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Bitter gourd (*Momordica charantia* L.) supplementation for twelve weeks improves biomarkers of glucose homeostasis in a prediabetic population

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ABSTRACT

Ethnopharmacological relevance: Bitter gourd (*Momordica charantia* L.) is known for its ability to reduce parameters of diabetes, but its effects on prediabetic subjects have been scarcely studied.
Aim of the study: To assess the efficacy of *Momordica charantia* supplementation in a prediabetic population on markers of glucose homeostasis.
Methods: Two randomized controlled studies were conducted to assess the effect of bitter gourd supplementation in a prediabetic population. Study 1 was a 4-week cross-over intervention trial (n = 30), with freeze-dried bitter gourd (BG) fruit juice (2.4 g/day) or a cucumber-based control product (CC). Study 2 was a parallel trial (n = 38) lasting 12 weeks, with freeze-dried whole fruits (3.6 g/day) or a cucumber-based matched control supplement. Effects on fasting plasma glucose (FPG), insulin, HbA1c, fructosamine, postprandial glucose after an oral glucose tolerance test, and several safety biomarkers were also analyzed in both trials before and after the interventions.
Results: In Study 1, no significant differences were found between the bitter gourd and placebo interventions. However, a reduction in FPG in subjects with higher baseline values were found following bitter gourd supplementation, which was not observed in the control group. However, in Study 2, we observed significant reductions of FPG ($p = 0.014$), fasting insulin ($p = 0.007$), and HOMA-IR ($p = 0.003$) after a 12-week intervention with the bitter gourd supplement. In addition, between treatment analysis resulted in significant effects on FPG levels ($p = 0.026$) and HOMA-IR ($p = 0.045$) with no significant effects on other biomarkers related to glucose metabolism. On average, bitter gourd intervention reduced FPG by ~0.05 mmol/L per week, whereas FPG remained unchanged following placebo. In both studies, there were no indications of health risks or side effects from consumption of the supplements.
Conclusion: Results suggest that supplementation with bitter gourd fruit can have positive effects on fasting plasma glucose and insulin among prediabetic subjects when provided over an extended period of at least 12 weeks.

1. Introduction

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) continues to rise. Moreover, there is an increasing awareness that these conditions contribute to co-morbidities, such as immune suppression, vascular diseases, and increased susceptibility to infections (Wu et al., 2014; Ferlita et al., 2019; Rey-Reñones et al., 2022). Next to non-modifiable factors such as age, genetic predisposition, and ethnicity, lifestyle factors, including lack of exercise, a Western diet and stress are determinants of T2DM development (Sami et al., 2017). Reversing and achieving remission of T2DM is possible through

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Abbreviations

ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
AUC	Area Under Curve
BG	bitter gourd
BMI	body mass index
CC	cucumber control
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
FPI	fasting plasma insulin
HbA1c	Hemoglobin A1c
HOMA-B	Homeostatic Model Assessment of Beta Cell Function
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	heart rate
ITT	intended-to-treat
LSD	least significant difference
NA	not analyzed
OGTT	oral glucose tolerance test
PP	per protocol
SBP	systolic blood pressure
T2DM	type 2 diabetes mellitus
WMA	World Medical Association
WMO	Wet Medisch-wetenschappelijk onderzoek (Medical Research Act)
WUR	Wageningen University & Research

appropriate lifestyle interventions (Kim and Kwon, 2022; Shibib et al., 2022). Prescribing medications may come with side-effects and are not always the optimal solution due to alterations in the body's endogenous homeostatic mechanisms. The most commonly used drug prescribed during the initial stages of T2DM, metformin, is chemically derived from a biguanide found in *Galega officinalis*. Although the compound is generally well tolerated, side-effects are seen in some individuals such as abdominal pain, bloating, diarrhea, nausea, vomiting, and interactions with various other drugs (Nabrdalik et al., 2022; Koslover et al., 2022).

In addition to *Galega offinalis*, many other plants have been studied for their potential positive effects on glucose homeostasis. One such plant that has undergone extensive research for its role in controlling glycemic responses in T2DM patients is *Momordica charantia* L., commonly known as bitter gourd or sopropo (Yeh et al., 2003; Peter et al., 2019). Its bitter fruits are not only consumed as vegetables, but also leaves are used in the form of extracts, tinctures, teas, or supplements to manage T2DM and symptoms for many years. Clinical trials have investigated the effectiveness of *M. charantia* preparations in improving glycemic control in T2DM patients. A meta-analysis, including ten studies (combined n = 1015), conducted by Peter and colleagues (Peter et al., 2019) indicated that *M. charantia* can lower elevated blood glucose levels in patients with T2DM. However, the authors noted that this conclusion was based on low to very low-quality evidence for primary outcomes, such as fasting glucose, OGTT measurements, and HbA1c. A more recent meta-analysis, including fewer studies, did not result in significant effects on parameters of metabolic syndrome (Laczkó-Zöld et al., 2024).

