Obesity Facts

Research Article

Obes Facts 2023;16:53–61
DOI: 10.1159/000527227

Received: April 14, 2022
Accepted: September 5, 2022
Published online: October 4, 2022

The Effects of Metabolism Tracker Device (Lumen) Usage on Metabolic Control in Adults with Prediabetes: Pilot Clinical Trial

Assaf Buch[a, b] Shlomo Yeshurun[c] Tomer Cramer[c] Axel Baumann[c] Yael Sencelsky[d] Shira Zelber Sagi[d] Merav Serebro[b, e] Yona Greenman[b, e] Merav Mor[c] Roy Eldor[b, e]

[a]Department of Nutritional Sciences, School of Health Sciences, Ariel University, Ariel, Israel; [b]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel; [c]Metaflow Ltd., Tel-Aviv, Israel; [d]School of Public Health, University of Haifa, Haifa, Israel; [e]The Sackler Faculty of Medicine Tel-Aviv University, Tel-Aviv, Israel

Keywords
Lifestyle intervention · Prediabetes · Diabetes prevention · Weight loss

Abstract
Introduction: Prediabetes is a risk factor for type 2 diabetes mellitus (T2DM). However, it may be reversed via lifestyle changes. Lumen is a novel handheld device that measures exhaled CO_2 producing results in agreement with those of indirect calorimetry when assessing metabolic fuel usage. The aim of this study was to examine the effects of following Lumen's personalized, measurement-guided lifestyle intervention program on anthropometric and metabolic variables in adults with prediabetes. ***Methods:*** A 12-week single-arm intervention study was conducted in 27 participants. Body composition and blood markers were measured at the start and end of the study. Each participant took a daily morning (fasted) measurement and received feedback on their metabolic state (i.e., their degree of fat vs. carbohydrate oxidation). Participants were then provided with personalized daily guidelines for their carbohydrate, fat, and protein consumption, along with recommended lifestyle changes. ***Results:*** Intention-to-treat analysis revealed a significant decrease in body weight (5.99 kg, $p < 0.001$), comprising a significant reduction in percentage body fat (2.93%, $p < 0.001$) and waist circumference (6.23 cm, $p < 0.001$). Significant reductions were also observed in glycated hemoglobin A_{1c} (0.27%, $p < 0.001$), triglycerides (0.45 mg/dL, $p < 0.001$), and systolic blood pressure (0.5 mm Hg, $p < 0.05$). ***Conclusion:*** In a 12-week pilot study of participants with prediabetes, Lumen usage significantly improved multiple metabolic parameters, demonstrating its potential to deliver better clinical outcomes for patients with T2DM and metabolic syndrome.

Introduction

Prediabetes (as defined in [1]) is an extremely common condition [2] and a recognized risk factor for type 2 diabetes mellitus and cardiovascular disease [3, 4]. Prediabetes is an inherent part of the metabolic syndrome and is often accompanied by obesity, dyslipidemia, and hypertension [5]. Currently recommended interventions

Karger@karger.com
www.karger.com/ofa

Correspondence to:
Shlomo Yeshurun, shlomi@lumen.me

in prediabetes to prevent conversion to type 2 diabetes mellitus include lifestyle changes that incorporate both exercise and standardized weight loss programs [6–8]. However, some individuals are more resistant to dietary interventions portraying a "thrifty" phenotype that is associated with reduced energy expenditure during caloric restriction [9].

A potential explanation for this is impaired metabolic flexibility which is an inherent part of prediabetes [10–13]. Impaired metabolic flexibility is the inability to shift between fuel sources, such as fats or carbohydrates, in response to their availability and metabolic demands resulting in enhanced muscle glucose oxidation (as opposed to fat oxidation) in the fasting state [14, 15]. Interventions such as exercise training and some weight loss programs have been shown to improve metabolic flexibility [16–18]. However, different nutritional interventions have been shown to have different and sometimes opposite effects on metabolic flexibility. For example, in a study examining the effect of high-fat versus standard overfeeding on healthy individuals, the extent of change in lipid oxidation in response to high-fat (but not standard) overfeeding predicted subsequent weight gain [19].

It would therefore be hypothesized that a nutritional intervention which varies in response to daily changes in metabolic flexibility may be beneficial in overcoming the "thrifty" phenotype and achieving therapeutic goals in subjects with prediabetes. However, the common method of measuring metabolic flexibility using indirect calorimetry necessitates a specialized laboratory facility, highly trained technicians, and is both time consuming and operator dependent. A more accessible method of assessing metabolic flexibility may be through measuring exhaled CO_2 since carbohydrate oxidation produces more CO_2 than fat oxidation [20].

