.1. Study participants' characteristics and compliance with intervention rates

Baseline characteristics of the study groups are described in Table 1. The study analyzed 67 participants (61 % female, mean age 70.53 years) with no significant differences in baseline characteristics, medical and clinical backgrounds, or functional characteristics across groups. Notable differences included higher abdominal obesity in the Empagliflozin group and lower mean diastolic blood pressure compared to CRT and VegMedD groups. Carbohydrate intake also varied significantly between groups. High compliance with

Table 1
Participant characteristics at baseline stratified by study group.

Variables	Total sample (n = 67): Mean (SD) OR %	Circuit resistance training (n = 19): Mean (SD) OR %	Empagliflozin (n = 24): Mean (SD) OR %	Vegeterranean diet (n = 24): Mean (SD) OR %
Sociodemographic characteristics				
Age (years): mean (SD)	70.53 (4.37)	72.12 (4.00)	69.99 (4.67)	69.80 (4.17)
Sex (females): %	61	53	67	63
Medical and clinical background				
Smokers (current): %	4.5	0	0	12.5
Physically active (yes)[d]: %	54	68	38	58
Sleep (hours/night): mean (SD)	6.57 (1.56)	6.86 (1.10)	6.63 (1.68)	6.27 (1.76)
Diabetes complications (yes): %	36	32	25	50
Polypharmacy (≥5 prescribed drugs): %	64	74	54	67
Insulin user (long or short): %	26	13	30	35
Glucagon-like peptide-1 analog users: %	19	16	17	25
Metabolic and anthropometric characteristics				
Body mass index (kg/m^2): mean (SD)	31.5 (4.73)	31.6 (3.08)	32.03 (6.11)*	30.89 (4.34)*
Waist circumference (cm): mean (SD)	108.92 (12.31)	109.09 (9.54)[a]	108.89 (13.5)	108.81 (13.47)*
Waist circumference ≥88 cm women: %	98	100	100	93
Waist circumference ≥102 cm men (%): %	89	**100**[b]	**63**[a,c]	**100**[b]
Total body fat: %	40.91 (6.47)	40.37 (6.49)	41.19 (7.87)*	41.06 (5.05)*
Visceral fat area (cm^2): mean (SD)	178.56 (44.15)	182 (41.79)	177.03 (53.78)*	177.29 (36.32)*
Skeletal muscle mass (kg): mean (SD)	27.04 (5.31)	28.07 (4.78)	26.56 (4.92)	26.71 (6.13)
Lean body mass – total (kg): mean (SD)	43.10 (8.74)	42.57 (9.72)	42.11 (8.16)	44.73 (8.39)
Lean body mass – arms (kg): mean (SD)	5.63 (1.39)	5.47 (1.47)	5.54 (1.35)	5.91 (1.36)
Lean body mass – legs (kg): mean (SD)	14.75 (3.19)	14.49 (3.82)	14.40 (2.50)	15.42 (3.15)
Lean body mass – trunk (kg): mean (SD)	22.87 (4.28)	22.60 (4.54)	22.44 (4.26)	23.61 (4.11)
Hemoglobin - A1C: mean (SD)	7.4 (1.14)	7.00 (0.75)	7.4 (0.92)*	7.7 (1.5)*
Insulin (MCU/ml): mean (SD)	16.58 (10.64)	15.77 (8.85)	18.62 (12.25)	15.31 (10.45)
Systolic blood pressure (mmHg): mean (SD)	134.25 (14.31)	133.21 (13.21)	132.22 (13.11)	137.67 (15.12)*
Diastolic blood pressure (mmHg): mean (SD)	71.23 (11.78)	70.00 (8.12)	**67.11 (11.00)**[c]	**74.66 (11.11)**[b]*
Functional characteristics				
Functional scoring[e]: mean (SD)	12.11 (3.72)	11.63 (2.43)	12.65 (5.44)	11.96 (2.39)
Problems walking or using stairs (yes): %	12	21	9	9
Hang grip maximal strength (kg): mean (SD)	31.20 (9.37)	30.10 (8.88)	30.11 (9.14)	33.52 (10.0)
Maximal extension isometric leg strength (kg)	27.40 (10.00)	27.08 (10.40)	27.46 (10.57)	27.45 (9.41)
Nutritional characteristics				
Energy intake (kcals)[f]: mean (SD)	1324.53 (469.82)	1358.00 (606.64)	1171.05 (309.25)	1433.63 (430.94)
Carbohydrate intake (%/kcals): mean (SD)	45.66 (32.11)	**40.65 (9.90)**[c]	42.89 (10.22)	**50.55 (45.1)**[a]
Protein intake (g/kg body weight): mean (SD)	1.79 (1.03)	1.88 (1.08)	1.92 (1.12)	1.57 (0.86)
Total fat intake (%/kcals): mean (SD)	37.45 (10.11)	36.76 (7.67)	36.12 (12.88)	38.67 (10.01)
Adherence to the Mediterranean diet (score)[g]: mean (SD)	9.59 (1.86)	9.79 (1.72)	9.65 (1.97)	9.38 (1.91)