Other meta-analyses have investigated the safety of *M. charantia* supplementation, primarily based on animal studies and adverse effects reported in human studies through questionnaires and markers for liver function (Peter et al., 2020; Demmers et al., 2023; Laczkó-Zöld et al., 2024). These analyses suggest that consuming *M. charantia* preparations is not expected to pose safety risks. However, conclusions remain inconclusive, as the available studies either report no adverse effects or provide low-quality reporting on safety outcomes. Proper comparison of outcomes is further hampered by the lack of a comprehensive description of the *M. charantia* preparation used in many studies. Factors such as the plant's genotype, cultivation and environmental conditions, type of plant material, preparation method, and dosage likely influence study outcomes. The primary bioactive compound(s) responsible for the effects of bittergourd on glucose homeostasis have not been definitively identified. Bittergourd contains various bioactive compounds that may contribute to its effects on glycemic control, including charantin, momordicosides, triterpenoids, saponins, (conjugated) linoleic acid, polypeptide-P, gastric-resistant peptides, polysaccharides. These compounds may act individually or through additive or synergistic effects (Peter et al., 2019; Liao et al., 2022; Sajadimajd et al., 2022; Xu et al., 2022). Therefore, optimizing products, assessing their stability and quality, and standardizing doses based on specific compounds remains challenging. Moreover, all conducted studies primarily involved individuals with diagnosed T2DM who may have been taking medications and often had a different disease history. To date, only one human intervention has focused on the effect of a bitter gourd supplement (2.5 g powder) in a prediabetic population (Krawinkel et al., 2018). This placebo controlled cross-over trial reported that an 8-week intervention led to a significant reduction in fasting glucose. No effects were observed on other metabolic markers such as HbA1c, insulin or cholesterol. The study of Krawinkel et al. (2018) also found a more pronounced decrease in fasting plasma glucose (FPG) during the bitter gourd intervention in those subjects that had a higher FPG at baseline. Since the potential for demonstrating improvements through interventions is more constrained for prediabetic subjects compared to those with T2DM, it is essential to focus on this prediabetic population, especially when emphasizing prevention through lifestyle interventions.

To address these knowledge gaps, we conducted two separate clinical studies to analyze the effects of suppletion with dried *M. charantia* preparations on glucose homeostasis in prediabetic individuals. The first trial had a randomized controlled cross-over design with a 4-week intervention period. The second trial employed a parallel design with a longer intervention period of 12 weeks. Notably, the second trial was powered based on the results of the first trial and incorporated new information that had become available from a comparison of different cultivars in a study with pigs (Koopmans et al., 2024). Consequently, the *M. charantia* cultivar, preparation of the supplement, and dosage differed from the first trial. Both studies evaluated a range of biomarkers related to glucose homeostasis, adverse effects, and safety indicators.

2. Materials and methods

2.1. Clinical trials

We conducted two distinct clinical trials, both adhering to the ethical principles outlined in the Declaration of Helsinki (World Medical Association, 2013) and in compliance with the Medical Research Involving Human Subjects Act (WMO, 1998; https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/laws/medical-research-involving-human-subjects-act-wmo). Both studies received approval from the local ethical committee (NL70259.081.19 and NL79294.091.21) and were registered on ClinicalTrials.gov under the identifiers NCT04090788 and NCT05215210, respectively. Participation in the trials was contingent upon subjects' completion of a screening process and formally accepting the study terms following a comprehensive verbal and written explanation of the research. Subjects were enrolled in the trials after signing informed consent.

2.2. Bitter gourd and cucumber control supplements

The plant, *Momordica charantia* L. and synonyms, and plant and fruit phenotype were checked with World Flora Online (most recent check July 10, 2024). Plant seeds can be requested from East-West Seeds company.

For Study 1, we used bitter gourd (BG) variety Bilai, organically cultivated in a Dutch greenhouse. We harvested mature fruits exceeding 30 cm in length, thoroughly cleaned them, and then halved the fruits to remove the seeds. The juice was obtained using an Angel Juicer AG-60k, freeze-dried, and pulverized into fine powder. Approximately 400 mg of this powder was encapsulated in semi-transparent capsules, by Cressana BVBA (Zalm, Belgium), in compliance with ISO and HACCP certification. Similarly, cucumbers grown in Dutch greenhouses, sourced from local groceries, were subjected to juicing, freeze-drying, and pulverization, then encapsulated under identical conditions, serving as the cucumber control (CC) supplement.

For Study 2, we utilized bitter gourd variety Palee, cultivated in India and harvested at a young, premature stage. Whole fruits, inclusive of their skin, were cut into pieces, freeze-dried, and powdered under Food Safety and Standard Authority of India licensing by P2S Food Process LLP in Pune, India. The batches of powders were subsequently combined, mixed and encapsulated in semi-transparent capsules, each containing approximately 400 mg, a process executed by Arspro Pharma BV in Almere, The Netherlands. Dutch-grown cucumbers were prepared by cutting them into pieces, freeze-drying, and powdering at WUR, all according to food-safe conditions. These cucumber powders were then encapsulated under equivalent conditions at Arspro Pharma BV.

2.3. Composition analysis

The intervention products underwent comprehensive analyses for macronutrients, heavy metals, pesticides, and microbial contaminants. These analyses were conducted following established standard methods (Groen Agro Control, Delfgauw, The Netherlands).

Upon thorough analysis of the nutritional composition and contaminants for the BG and CC products (see Supplementary Table S1), it was confirmed that both products met the criteria for safe human consumption. Notably, the CC product contained a slightly higher sugar content than the BG product. Nevertheless, the sugar content of the CC supplements remained below 1g per day, rendering any potential impact on blood glucose levels negligible.