Lumen is a novel handheld exhaled CO_2 measurement device which was recently found to be in agreement with indirect calorimetry in providing an accurate assessment of metabolic fuel usage [21]. This is incorporated into a comprehensive lifestyle intervention using a mobile phone application to provide daily personalized nutritional and lifestyle recommendations. Nutritional advice is based on adjustment of macronutrient consumption based on the metabolic fuel usage assessment each morning. Moreover, the program recommends minimally processed food and preference of carbohydrate sources with a low glycemic index. This pilot study evaluated the anthropometric and metabolic outcomes after 12 weeks of lifestyle intervention program utilizing the Lumen system in adults with prediabetes.

Methods

Participant Recruitment and Eligibility Criteria

The trial took place in the Endocrinology, Metabolism and Hypertension Department at Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, between November 2020 and June 2021. The study was approved by the Institutional Review Board of Tel Aviv Sourasky Medical Center and was a-priori registered at ClinicalTrials.gov (NCT04555421). Participants were recruited by either clinical referrals from the endocrinology department, local recruitment posters, or by online advertisements. The eligibility of each participant was initially considered by the study co-investigator (A.Bu.) via telephone or email and was subsequently evaluated by the study's physician (R.E.) when they arrived at the clinic.

The main inclusion criteria were age between 25 and 65; BMI between 27 and 40 kg/m^2; and a glycated hemoglobin A_{1c} (HbA_{1c}) between 5.7% and 6.4%, or fasting plasma glucose between 100 mg/dL and 125 mg/dL (if the HbA_{1c} was unavailable or lower than 5.7%). Participants were excluded if they were on anti-hyperglycemic medication (e.g., metformin or liraglutide); were previously diagnosed with diabetes; were pregnant or breastfeeding; participated in an active weight loss program in the last 3 months or lost >3 kg in the past month. In addition, participants were required to have a mobile phone which can support the Lumen mobile application, to read and understand English, and to be able to perform a valid Lumen breathing maneuver. Figure 1 depicts the study flow from recruitment to analysis.

Study Design

The study was designed as a single-arm 12-week intervention. Following written informed consent and initial assessment, participants received a Lumen device and instructions on how to use it as well as its accompanying mobile app. Following a 2-day run-in period, participants returned to the clinic for baseline measurements, including blood tests and anthropometric measurements. They were then instructed to use Lumen at home on a daily basis for a period of 12 weeks. The participants took a Lumen measurement in a fasted state every morning, and a nutritional plan was created based on the results. Additionally, participants were instructed to note in the mobile application when they consumed their last meal every day, how long they slept, and if they followed the previous day's nutritional recommendations. Moreover, the Lumen mobile phone application encouraged the participants to take more measurements throughout the day, mainly in response to food intake as well as before and after exercise. A Lumen coach was assigned for remotely supporting the participants via Lumen's mobile phone application and to provide clarifications and guidelines if needed based on Lumen metrics. After 12 weeks, participants returned to the clinic for a post-intervention repeated collection of blood tests and anthropometric measurements.

Intervention

Upon using Lumen participants received an estimation of their current metabolic fuel source (fat vs. carbohydrate metabolism and the degree of each component). They were then provided with instructions for their carbohydrates, fat, and protein intake for the rest of the day, as well as guidance to optimize their lifestyles, in terms of nutrition, sleeping habits, and physical activity. Figure 2 depicts the Lumen device app interface and data presentation for the participants.