Notes.*indicates significant within-group changes from baseline to week 10; for continuous variables, one-way analysis of variance was used to test baseline between-group differences. For categorical variables, the chi-square test was performed.

[a] statistically significantly different from "Circuit resistance training" group (p < 0.05; 2-tailed).

[b] statistically significantly different from "Empagliflozin" group (p < 0.05; 2-tailed).

[c] statistically significantly different from "Vegeterranean diet" group (p < 0.05; 2-tailed); SD, standard deviation.

[d] perform at least 10 min of intentional physical activity of any kind.

[e] using the Comprehensive Functional Assessment Questionnaire to assess physical function state using questions on activities of daily living. The score ranges from 0 to 36 (a higher score indicates higher functional impairment) (see suplementaty methods).

[f] based on standardized 24-hr recall.

[g] based on a valid screening tool for assessing Mediterranean Diet adherence—a score ≥9 was considered good adherence.

interventions was observed at week 10 across all groups.

3.2. Resting metabolic rate at baseline and after 10 weeks

Energy expenditure expressed by measured RMR was similar across groups at both baseline and week 10. Similarly, the three groups did not present statistically significant changes from baseline to week 10 in RMR ($p > 0.05$), with effect sizes being trivial in the VegMedD group (effect size = −0.13) and CRT group (effect size = 0.01) and slightly higher (small effect size) in the Empagliflozin group (effect size = −0.20). For additional information, refer to Fig. 1A.

Significant improvements in BMI and fat percentage were noted in the VegMedD and Empagliflozin groups (BMI: 0.84 ± 0.69 and -0.56 ± 0.71 kg/m^2, respectively; $p < 0.05$; VegMedD vs. CRT, $p = 0.002$). Conversely, skeletal muscle mass remained stable across all interventions. Notable within-group decreases in HbA1c were observed in the Empagliflozin and VegMedD groups (-0.4 ± 0.8 and -0.7 ± 0.9 %, respectively; $p < 0.05$ for both), while insulin levels stayed constant. Only the VegMedD group experienced a significant reduction in systolic blood pressure (-6.83 ± 15.64 mm/Hg, $p < 0.05$). There were no notable changes in functional or nutritional characteristics across the groups.