The intervention product used in Study 1 was chemically characterized in more detail by LC-MS, GC-MS and HPTLC and published previously (Koopmans et al., 2024), as the same product was used in a piglet study.

2.4. Study designs

Study 1 employed a 4-week, randomized, double-blind, controlled cross-over trial with two treatment groups. Thirty subjects were randomly assigned to either the AB or BA treatment sequence. Blood samples were collected before and after each intervention period. The intervention periods were spaced by a wash out period of four weeks. The participants were instructed to take 6 capsules daily, distributed as 2 capsules with each main meal (breakfast, lunch, and dinner), amounting to 2.4 g per day.

Study 2 was a randomized, double-blind, controlled parallel trial with two 12-week arms, involving thirty-eight participants. Subjects' measurements were taken at four time points: the beginning, and at the end of the 4-, 8-, and 12-week intervention periods. For Study 2, participants consumed 9 capsules daily, distributed as 3 capsules per main meal, totaling 3.6 g per day.

Compliance in both studies was assessed through regular questionnaires and by counting the remaining unused capsules at the end of each study period.

2.5. Study participants

For both studies, subjects were recruited through the Wageningen University & Research database, LinkedIn, and local newspaper advertisements. Both studies employed slightly different inclusion criteria.

Study 1 involved a total of 30, participants of both sexes, aged 50 to 75, with a BMI greater than 25 kg/m2, and with one or more of the following conditions: HbA1c greater than 5.7 % (39 mmol/L), fasting glucose above 5.6 mmol/L, or a 2-h glucose level surpassing 7.8 mmol/L following a 75g oral glucose tolerance test (OGTT).

In Study 2, less stringent inclusion criteria were applied. It comprised of a total of 38 male and female subjects, aged 40 to 70 with a BMI over 25 kg/m2, and fasting glucose levels above 5.6 mmol/L (being lower than the initial criterion of over 6.1 mmol/L due to insufficient subjects meeting the original threshold).

Both studies used identical exclusion criteria, which comprised of the absence of clinically diagnosed chronic diseases, current use of blood glucose-regulating medication, a history of gut or liver-related diseases, current smoking, heavy alcohol consumption, pregnancy, and lactation.

2.6. Outcome measures

The primary outcome measures for Study 1 included fasting plasma glucose levels and 2-h plasma glucose levels following the OGTT. Secondary study parameters included plasma HbA1c, fructosamine, and insulin levels (both fasting and in response to the OGTT). Additionally, HOMA-IR and HOMA-B scores were calculated based on the fasting glucose and insulin values. Fasting plasma lipid levels (triglycerides and cholesterol), liver enzymes (ALAT and ASAT), and eGFR (estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI formula) were also assessed in study 1.

In Study 2, the primary outcome measure was fasting glucose levels, measured before and after the 12-week intervention. Secondary parameters included fasting plasma HbA1c, fasting insulin, the 2-h plasma glucose and insulin levels after the OGTT, and the corresponding calculated HOMA-IR and HOMA-B scores. Additional safety analyses encompassed measurements of ALAT, ASAT, and eGFR (CKD-EPI formula).

In both studies, the analytic measurements were conducted by the hospital laboratory at Ziekenhuis Gelderse Vallei in Ede, the Netherlands.

2.7. Questionnaires

Subjects were requested to self-report their overall well-being, compliance, and any potential adverse effects associated with the study using daily questionnaires in Study 1 and weekly questionnaires in Study 2.

2.8. Statistical analysis

Statistical analyses were performed blinded and only unblinded after completing the analyses. Analyses were performed in R (Version 4.3.2).

In Study 1, the statistical analysis involved linear mixed models for repeated measures. The impact of the intervention was determined using treatment (BG or CC), time (before or after the intervention), and the interaction between treatment and time as fixed effects, and participant as random effect. The difference in OGTT responses of plasma glucose and insulin due to the intervention was assessed by comparing the concentrations at 120 min after the OGTT, and by calculating the incremental area under the curve (iAUC) using the trapezoidal method. To test if there was an effect within treatment groups after 4-week supplementation with either BG or CC, paired T-tests were performed. A p-value of <0.05 was considered statistically significant.

In Study 2, the statistical analysis involved linear mixed models, to compare the between-treatment effects on fasting samples. The impact of the intervention was determined using treatment (BG or CC), time (week 0, week 4, week 8 and week 12 as factor variables), the interaction between treatment and time as fixed effects and participant as random effect. To test whether there was an effect within treatment groups after 4, 8 and 12-week of supplementation with either BG or CC, paired T-tests were performed. Subjects with major protocol deviations (low supplement compliance) were excluded from the per protocol (PP) analysis. All statistical analyses were performed on both the 38 intended-to-treat (ITT) subjects and the 36 PP subjects. Here, we report on the analysis of the 36 PP subjects, for which the overall conclusions align with the ITT analysis. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Subject characteristics and compliance (studies 1 and 2)

Study 1: Initially, 197 subjects were screened, and 30 eligible participants selected. Subjects were stratified by gender, age, and fasting glucose levels and assigned to groups AB and BA. Baseline characteristics of both groups (AB and BA) were similar (Table 1, flow diagram in Fig. 1). At the beginning of the first intervention period, all 30 subjects exhibited either an HbA1c $>$ 39 mmol/ml, FPG $>$5.6 mmol/l, or 2h OGGT $>$7.8 mmol/l. However, during the first intervention period and the subsequent washout period, these markers changed, resulting in only 27 of the 30 subjects meeting the inclusion criteria at the start of the second intervention period. We have not excluded these three subjects from our analysis. All subjects demonstrated good compliance, with over 94 % of the expected capsules consumed, and there were no dropouts.