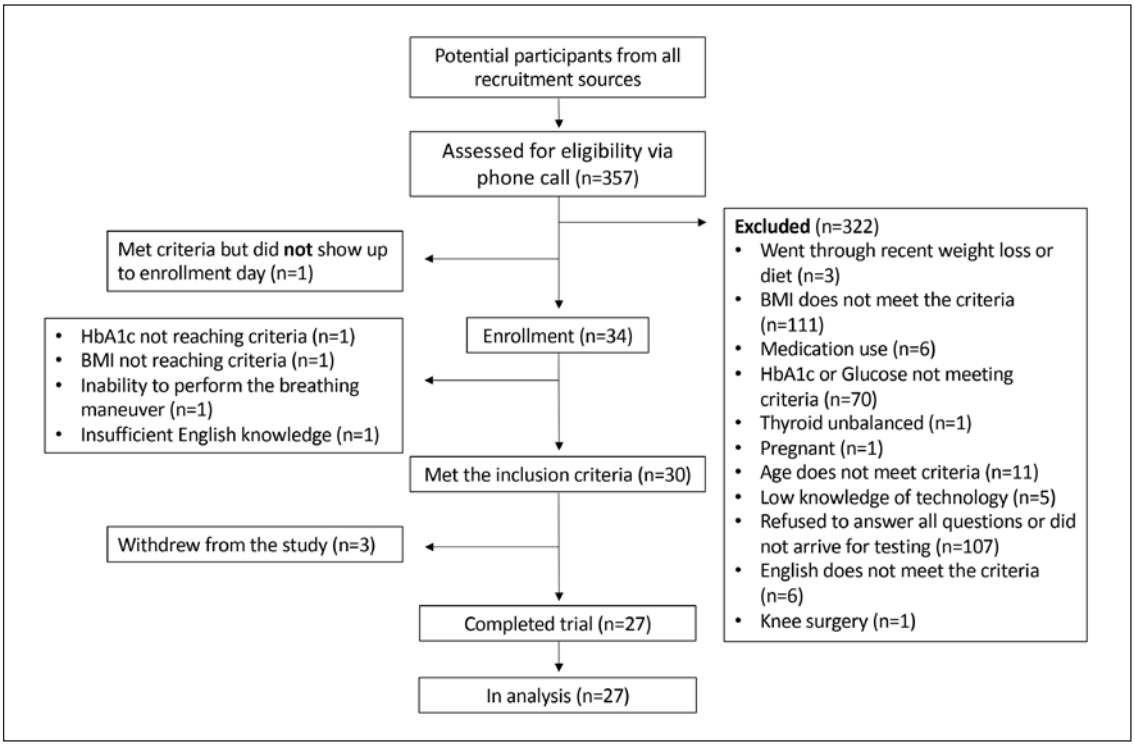

Fig. 1. Flowchart depicting the recruitment and selection process of the study population.

Daily nutritional recommendations were determined by calculating the total daily energy expenditure using the Mifflin-revised Harris-Benedict equation [22]. This equation is then adjusted by the physical activity factor, which is a function of the types, durations, and intensities of the daily activities reported by the participant. Energy intake was restricted to 500 calories fewer than the estimated requirements. Carbohydrates were recommended to account for 20–45% (in accordance with the results from the exhaled CO_2 measurement) of the daily calorie intake with a focus on complex carbohydrates such as whole grains and legumes. Protein intake accounted for 20–25% of the total daily energy expenditure (1.6–1.8 g per kg of body weight). A further 30–60% (adjusted according to Lumen score) of the caloric recommendation was represented by fats, preferably from food sources rich in mono- and polyunsaturated fats (such as avocado and olives). Additionally, participants were advised to consume nonstarchy vegetables freely, with a target goal of at least 250 g per day.

Outcome Measures

Anthropometric variables included weight and body composition analysis measured with a bioelectrical impedance analyzer (InBody 770 body composition analyzer, Cerritos, CA, USA) – a method found to be valid and reliable for the purpose [23–25], height measured with a Health-o-Meter (Health-o-Meter Professional, Health-o-Meter, FL, USA), and waist circumference measured twice around the umbilical cord [26]. Blood pressure was measured by an experienced technician following a uniform protocol [27]. Sitting blood pressure was measured by an automated device (OMRON M2 digital monitor) after a 5-min rest period in a quiet setting without distractions. To minimize random error, the average of 3 measurements (with 1-min rest between each measurement) was calculated.

All blood samples were collected after a 12-h fast in vacuum blood collection tubes with gel and centrifuged for 15 min at 4,000 *g* to obtain serum. Blood tests were measured by routine commercial automated assays and included fasting serum glucose, lipid profile, liver enzymes, HbA_{1c}, and C-reactive protein (CRP) levels. Fasting glucose was determined with the glucose oxidase method using an autoanalyzer (Beckman Instruments, Fullerton, CA, USA). Total serum cholesterol was measured with the Roche/Hitachi 747 Analyzer (Roche Diagnostics, Mannheim, Germany) and the Raichem Kit (Reagents Applications, San Diego, CA, USA). HbA_{1c} was measured using the Tosoh G8 HPLC Analyzer (Tosoh Bioscience, Inc., South San Francisco, CA, USA) according to manufacturer's instructions. CRP levels were assessed by using BN2 model nephelometer (Dade Behring, Cardio Phase hsCRP Assay, Marburg, Germany) as described elsewhere [28].

Statistical Analysis

The primary aim of the study was to evaluate the impact of Lumen usage for 12 weeks on body composition in subjects with prediabetes. Secondary objectives included the effects of Lumen usage on glycemic control and lipid profiles. All variables were tested for normal distribution before the tests. Intention-to-treat analyses of the primary and secondary outcomes at baseline and after 12 weeks of Lumen usage included all subjects who had baseline and end of study measurements and were performed by utilizing two-tailed paired parametric *t* tests with the Holm-Sidak adjustment for mul-

Fig. 2. Example of main data taken for determining the daily nutritional plan using the Lumen device app integration process.