In the next step, analysis was also conducted separately for males and females (Table 2). The results indicated that in comparison to females, baseline and week 10 RMR for males were statistically significantly higher in the VegMedD and CRT groups (p range: 0.002 to 0.01), whereas in the Empagliflozin group, RMR was higher only at week 10 ($p = 0.05$). However, in all groups, both the female and male effect sizes were trivial to small and ranged from −0.01 for CRT-males to 0.25 for CRT-females. A similar analysis was also conducted for RQ. Like for RMR, several between-sex differences were observed. First, in the VegMed group, in comparison to females, males had a smaller change in RQ (−0.00 in males vs. −0.2 in females). In contrast, in the Empagliflozin group, for males the changes were greater (−0.06 in males vs. 0.03 in females). However, in this study group, baseline RQ for males was higher than in females (0.82
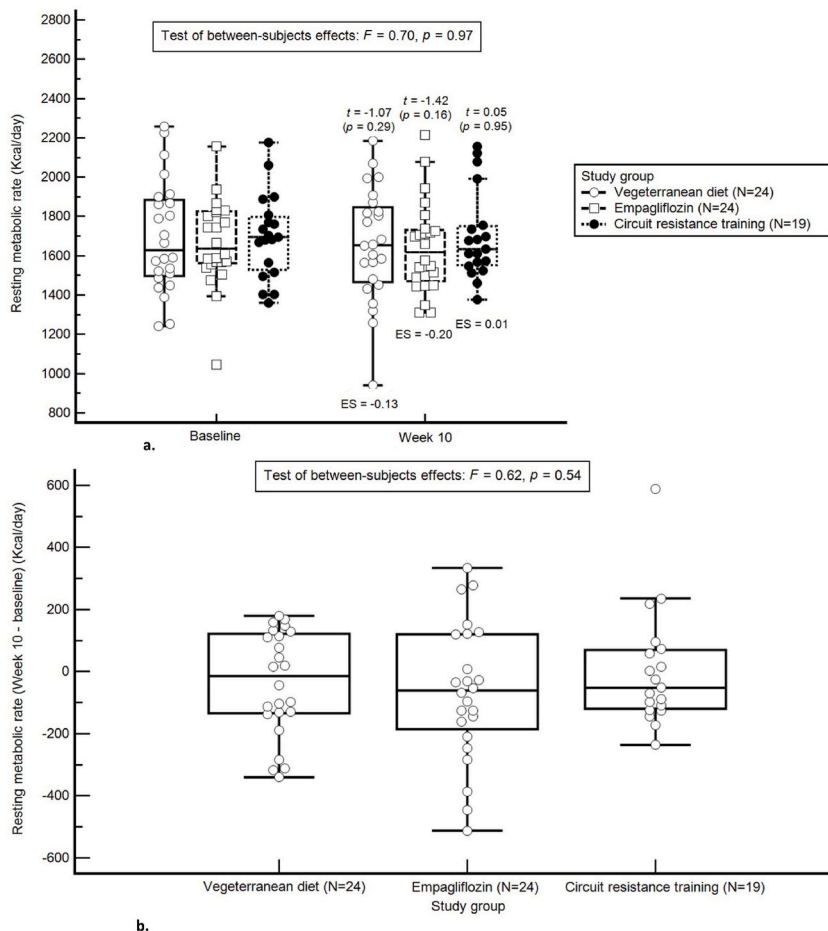

Fig. 1. Resting metabolic rate at baseline and week 10 (A) and from baseline to week 10 (B): within- and between-group differences. Notes. The box represents the interquartile range, the line within indicates the median, and separate points show outliers. The t values are from t-tests, and ES denotes effect size, with values < 0.20 being trivial, 0.20–0.50 small, 0.51–0.80 moderate, and >0.80 large. A) shows RMR at the two time points, B) illustrates the mean RMR changes. The F values represents between-subjects effects using One Way Analysis of Variance.

Table 2
Resting metabolic rate at baseline, week 10 and changes: between-sex differences.

	Vegeteranean diet (N = 24)			Empagliflozin (N = 24)			Circuit resistance training (N = 19)		
	Baseline: Mean (SD)	Week 10: Mean (SD)	Change: Mean (SD)	Baseline: Mean (SD)	Week 10: Mean (SD)	Change: Mean (SD)	Baseline: Mean (SD)	Week 10: Mean (SD)	Change: Mean (SD)
Resting metabolic rate									
Males	1886.11 (233.28)	1873.11 (224.56)	−13.00 (126.21)	1852.62 (408.30)	1792.62 (280.38)	−60.00 (326.04)	1828 (215.79)	1833.32 (250.07)	22.33 (256.17)
Effect size	0.05			0.14			−0.01		
Females	1581.46 (250.68)	1529.66 (243.90)	−51.80 (193.35)	1601.23 (242.37)	1563.12 (161.68)	−38.00 (158.23)	1611.28 (147.25)	1542.90 (170.98)	−15.52 (110.72)
Effect size	0.19			0.16				0.25	
t value (*p* value)	**−2.96 (0.007)**	**−3.45 (0.002)**	−0.52 (0.60)	−1.56 (0.13)	**−2.09 (0.05)**	−0.04 (0.96)	**−2.59 (0.01)**	**−2.94 (0.008)**	−0.41 (0.68)
Respiratory quotient									
Males	0.77 (0.07)	0.76 (0.10)	−0.00 (0.07)	0.82 (0.07)	0.75 (0.06)	−0.06 (0.07)	0.75 (0.05)	0.73 (0.05)	−0.09 (0.26)
Effect size	0.10			0.9				0.36	
Females	0.78 (0.06)	0.75 (0.05)	−0.2 (0.06)	0.72 (0.05)	0.75 (0.10)	0.03 (0.08)	0.80 (0.11)	0.77 (0.04)	−0.16 (0.28)
Effect size	0.49			−0.34				0.33	
t value (*p* value)	0.00 (0.99)	−0.28 (0.78)	**−8.49 (<0.001)**	**−3.67 (0.001)**	0.00 (1.00)	**2.67 (0.01)**	1.30 (0.20)	1.97 (0.06)	−0.57 (0.56)