Study 2: A total of 157 individuals were screened, and 40 subjects were deemed eligible for enrollment in the study. Subjects were stratified similarly to Study 1, ensuring no significant differences in baseline characteristics between both groups (Table 1, Fig. 1). Two subjects dropped out of the study, one due to personal circumstances, and another because of difficulties accessing veins for venipuncture, which posed an excessive burden for the participant. Out of the 38 subjects, two showed low compliance when capsules were counted (<82 %) and results from these two participants were not included in data analysis.

Table 1
Baseline characteristics of the subject for both studies.

Parameter	Study 1			Study 2 (PP)		
	CC-BG (n = 15) Mean (SD)	BG-CC (n = 15) Mean (SD)	*p* Value	CC (n = 17) Mean (SD)	BG (n = 19) Mean (SD)	*p* Value
Gender	4F/11M	5F/10M	0.719	10F/7M	8F/11M	0.504
Age (y)	68.1 (4.8)	67.5 (6.6)	0.822	64.5 (5.7)	62 (8.1)	0.283
BMI (kg/m^2)	28.3 (3.2)	29.1 (2.2)	0.495	30.7 (4.0)	30.3 (5.0)	0.792
HbA1c (mmol/L)	40.4 (3.1)	40.2 (2.8)	0.854	43.8 (8.1)	43.4 (8.3)	0.885
FPG (mmol/L)	6.3 (0.5)	6.2 (0.9)[a]	0.573	7.0 (1.6)[a]	7.1 (1.5)	0.812
FPI (mlU/L)	16.4 (12.8)	12.8 (8.7)	0.384	15.0 (9.7)	15.2 (8.9)[a]	0.958
2h OGTT glucose (mmol/L)	8.3 (2.3)	9.23 (2.4)	0.267	9.6 (4.9)	9.6 (4.0)	0.950
2h OGTT insulin (mlU/L)	152.0 (89.2)	148.0 (85.8)	0.898	75.7 (52.0)	84.6 (76.0)	0.683

CC - cucumber control, BG - bitter gourd, PP - per protocol, SD - standard deviation, F - female, M - male, BMI - body mass index, FPG - fasting plasma glucose, FPI - fasting plasma insulin, OGTT – Oral Glucose Tolerance Test.
[a] One missing value due to analytical error.

3.2. Measures of glycemic control

3.2.1. Effect of 4-week BG supplementation on measures of glycemic control (study 1)

In study 1, the cross-over trial, there were no significant differences between the two intervention arms (BG and CC) after 4 weeks in FPG, FPI and HbA1c (Table 2). Notably, during the first intervention period, both arms of the trial displayed reductions in several of the biomarkers. This reduction was particularly evident in the HbA1c values during the first period, whereas they remained relatively stable during the second period (Supplementary Fig. S1).

Despite the absence of a significant intervention effect, further analysis revealed that subjects in the BG intervention group with higher baseline FPG levels showed greater reductions in FPG, a trend not seen in the CC group (Fig. 2). Similar trends were noted for OGTT 2h glucose and OGTT glucose iAUC values (data not shown). These findings prompted us to conduct a second trial with a longer 12-week intervention period and a slightly higher dose of a different bitter gourd cultivar as suggested by results from a piglet study (Koopmans et al., 2024).

3.2.2. Effect of the 12-week BG supplementation on measures of glycemic control (study 2)

In Study 2, the biomarker data from 36 PP subjects were analyzed using mixed model analysis and a paired T-test for within group comparisons between baseline and the 12-week intervention period (Table 3). Based on the within group effects, there was a significant reduction in FPG ($p = 0.014$) and FPI ($p = 0.007$) in the BG group, and not in the CC group. A linear mixed model between treatment analysis revealed an almost significant effect after 8 weeks ($p = 0.058$) and a significant reduction of fasting plasma glucose after 12-week intervention ($p = 0.026$). These between groups comparative analysis indicated only a trend for fasting plasma insulin after 8- and 12-weeks intervention ($p = 0.071$, $p = 0.105$, respectively) compared to the CC (see Table 3 and Supplementary Fig. S2). An unpaired T-test on the delta FPG values and delta FPI data at 12 weeks resulted in significant effect of the BG supplementation compared to CC supplementation (FPG $p = 0.038$, FPI $p = 0.016$) but not after 4- and 8-week of intervention (see Supplementary Table 2).

The primary outcome of the trial was a significant reduction in fasting glucose levels after 12-weeks of BG intervention compared to CC. The results confirm that this primary objective was met.

Consistent with Study 1, subjects with the highest baseline FPG values exhibit the largest reduction in FPG, and this effect is exclusive to the BG arm of the trial (see Supplementary Fig. S3).