Table 1. Baseline participant characteristics

	Females (n = 13)		Males (n = 14)		All, n = 27	
	mean	SD	mean	SD	mean	SD
Age, years	47.3	9.0	47.0	9.2	47.2	9.0
Weight, kg	95.4	14.0	99.1	12.4	97.3	13.0
Height, cm	162.0	5.8	174.7	5.3	168.6	8.5
Body mass index, kg/m^2	36.2	4.1	32.5	4.3	34.3	11.3

tiple comparisons. Sample size was determined based on power analysis made according to a study evaluating HbA_{1c} levels in prediabetic subjects who received low-carb diet for 12 weeks [29]. However, we expected the reduction to be lower, of 0.2% with SD of 0.3 (effect size of 0.67). Accordingly, α of 0.05 produced a final sample of study participants of 26 at 90% power.

Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software Inc.). The threshold for significance was set at $p < 0.05$ after adjustment for multiple comparisons.

Results

Clinical Characteristics of Study Population

A total of 357 potential participants were assessed for their eligibility to participate in the study. 332 applicants did not meet inclusion criteria as detailed in the methods section. Among the remaining 35, one was lost to follow-up. Following the initial assessment at the clinic, four applicants failed to meet the inclusion criteria and were excluded from the study. Of the remaining 30 participants, three withdrew consent due to reasons unrelated to the trial and trial procedures. Twenty-seven participants had baseline and end of study assessments and were included in the intention-to-treat analysis (Table 1). Participants showed a high level of engagement with 84.63 ± 9.59 morning Lumen measurements out of the 94 days of intervention.

Primary Outcomes

Body composition outcomes were exhibited by several anthropometric improvements (Table 2). Body weight reduced significantly from baseline by 5.99 kg (6.15% reduction; $t_{26} = 7.47$, $p < 0.001$; Fig. 3a), comprised a significant reduction of 5.11 kg in body fat mass ($t_{26} = 8.35$, $p < 0.001$) and 0.58 kg of skeletal muscle mass ($t_{26} = 3.89$, $p = 0.001$). Consequently, a significant loss of 2.93% percentage body fat was observed ($t_{26} = 8.53$, $p < 0.001$; Fig. 3b). In addition, BMI reduced by 2.09 kg/m^2 (t_{26} =

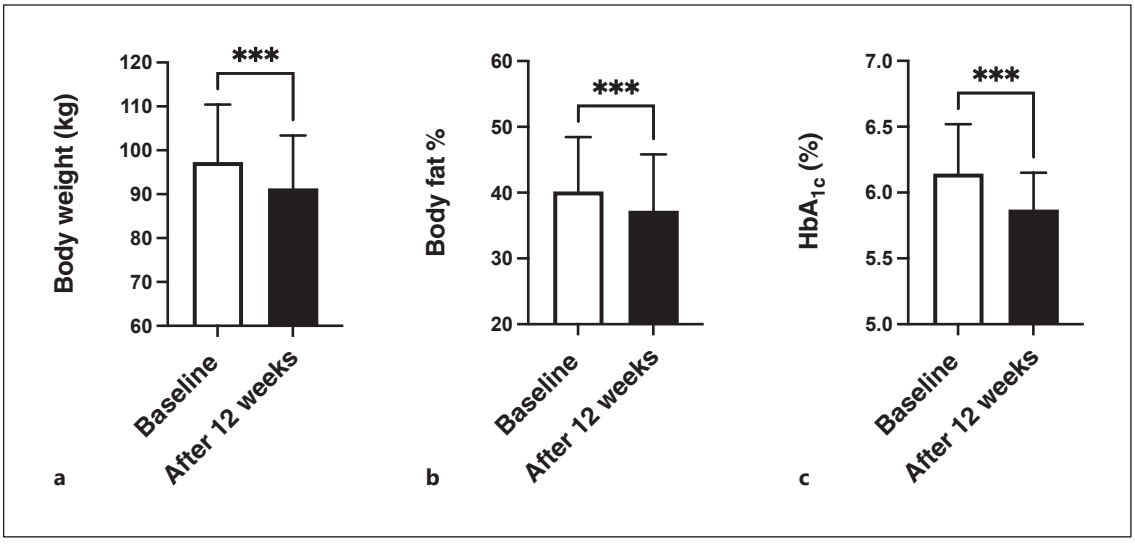

Fig. 3. a–c Changes in body weight, body fat percentage, and HbA_{1c} after 12 weeks of Lumen usage. Data are presented as mean (SD). $N = 27$. *** indicates $p < 0.001$.