Notes: SD, standard deviation; effect size: generally, values < 0.20 are considered trivial effect sizes; between 0.20 and 0.50, small effect sizes; between 0.51 and 0.80, moderate effect sizes; and >0.80, large effect sizes.

in males vs. 0.72 in females). In terms of effect sizes, among males, the effect size ranged from 0.10 (trivial) in the VegMed group to 0.9 in the Empagliflozin group. Among females, all effect sizes were small (0.20–0.50).

Mean changes in RMR from baseline to week 10 were also calculated and are presented graphically in Fig. 1B. No statistically significant between-group mean changes were observed (F = 0.62, p = 0.54). However, the graphic illustration of the results indicates that the change range in the Empagliflzin group (−500 to 350 Kcal/day) appears to be greater than that in the other two study groups (−380 to 190 Kcal/day and −220 to 220 Kcal/day in the VegMedD and CRT groups, respectively).

When the data were nalyzed separately for males and females, no statistically significant differences between males and females in mean RMR changes were observed (Table 2).

Finally, all study participants were grouped according to their baseline to week 10 RMR change status; namely, no change, increase or decrease. When analysis was conducted for the entire sample in each study group, no statistically significant between-group differences were observed in those presenting an increase in RMR (25 % in both the VegMedD and Empagliflozin groups and 16 % in the
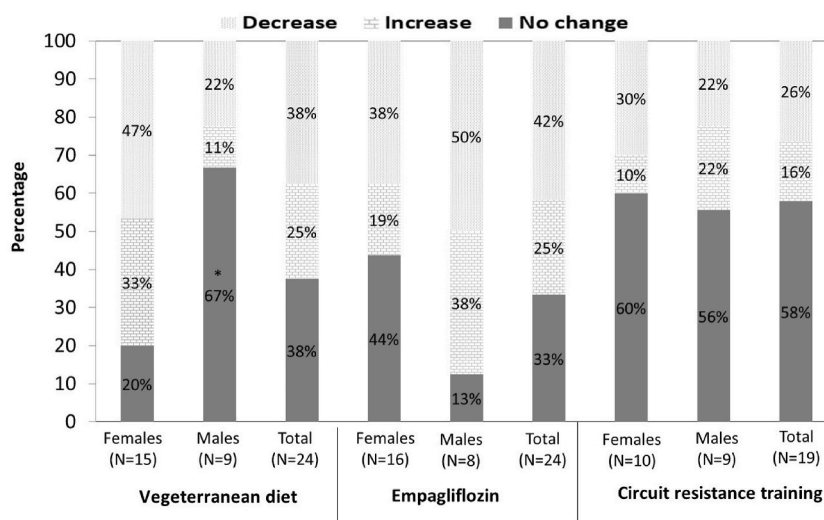

Fig. 2. Change in resting metabolic rate from baseline to week 10: within- and between-group differences. Notes: *Statistically significant difference between males and females (p < 0.05; 2-tailed); total group: no between-group differences were observed in the prevalence of resting metabolic rate change groups.

CRT group). When analyses were conducted for males and females separately, the only between-sex difference was observed in the VegMedD, in which, in comparison to females, a greater percentage of males presented no changes in RMR (20 and 67 %, respectively). For additional information, refer to Fig. 2.

3.3. Factors associated with changes in RMR

Considering the overall null between-group differences at baseline and week 10 and changes in RMR, all subsequent analyses were conducted for the entire group to better understand the factors associated with changes in RMR. First, correlations between participants' characteristics and RMR change (continuous variable) were examined (Table S1). A total of four factors were significantly correlated with changes in RMR, namely, sleep hours (r = 0.25, p = 0.04), total body fat percentage (r = −0.27, p = 0.02), maximal extension isometric leg strength (r = 0.29, p = 0.01), and systolic blood pressure (r = 0.24, p = 0.05). No categorical variables evaluated differed in terms of mean changes in RMR (Table S2).

3.4. Factors predicting changes in RMR

All four variables associated with changes in RMR were entered into a multiple linear regression analysis model (Table 3). Overall, the model explained 22 % of the variance in the RMR changes (F-ratio = 7.14, p = 0.001; R^2 adjusted = 0.22). Three out of the four factors were found to be significant predictors, namely, maximal extension isometric leg strength change (t = 2.16, p = 0.03), total body fat percent change (t = −2.77, p = 0.007), and sleep hours (t = 2.71, p = 0.008).