The calculated HOMA-IR also resulted in significant effects ($p = 0.045$) and the reduction in HbA1c was just not significant ($p = 0.051$), based on the linear mixed model analysis, while other analyzed biomarkers did not yield significant differences between the two intervention arms (Table 3).

3.3. Effect on other health outcomes based on biomarker analysis and self-reporting

Some anti-diabetic treatments have shown negative impact towards liver function and other metabolic parameters. Therefore, in Study 1, and to a lesser extent in Study 2, biomarkers for liver and cardiovascular risk were analyzed (Table 4). These biomarkers did not significantly change during the intervention periods, except for ASAT, which was significantly reduced in the BG intervention group of Study 2. All ASAT values before and after intervention were maintained within the normal healthy range. Based on these values, we concluded that the interventions did not negatively impact these health-related biomarkers.

Both studies included a questionnaire to collect self-reported potential side effects (Table 5). Based on the results, it can be concluded

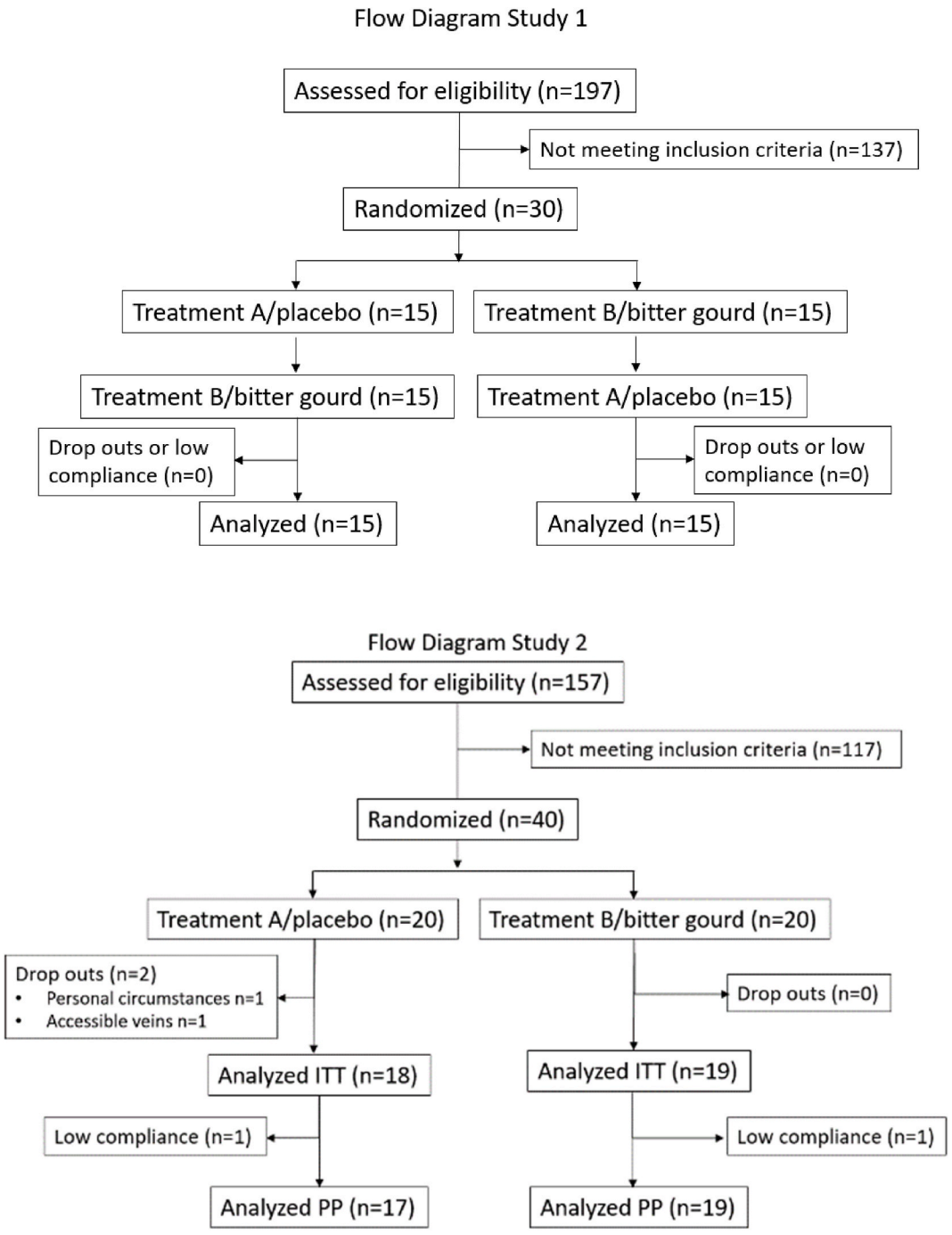

Fig. 1. Flow diagram of Studies 1 and 2.

that the number of side effects reported was small and not different between both arms of the intervention studies. Based on these results, we concluded that the BG interventions did not result in any clear side effects.