Table 2. Changes in clinical outcomes

	Baseline ($n = 27$)		After 12 weeks ($n = 27$)		Change from baseline	
	mean	SD	mean	SD	mean	adjusted *p* value
Weight, kg	97.3	13.1	91.4	12.0	−5.9	<0.001
BMI, kg/m^2	34.3	4.5	32.2	4.1	−2.1	<0.001
Body fat, %	40.2	8.3	37.2	8.6	−3	<0.001
Body fat mass, kg	39.4	10.5	34.2	9.7	−5.2	<0.001
Skeletal muscle mass, kg	32.5	6.0	32.0	5.9	−0.5	0.001
Visceral fat area, cm^2	187.6	51.5	163.6	50.1	−24.0	<0.001
Circumference, cm	114.4	10.9	108.1	10.4	−6.3	<0.001
Systolic blood pressure, mm Hg	127.8	11.3	122.7	13.0	−5.1	0.044
Diastolic blood pressure, mm Hg	80.0	11.3	78.8	11.9	−1.2	0.48
HbA_{1c}, mmol/mol	43.7	4.0	40.6	3.0	−3.1	<0.001
HbA_{1c}, %	6.1	0.4	5.9	0.3	−0.2	<0.001
Glucose, mmol/L	5.3	0.6	5.1	0.6	−0.2	0.212
Triglycerides, mmol/L	1.8	0.7	1.4	0.8	−0.4	0.006
HDL cholesterol, mmol/L	1.2	0.2	1.1	0.2	−0.1	0.086
LDL cholesterol, mmol/L	3.2	0.9	3.0	0.9	−0.2	0.228
Total cholesterol, mmol/L	5.1	1.0	4.8	1.0	−0.3	0.151
CRP, nmol/L	61.6	60.6	91.1	166.1	29.5	0.25
ALP, µkat/L	1.2	0.3	1.1	0.3	−0.1	0.005
AST, µkat/L	0.4	0.1	0.4	0.1	0.0	0.159
ALT, µkat/L	0.5	0.3	0.4	0.2	−0.1	0.159
GGT, µkat/L	0.5	0.5	0.4	0.4	−0.1	0.142

Multiple *t* tests were performed for baseline measurements versus after 12-week measurements. Adjusted *p* value, according to the multiple comparison correction using the Holm-Sidak method. CRP, C-reactive protein; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine amino transferase; GGT, gamma glutamyltransferase.

7.14, $p < 0.001$), visceral fat area declined by 24 cm^2 ($t_{26} = 8.59$, $p < 0.001$), and waist circumference decreased by 6.23 cm ($t_{26} = 7.79$, $p < 0.001$).

Secondary Outcomes

HbA_{1c} decreased by 3.08 mmol/mol (0.27%) after 12 weeks of intervention (7.05% reduction; $t_{26} = 6.91$, $p < 0.001$; Table 2; Fig. 3c), while fasting blood glucose did not change (−0.18 mmol, $p = 0.212$; Table 2). Triglycerides were reduced by 0.45 mmol/L ($p = 0.006$), and CRP which displayed high variability between and within the participants did not significantly change (29 nmol/L, $p = 0.25$). Systolic blood pressure decreased (5.02 mm Hg, $p = 0.044$), but no changes were observed in diastolic blood pressure, total cholesterol, HDL cholesterol, and LDL cholesterol. Tests of liver function revealed a significant decrease from baseline in alkaline phosphatase (ALP) ($t_{26} = 3.68$, $p = 0.005$), but no significant difference in aspartate aminotransferase, alanine amino transferase, or gamma glutamyltransferase (Table 2).

Discussion

In this pilot study, we investigated the benefits of using the Lumen device for lifestyle interventions in adults with prediabetes. A 12-week program utilizing the Lumen device with its accompanying mobile app exhibited improved metabolic control of participants as indicated by successful weight loss of 5.99 kg, 2.93 percent body fat reduction, HbA_{1c} decrease of 0.27%, waist circumference narrowed by 6.23 cm, systolic blood pressure reduced by 5.02 mm Hg, and triglycerides reduced by 0.42 mmol/L.

The average weight loss percentage in our study was 6.15%, which is within the CDC and ADA guidelines for preventing diabetes-related complications [30, 31]. Furthermore, our results were comparable to other lifestyle interventions using mobile platforms that have demonstrated both feasibility and efficacy [32–34]. In a recent meta-analysis, weight loss was found to be significantly greater with lifestyle interventions compared with usual treatment [35]. Furthermore, a scoping review of nutrition approaches to prediabetes found significant weight loss in 57.7% of the cases, waist circumference reduction in 53.1%, and systolic blood pressure reduction in 51.6% of the cases, as well as HbA_{1c} reduction in 57.7% of the cases [36]. This shows the feasibility of nutritional interventions on the one hand, but also demonstrates the challenges of standardized approaches on the other. Lifestyle interventions have been shown to be beneficial for reducing the prevalence of metabolic syndrome [37–39]. Such outcomes have been shown at both long and short (12 weeks) intervention studies. The findings from this current study, such as a decrease in waist circumference, blood pressure, and triglycerides, can provide evidence that metabolic syndrome characteristics have improved.