To better understand the impact of the significant RMR change predictors, the differences in those variables between participants who presented a decrease in RMR and those who increased or did not change their RMR were compared. Significant between-group differences were observed for all three significant RMR change predictors. For further details, refer to Table S3.

4. Discussion

In this study, we compared the effects of CRT, empagliflozin, and VegMedD on RMR in older adults with T2DM. None of these treatments significantly changed the RMR after 10 weeks. This finding contrasts with that of Daniele et al., who reported increased RMR in individuals fed a Mediterranean diet, which was attributed to improved microbiota in younger subjects [20]. In our study, 68 % of the VegMedD participants either increased or maintained their RMR, potentially due to a reduced fat percentage (−1.69 ± 1.42 %, p < 0.05). Notably, males in this group showed less RMR reduction than females (22 % vs 47 %, respectively; p < 0.05), suggesting gender differences in response.

In contrast to the findings of Javed et al. on the ability of empagliflozin to reduce the basal metabolic rate by −1.8 ± 2.9 % in polycystic ovary syndrome patients after 12 weeks [35], our study revealed no significant change in RMR in T2DM patients. Empagliflozin led to a 1–2 kg weight loss (mostly fat), which was also observed in our cohort (% fat loss of −0.70 ± 1.28, p < 0.05) without affecting knee extension strength (−2±8 kg, NS). This finding aligns with the notion that fat loss is associated with an increase in RMR, yet the overall impact on RMR was not significant, indicating the complex interplay of empagliflozin's effects. Additionally, the change in RMR with empagliflozin may be of interest since this drug has been found to reduce skeletal muscle mass after a 20-week intervention (~1.6 %) [36], a finding not shared by our research.

Contrary to expectations [25], our study found no significant increase in RMR following 10 weeks of CRT, although there was a favorable trend, with the lowest proportion of participants experiencing a decrease in RMR (26 % vs. 38 % and 42 % in the VegMedD and empagliflozin groups, respectively; NS). Notably, exercising males showed a slight increase in RMR compared to females (+22 Kcals vs a decrease of 16 Kcals, respectively; NS). The absence of a significant change in RMR within the CRT group could be due to minimal changes in skeletal muscle mass and body fat percentage (0.01 ± 0.72 kg and - 0.27 ± 1.95 % fat, respectively; NS for both). This outcome reflects the real-life applicability of home-based, minimally supervised CRT, which differs from more intensive, gym-based training, as expressed in our previous report [32]. In studies of adults and young older adults with T2DM, even a longer, more intense resistance training regimen did not significantly affect RMR, despite positive body composition changes [28]. Similarly, physical activity interventions of comparable or shorter lengths only impacted RMR when accompanied by body composition changes

Table 3
Summary of multiple linear regression analysis for predicting changes in resting metabolic rate from baseline to week 10.

Predictors	Coefficient	Standard Error	t value	p value	variance of inflation factor
Constant	−230.36	–	–	–	–
Maximal extension isometric leg strength -change (kg)	**10.95**	**5.06**	**2.16**	**0.03**	**1.3**
Total body fat -change (%)	**−299.04**	**107.74**	**−2.77**	**0.007**	**1.2**
Systolic blood pressure – change (mmHg)	2.10	1.61	1.20	0.20	1.2
Sleep (hours/night)	**40.23**	**14.84**	**2.71**	**0.008**	**1.3**
Model summary	*F-ratio = 7.14, p = 0.001, R^2 adjusted = 0.22*				

Note: Only variables that significantly correlated with changes in resting metabolic rate were included in the model; all predictors are continues variables; multicollinearity exists when the variance inflation factor is greater than 5 (further investigation is warranted) to 10 (serious multicollinearity requiring correction [53]).

[37]. This finding suggested that resistance training alone may not be sufficient to significantly alter RMR, highlighting the complex interplay between exercise, body composition, and metabolic rate.