4. Discussion

The 12-week BG supplementation yielded significant results on the primary outcome, fasting blood glucose, showing a significant reduction in those individuals in this prediabetic population who had elevated FPG (>5.6 mmol/L) at baseline. After 4-weeks, the BG intervention did not demonstrate a significant reduction in FPG levels, confirming the results of Study 1. However, significant differences between the two intervention arms began to emerge at 8 weeks, reaching statistical significance by 12 weeks. These results indicate that the effect of BG supplement intervention on FPG requires consistent intake over a longer period for the effects to become apparent. This is in line with previous research on BG interventions in diabetic population as reviewed by Peter and colleagues (Peter et al., 2019) and subsequent studies. For example, Kim et al. (2020) found a reduced FPG after 12 weeks (−0.025 mmol/L/wk) in T2DM patients following bitter gourd supplementation, while no effect was seen on HbA1c. The meta-analysis (Peter et al., 2019) indicated that prolonged use of BG at a dose between 2 and 6 g/day was more effective than placebo in lowering elevated FPG levels (mean difference −0.72 mmol/L 95 % CI: −1.33 to −0.12). Especially the study of Suthar et al. (2016) will have made a major contribution to

Table 2
Baseline values and changes in metabolic risk markers after 4-week cucumber control (CC) or bitter gourd (BG) supplementation in prediabetic subjects (Study 1).

Biomarker	Intervention	Baseline	After 4-wk	*p* Value between treatments[b]
		Mean (SD)	Mean (SD)	
FPG (mmol/L)	CC	6.3 (0.7)	6.1 (0.8)[a]	0.417
	BG	6.2 (0.7)	6.0 (0.7)[a]	
FPI (mIU/L)	CC	16.3 (12.2)	15.0 (12.0)	0.773
	BG	14.8 (8.5)	14.3 (9.3)	
HbA1c (mmol/mol)	CC	40.1 (3.6)	39.2 (3.2)[a]	0.316
	BG	39.6(2.7)	38.2 (3.0)[a]	
Fructosamine (umol/L)	CC	249 (21)	247 (17)	0.725
	BG	248 (19)	248 (16)	
OGTT -2h glucose (mmol/L)	CC	8.5 (2.2)	8.4 (2.4)	0.400
	BG	8.5 (2.2)	8.0 (2.1)	
OGTT – glucose iAUC	CC	1562 (289)	1484 (337)[a]	0.691
	BG	1535 (297)	1440 (231)[a]	
OGTT – 2h insulin (mIU/L)	CC	143 (83)	131 (76)	0.200
	BG	148 (84)	120 (65) [a]	
OGTT – insulin iAUC	CC	19451 (10121)	16434 (9245)[a]	0.141
	BG	17810 (8744)	16628 (9128)	
HOMA-IR	CC	4.8 (4.0)	4.4 (4.1)	0.954
	BG	4.2 (2.8)	3.9 (2.7)	
HOMA-B	CC	115 (68)	109 (61)	0.350
	BG	109 (54)	117 (70)	

CC - cucumber control, BG - bitter gourd, SD−standard deviation, FPG - fasting plasma glucose, FPI - fasting plasma insulin, OGTT - Oral Glucose Tolerance Test, HOMA-IR - Homeostatic Model Assessment for Insulin Resistance, HOMA-B - Homeostatic Model Assessment of Beta Cell Function.

[a] Statistically different from baseline within same intervention, based on paired *t*-test, $P < 0.05$.

[b] Analyzed using linear mixed models. P-values show the interaction between treatment and time.

these results. This study was based on a 13-week intervention with 1.2g/day of BG dried fruit juice powder in sixty-four T2DM patients compared to twenty-one patients receiving placebo capsules. In that study, FPG levels were reduced significantly ($p = 0.013$) compared to control (Suthar et al., 2016). Expressed in mmol/L this accounted to a decrease of 1.2 mmol/L (−0.09 mmol/wk). Our Study 2 showed that 8- or 12-weeks of BG supplementation resulted in a mean lowering FPG of −0.47 mol/L ($p = 0.092$) at 8 weeks and −0.42 mmol/L ($p = 0.038$) at 12 weeks compared to control (8wk−0.10 mmol/L; 12wk 0.03 mmol/L). According to the measurements at 8-weeks this would result in ~ −0.05 mmol/L per week, which indicates that our intervention was less effective, while our BG dose was three times that administered in the study of Suthar et al. (2016). This higher effectivity in the study of Suthar et al. (2016) might be due to the diabetic population used in their study, while our study was based on prediabetic subjects. The only published study on BG supplementation involving prediabetic subjects is the one conducted by Krawinkel et al. (2018). Their 8-week intervention resulted in a −0.31 mmol/L reduction (~−0.04 mmol/L per week) which is highly similar to our results.

The difference in BG effectiveness towards prediabetic and diabetic subjects may depend on baseline FPG values. In both our studies with prediabetic subjects (with mean baseline FPG values of 6.2 and 7.1 mmol/L for subsequent Studies 1 and 2), those subjects with higher baseline levels also showed a stronger reduction of FPG after the BG intervention. The study of Suthar et al. (2016) investigated T2DM patients with a mean FPG of 8.4 mmol/L at baseline giving a larger window for improvement. Studies on metformin, the most widely prescribed antidiabetic drug, also demonstrate greater effects in individuals with an elevated FPG. For example, Knowler et al. (2002) found a 48 % reduction in individuals with baseline FPG levels between 6.1 and 7.0 mmol/L, compared to 15 % in those with a baseline FPG of 5.3–6.1 mmol/L. A 16-week study with pediatric T2DM patients resulted in a FPG of −2.4 mmol/L in the 1000 mg metformin twice daily arm of the study (Jones et al., 2002). This equals to ~ -0.15 mmol/L/wk, which is 3 times stronger compared to the effect found in our BG supplementation Study 2.