Data-driven approaches have been incorporated into several recent studies in an attempt to improve diabetes risk parameters. Using an algorithm-based dietary intervention incorporating microbiome data, a recent study revealed major HbA_{1c} reduction, which was significantly greater than a Mediterranean diet (0.08%) accompanied by ~3% weight loss [40]. According to a recent mobile app-based study examining the effect of low carbohydrate diet guidance for 3 months, participants lost 2.2 kg, 0.23%, and 0.38 mmol/L in body weight, HbA_{1c}, and triglycerides, respectively [41].

In addition to the aforementioned ameliorations, we found that ALP level decreased by 0.1 kat/L (6.48 U/L) between baseline and end of trial. High levels of ALP have been associated with an increased risk of diabetes [42]. Notwithstanding, glucose levels did not differ significantly from baseline. This is attributed to initial screening criteria that determined the glucose threshold should be advised when HbA_{1c} was unavailable or lower than 5.7%. Consequentially, some individuals were recruited while having relatively low fasting glucose levels. These findings emphasize the beneficial effects of lifestyle modifications via Lumen, which are in concordance with the DPP study [43], CDC guidelines, and ADA recommendations [30, 31].

We hypothesized that the incorporation of daily changes in metabolic flexibility into nutritional recommendations will assist in overcoming the "thrifty" phenotype. The term metabolic flexibility refers to the ability to easily switch between fuel sources [11, 15, 44]. The state of ones metabolic flexibility is detected by examining the change from resting state fuel oxidation to the peak oxidation, as indicated by the respiratory exchange ratio during a glucose stimulated state [15, 45, 46]. Respiratory exchange ratio measurement is obtained via indirect calorimetry measures using the metabolic cart. The use of the metabolic cart for optimizing nutritional and metabolic requirements can be referred to as ambitious or challenging, due to the hazardous nature of this method, since it requires arrival to the clinic and is time consuming. The use of Lumen, which has been found to be in agreement with the metabolic cart [21], can be performed by oneself daily, in a household environment. This simplifies the assessment of the metabolic flexibility degree, which can serve as a personalized lifestyle intervention tool.

The present study has several limitations including the lack of a control arm, the small number of participants, and short duration of follow-up. As this is the first intervention study conducted using Lumen's metabolic device, we first tested in a clinical setting whether weight loss and improved metabolic parameters are feasible. For this aim, a single-arm design study was conducted. Due to the lack of a comparison group, we were not able to directly compare the benefits of this intervention with other traditional nutrition and coaching interventions. A possible limitation of the current study is the limited number of participants. This was pre-determined based on power analysis, and accordingly 27 people completed the entire trial. The duration of the trial is another possible limitation. To fully appreciate the efficacy of the Lumen intervention, a larger study with a more representative sample examining long-term adherence is needed. The studies' strengths are its prospective nature and thorough collection of multiple clinically important parameters of the metabolic syndrome as well as body composition.

Conclusion

In conclusion, the utilization of the Lumen handheld metabolism tracker device, incorporating daily metabolic fuel use assessments with a mobile application interface, indicated a high short-term adherence, weight reduction, and a significant improvement in multiple parameters of the metabolic syndrome in adults with prediabetes. Further controlled studies are needed to determine the potential long-term benefit of this approach.

Acknowledgments

We are grateful for the participation of the research volunteers and acknowledge the help and cooperation of the nursing and nutritional staffs at the Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel. We wish to thank the Lumen team for their collaboration. We are also grateful for the support of the coaches in their assistance with the participants, specifically the efforts of Ashira Krakowski, Liraz Blumenfeld, Lily Aronin, and Sarice Holley.

Statement of Ethics

The study complied with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was reviewed and approved by the Institutional Review Board of Tel Aviv Sourasky Medical Center (approval number 0523-20-TLV) and was a-priori registered at ClinicalTrials.gov (NCT04555421). All study participants provided their written informed consent to participate in the study.

Conflict of Interest Statement

Shlomo Yeshurun, Tomer Cramer, Axel Baumann, and Merav Mor are employees of Metaflow Ltd. and contributed to the design and analysis of the study as well as the preparation of the manuscript. The others have no conflicts of interest to declare.

Funding Sources

The research was funded by Metaflow Ltd. The study was initiated by the staff of the Institute of Endocrinology and Diabetes at Tel Aviv Medical Center after familiarization with Lumen's product in search of new methods to increase compliance to lifestyle changes among obese and prediabetic people.