Our study revealed a unique relationship between RMR changes and specific factors in older adults with T2DM. Multivariate analysis showed that each 1 kg increase in knee extension strength led to an increase in RMR of approximately 11 Kcals, while an extra hour of sleep raised RMR by approximately 40 Kcals. Conversely, a 1 % increase in body fat reduced RMR by 300 Kcals. The finding on leg strength to predict RMR is of special interest, as studies have demonstrated that decreased RMR is associated with sarcopenia or with loss of muscle mass [38,39]. However, little is known about the relationship between RMR and muscle strength. Evaluating this relationship is of special importance because muscle strength and muscle mass do not necessarily correlate with or affect each other [40]. Leg strength is crucial in diagnosing functional disorders and sarcopenia, including obesity/diabetes [41,42], and is even superior to hand grip strength in the screening of sarcopenia in older adults with T2DM based on our previous analysis [43]. These findings suggest that leg strength might be a better intervention target for moderate age-related RMR decline. The differences of 3 kg in maximal leg strength between those who increased or did not change RMR and those who decreased RMR are achievable through strength training in diabetic older adults [44,45] and through CRT in older adults, as we showed in a previous meta-analysis [31]. Our results suggest that knee extension strength could be an effective screening tool for determining the risk of RMR reduction in older adults with T2DM.

The inverse association between changes in RMR and changes in % fat may indicate a possible metabolic emphasis indicating an advantage of changing the body composition of fat over changes in muscle in the context of changing RMR in elderly individuals with T2DM. The difference found in this study between participants who increased or did not change RMR and those whose RMR decreased was ≈2 % fat—an achievable difference in T2DM treatments. Body composition criteria, including body fat and body fat percentage, are well recognized factors explaining RMR even in diabetic patients with complications [46]; however, the superiority of fat percentage change over lean change in terms of RMR is somewhat surprising. The favorable possible superior effect of fat percentage over lean mass on RMR may be due to a "confounding effect" of lean mass preservation. Our possible explanation for this confounding effect of lean mass is based on observations of the long-term effectiveness of weight loss programs with respect to RMR preservation, where the loss of fat mass while maintaining lean mass (resulting in a reduction in fat percentage) may be beneficial [47]. A potential mechanistic explanation for the superior effect of fat percentage in our population is that a reduction in body fat is accompanied by a reduction in inflammation [48], and as inflammation increases RMR [49], reduced inflammation will reduce RMR.

Finally, the relationship between sleep hours and a change in RMR has been described in previous findings and in other populations [50] and, for the first time, was also presented in older adults with T2DM, to the best of our knowledge. Sleep is important at any age and, of course, in old age. Given that sleep duration is positively associated with muscle strength training [51] and that sleep duration is important for weight loss [52], the relationship we observed with RMR has additional significance.

The study has limitations: 1) It is a post hoc analysis, not originally intended to explore RMR differences. The findings might differ with a larger sample or longer duration. While the study's sample size is limited, it is common for lifestyle intervention research, such as studies on the impact of physical activity on RMR, to include smaller participant groups [25]. 2) The lack of a non-intervention control group limits the ability to isolate the specific effects of each intervention, as potential background interactions and participant characteristics may have influenced the outcomes. However, it should be noticed that due to the nature of this study as an RCT – background characteristics of the subjects in the three interventions were distributed equally. 3) Caution is needed in applying the results to the reference population of older adults with T2DM, as they are specific to this cohort. 4) Additionally, although expressed longitudinally in a prospective RCT, these are still associations and for this reason should be considered hypothesis generating and explored a priori in a separate, longer study focusing on these variables (fat %, leg strength and sleep).

5. Conclusions

In older T2DM adults, CRT, a plant-based moderate-carbohydrate, high-fat diet, and empagliflozin treatment showed no differential impact on RMR after 10 weeks. The key factors associated with RMR change were fat percentage, maximal leg strength (via knee extension), and sleep duration. Those with increased or stable RMR generally showed greater improvements in leg strength, more hours of sleep, and higher fat loss. However, additional studies with larger sample sizes and longer follow-up periods are needed to explore the effects of various treatments on RMR according to demographic factors.

CRediT authorship contribution statement

Assaf Buch: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roy Eldor:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Ofer Kis:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Arie Ben-Yehuda:** Writing – review & editing, Supervision, Conceptualization. **Gizell Green:** Writing – original draft, Formal analysis. **Yona Greenman:** Writing – review & editing, Supervision, Resources, Project administration. **Sharon Barak:** Writing – original draft, Software, Methodology, Formal analysis.

Informed consent statement:

Informed consent was obtained from all subjects involved in the study.

Institutional review board statement

Data availability

Data are available from the authors upon reasonable request and with permission of the CEV-65 investigators.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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