A long-term parallel study (as used in Study 2) has major advantages over a cross-over study (Study 1). First, a cross-over study requires participation for twice as long plus a wash-out period, which increases the risk of dropouts and lower compliance. Second, we have seen a change in biomarkers in the first treatment period of both arms of the cross-over trial. This could be explained by the fact that participants became aware of their risk for T2DM and adjusted their lifestyle in response, either intentionally or unintentionally. During a long-term parallel trial this effect might also occur, but participants are more likely to revert to their old habits over time. The third advantage of a parallel design compared to a cross-over design is the risk of carry-over effects within a cross-over design. In our Study 1, we encountered that 3 out the 15 subjects that no longer classified as prediabetic based on their biomarkers (FPG, HbA1c, 2h OGTT glucose). Consequently, treatment arms became unbalanced at the start of the second intervention period.

Besides the difference in intervention duration, the products used in both intervention studies 1 and 2 also slightly differed. Study 1 used dried fruit juice from the Bilai variety, grown in a greenhouse in The Netherlands, while Study 2 made use of dried whole fruits from the Palee variety, grown in India. This change in cultivar and processing method was based on the results obtained with diabetic piglets performed around the same period as Study 1 (Koopmans et al., 2024). In this piglet study, five different BG products were tested. The study

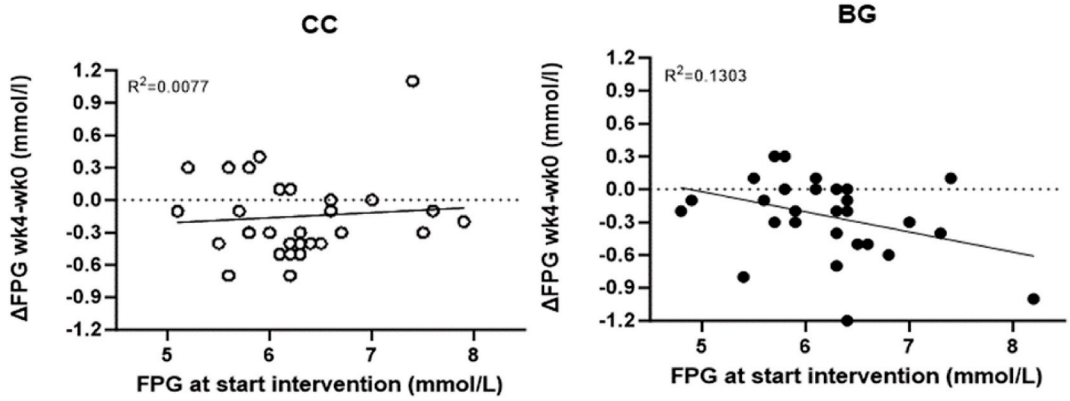

Fig. 2. Association between initial fasting plasma glucose (FPG) of the 30 subjects in Study 1 and change after a 4-weeks intervention of cucumber control (CC) supplements (left panel) and bitter gourd (BG) supplementation (right panel).

Table 3
Fasted baseline values and changes in metabolic risk markers after 4, 8 and 12-week cucumber control (CC) or bitter gourd (BG) supplementation in prediabetic subjects (Study 2).

Biomarker	Intervention	Baseline	After 4-wk	After 8-wk	After 12-wk	*p* Value between treatments[b]			
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	wk0	wk4	wk8	wk12
FPG (mmol/L)	CC	7.0 (1.6)	6.9 (1.7)	6.9 (1.7)	7.1 (1.9)	0.968	0.873	0.058	**0.026**
	BG	7.1 (1.5)	6.9 (1.8)	6.6 (1.6)[a]	6.6 (1.3)[a]				
FPI (mIU/L)[c]	CC	15.0 (9.7)	15.0 (9.4)	15.8 (11.0)	15.5 (8.2)	0.955	0.356	0.071	0.105
	BG	15.2 (8.9)	13.4 (6.9)	13.0 (7.8)[a]	12.5 (7.3)[a]				
HbA1c (mmol/mol)	CC	43.8 (8.1)	45.2 (8.8)[a]	43.3 (8.2)	45.2 (10.2)	0.894	0.106	0.103	0.051
	BG	43.4 (8.3)	43.6 (8.7)	42.6 (9.0)	43.3 (8.6)				
OGTT 2h glucose (mmol/L)	CC	9.6 (4.9)	NA	NA	9.3 (5.0)	0.949	NA	NA	0.872
	BG	9.6 (4.0)	NA	NA	9.3 (3.6)				
OGTT - 2h insulin (mIU/L)[3]	CC	75.7 (52.0)	NA	NA	69.6 (33.4)	0.654	NA	NA	0.859
	BG	84.6 (76.0)	NA	NA	80.9 (61.0)				
HOMA-IR[3]	CC	4.5 (3.3)	4.8 (3.0)	4.7 (3.1)	4,9 (2.8)	0.899	0.296	0.063	**0.045**
	BG	4.7 (2.6)	4.0 (2.0)	3.7 (2.2)[a]	3.6 (2.0)[a]				
HOMA-B[3]	CC	96.0 (71.3)	107.0 (68.9)	112.0 (95.6)	102.0 (71.1)	0.905	0.254	0.149	0.204
	BG	96.3 (67.8)	91.7 (59.0)	99.4 (76.0)	89.4 (61.3)				