Author Contributions

Assaf Buch, Shlomo Yeshurun, Roy Eldor, Yona Greenman, and Merav Mor led the design and conception of the study. Roy Eldor was the principal investigator of the study. Merav Serebro and Yona Greenman assisted with the recruitment of patients to the study. Shlomo Yeshurun and Tomer Cramer conducted data interpretation and data analysis. Assaf Buch contributed to the data analysis and led the acquisition of data. Shlomo Yeshurun, Tomer Cramer, Assaf Buch, and Shira Zelber Sagi drafted the manuscript. Axel Baumann and Yael Sencelsky contributed to the acquisition of data. All authors critically revised the manuscript and gave final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2020. Diabetes Care. 2020;43(Suppl 1):S14–31.
2 Centers for Disease Control and Prevention. Natl Diabetes Stat Report, 2020. 2020;2 [cited 2021 Nov 17].
3 Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012; 379(9833):2279–90.
4 Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med. 2004 Oct; 164(19):2147–55.

5 Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood Institute; American heart association; World heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation. 2009 Oct; 120(16):1640–5.
6 Briggs Early K, Stanley K. Position of the academy of nutrition and dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. J Acad Nutr Diet. 2018 Feb;118(2):343–53.
7 Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, et al. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care. 2003;26(12):3230–6.
8 Diabetes Prevention Program Research Group; Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009 Nov;374(9702): 1677–86.
9 Reinhardt M, Thearle MS, Ibrahim M, Hohenadel MG, Bogardus C, Krakoff J, et al. A human thrifty phenotype associated with less weight loss during caloric restriction. Diabetes. 2015 Aug;64(8):2859–67.
10 Battista F, Belligoli A, Neunhaeuserer D, Gasperetti A, Bettini S, Compagnin C, et al. Metabolic response to submaximal and maximal exercise in people with severe obesity, prediabetes, and diabetes. Obes Facts. 2021;14(4): 415–24.
11 Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol. 1999 Dec;277(6):E1130–41.
12 Færch K, Vaag A. Metabolic inflexibility is a common feature of impaired fasting glycaemia and impaired glucose tolerance. Acta Diabetol. 2011;48(4):349–53.
13 Smith RL, Soeters MR, Wüst RCI, Houtkooper RH. Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. Endocr Rev. 2018;39(4):489–517.
14 Goodpaster BH, Sparks LM. Metabolic flexibility in health and disease. Cell Metab. 2017; 25(5):1027–36.
15 Kelley DE, Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes. 2000;49(5):677–83.
16 Meex RCR, Schrauwen-Hinderling VB, Moonen-Kornips E, Schaart G, Mensink M, Phielix E, et al. Restoration of muscle mitochondrial function and metabolic flexibility in type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. Diabetes. 2010;59(3):572–9.
17 Van Loon LJC, Jeukendrup AE, Saris WH, Wagenmakers AJ. Effect of training status on fuel selection during submaximal exercise with glucose ingestion. J Appl Physiol. 1999; 87(4):1413–20.
18 Toledo FGS, Goodpaster BH. The role of weight loss and exercise in correcting skeletal muscle mitochondrial abnormalities in obesity, diabetes and aging. Mol Cell Endocrinol. 2013 Oct;379(1–2):30–4.
19 Begaye B, Vinales KL, Hollstein T, Ando T, Walter M, Bogardus C, et al. Impaired metabolic flexibility to high-fat overfeeding predicts future weight gain in healthy adults. Diabetes. 2020 Feb;69(2):181–92.
20 Elia M, Livesey G. Theory and validity of indirect calorimetry during net lipid synthesis. Am J Clin Nutr. 1988 Apr;47(4):591–607.
21 Lorenz KA, Yeshurun S, Aziz R, Ortiz-Delatorre J, Bagley JR, Mor M, et al. A handheld metabolic device (lumen) to measure fuel utilization in healthy young adults: device validation study. Interact J Med Res. 2021 May; 10(2):e25371.
22 Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241–7.
23 Antonio J, Kenyon M, Ellerbroek A, Carson C, Burgess V, Tyler-Palmer D, et al. Comparison of dual-energy X-ray absorptiometry (DXA) versus a multi-frequency bioelectrical impedance (InBody 770) device for body composition assessment after a 4-week hypoenergetic diet. J Funct Morphol Kinesiol. 2019 Jun;4(2):23.
24 Hurt RT, Ebbert JO, Croghan I, Nanda S, Schroeder DR, Teigen LM, et al. The comparison of segmental multifrequency bioelectrical impedance analysis and dual-energy X-ray absorptiometry for estimating fat free mass and percentage body fat in an ambulatory population. J Parenter Enteral Nutr. 2021 Aug;45(6):1231–8.
25 Ling CHY, de Craen AJM, Slagboom PE, Gunn DA, Stokkel MPM, Westendorp RGJ, et al. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr. 2011 Oct;30(5):610–5.
26 Ness-Abramof R, Apovian CM. Waist circumference measurement in clinical practice. Nutr Clin Pract. 2008 Aug;23(4):397–404.
27 Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension. 2018 Jun;71(6):E13–115.
28 Ziv-Baran T, Shenhar-Tsarfaty S, Etz-Hadar I, Goldiner I, Gottreich A, Alcalay Y, et al. The ability of the wide range CRP assay to classify individuals with low grade inflammation into cardiovascular risk groups. Clin Chim Acta. 2017 Aug;471:185–90.
29 Saslow LR, Kim S, Daubenmier JJ, Moskowitz JT, Phinney SD, Goldman V, et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. PLoS One. 2014 Apr;9(4):e91027.
30 US Department of Health and Human Services. National Diabetes Statistics Report, 2020. Natl Diabetes Stat Rep. 2020;2.
31 Diabetes Prevention Program (DPP) | NIDDK [Internet].
32 Block G, Azar KMJ, Romanelli RJ, Block TJ, Hopkins D, Carpenter HA, et al. Diabetes prevention and weight loss with a fully automated behavioral intervention by email, web, and mobile phone: a randomized controlled trial among persons with prediabetes. J Med Internet Res. 2015;17(10):e240. https//www.jmir.org/2015/10/e240.
33 Alharbi NS, Alsubki N, Jones S, Khunti K, Munro N, de Lusignan S. Impact of information technology: based interventions for type 2 diabetes mellitus on glycemic control–a systematic review and meta-analysis. J Med Internet Res. 2016;18(11):e310.
34 Bacigalupo R, Cudd P, Littlewood C, Bissell P, Hawley MS, Buckley Woods H. Interventions employing mobile technology for overweight and obesity: an early systematic review of randomized controlled trials. Obes Rev. 2013; 14(4):279–91.
35 Glechner A, Keuchel L, Affengruber L, Titscher V, Sommer I, Matyas N, et al. Effects of lifestyle changes on adults with prediabetes: a systematic review and meta-analysis. Prim Care Diabetes. 2018 Oct;12(5):393–408.
36 Yau JW, Thor SM, Ramadas A. Nutritional strategies in prediabetes: a scoping review of recent evidence. Nutrients. 2020;12(10):2990.
37 Ilanne-Parikka P, Eriksson JG, Lindström J, Peltonen M, Aunola S, Hämäläinen H, et al. Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish diabetes prevention study. Diabetes Care. 2008 Apr;31(4):805–7.
38 van Namen M, Prendergast L, Peiris C. Supervised lifestyle intervention for people with metabolic syndrome improves outcomes and reduces individual risk factors of metabolic syndrome: a systematic review and meta-analysis. Metabolism. 2019 Dec;101:153988.
39 Saboya PP, Bodanese LC, Zimmermann PR, Gustavo AS, Macagnan FE, Feoli AP, et al. Lifestyle intervention on metabolic syndrome and its impact on quality of life: a aandomized controlled trial. Arq Bras Cardiol. 2017; 108(1):60–9.

40 Ben-Yacov O, Godneva A, Rein M, Shilo S, Kolobkov D, Koren N, et al. Personalized postprandial glucose response-targeting diet versus mediterranean diet for glycemic control in prediabetes. Diabetes Care. 2021;44(9):1980–91.
41 Chen X, Su H, Kunii D, Kudou K, Zhang Y, Zhao Y, et al. The effects of mobile-app-based low-carbohydrate dietary guidance on postprandial hyperglycemia in adults with prediabetes. Diabetes Ther. 2020;11(10):2341–55.
42 Chen SCC, Tsai SP, Jhao JY, Jiang WK, Tsao CK, Chang LY. Liver fat, hepatic enzymes, alkaline phosphatase and the risk of incident type 2 diabetes: a prospective study of 132, 377 adults. Sci Rep. 2017 Jul;7(1):4649.
43 Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. 2002;346(6):393–403.
44 Storlien L, Oakes ND, Kelley DE. Metabolic flexibility. Proc Nutr Soc. 2004;63(2):363–8.
45 Galgani JE, Heilbronn LK, Azuma K, Kelley DE, Albu JB, Pi-Sunyer X, et al. Metabolic flexibility in response to glucose is not impaired in people with type 2 diabetes after controlling for glucose disposal rate. Diabetes. 2008;57(4):841–5.
46 Galgani JE, Moro C, Ravussin E. Metabolic flexibility and insulin resistance. Am J Physiol Endocrinol Metab. 2008;295(5):1009–17.