CC - cucumber control, BG - bitter gourd, SD−standard deviation, wk – week,FPG - fasting plasma glucose, FPI - fasting plasma insulin, OGTT - Oral Glucose Tolerance Test, HOMA-IR - Homeostatic Model Assessment for Insulin Resistance, HOMA-B - Homeostatic Model Assessment of Beta Cell Function.
[a] Statistically different from baseline within same intervention, based on paired *t*-test, $P < 0.05$.
[b] Analyzed using linear mixed models. P-values show the interaction between treatment and time.
[c] Due to missing values for insulin for one subject in the BG group, analysis are performed on 35 subjects instead of 36.

Table 4
Effect of both studies on other health related biomarkers. In Study 2 less markers were analyzed compared to Study 1.

		Study 1			Study 2		
		Baseline	After 4-wk	*p* Value between groups	Baseline	After 12-k	*p* Value between groups[b]
Biomarker	Intervention	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
ALAT (U/l)	CC	29.9 (14.9)	32.5 (21.0)	0.902	28.8 (13.3)	28.1 (15.9)	0.439
	BG	31.1 (16.3)	34.0 (20.6)		31.6 (14.3)	29.3 (12.0)	
ASAT (U/l)	CC	24.9 (6.9)	25.1 (7.8)	0.492	24.6 (7.2)	25.1 (8.8)	**0.042**
	BG	30.1 (17.9)	28.4 (13.8)		26.0 (8.3)	23.4 (6.9) [a]	
Cholesterol (mmol/l)	CC	5.2 (0.9)	4.9 (0.8) [a]	0.440	NA	NA	NA
	BG	5.3 (0.9)	5.1 (0.9) [a]		NA	NA	
eGFR (ml/min)	CC	81.4 (15.6)	83.5 (18.5)	0.929	77.0 (15.8)	78.0 (16.0)	0.709
	BG	83.3 (17.2)	83.1 (16.5)		73.7 (13.8)	74.0 (15.7)	
Triglycerides (mmol/L)	CC	1.6 (0.8)	1.6 (0.8)	0.691			
	BG	1.7 (1.0)	1.7 (0.9)		NA	NA	
SBP (mmHg)	CC	138.1 (14.6)	132.8 (12.2) [a]	0.906	NA	NA	
	BG	136.0 (17.1)	133.3 (15.8)		NA	NA	
DBP (mmHg)	CC	76.3 (7.3)	72.1 (9.0)	0.532	NA	NA	
	BG	75.0 (9.3)	73.5 (9.1)		NA	NA	
HR (bpm)	CC	64.0 (8.6)	65.4 (9.0)	0.761	NA	NA	
	BG	67.2 (10.9)	66.1 (8.7)		NA	NA	

CC - cucumber control, BG - bitter gourd, SD – standard deviation, ALAT - alanine amino transferase, ASAT - aspartate aminotransferase, eGFR - estimated glomerular filtration rate, SBP - systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, NA – non-analyzed.
[a] Statistically different from baseline within same intervention based on paired *t*-test, $P < 0.05$.
[b] Based on unpaired T test.

indicated that dried fruits of Palee (grown in Vietnam) had a significant effect on fructosamine levels in these piglets, whereas the Bilai (grown in The Netherlands) did not (Koopmans et al., 2024). At this stage, we cannot conclude whether the difference in cultivar or other differences in the supplement influenced the outcome of both human studies. For now, we assume that the intervention period of Study 1 was just too short to demonstrate effects. Koopmans and colleagues identified three compounds that could be linked to the positive effects observed in the piglet study. The intervention products from Study 1 were also analyzed by GC-MS and LC-MS (data not shown), revealing that the BG and CC samples had markedly different compositions. Furthermore, the BG samples from Studies 1 and 2 clustered more closely in the PCA analysis (data not shown). Our research does not allow us to identify any specific bioactive compound as being responsible for these effects, and additional studies would be needed to investigate this further.

The varying effects observed in the piglet study (Koopmans et al., 2024) associated with different varieties, align well with our previous *in vitro* studies in which we measured GLP-1 (Glucagon-like peptide 1) secretion from enteroendocrine cells exposed to extracts of these same cultivars (Noya Leal et al., 2021). This would point to an underlying mechanism whereby BG stimulates GLP-1 secretion in the gut, a key determinant of blood glucose homeostasis, acting by slowing down gastric emptying, enhancing pancreatic insulin secretion, and suppressing pancreatic glucagon secretion (Nadkarni et al., 2014). Other potential mechanisms of action for BG have been proposed as well and include increasing the flow of glucose from blood to urine, inhibition of α-amylase and α-glucosidase resulting in reduced transport of starch-derived glucose from the gut to blood, and modulation of diabetes by antioxidant-related properties (Simes and MacGregor, 2019; Fonseca-Correa and Correa-Rotter, 2021; Perera et al., 2021; Liu et al., 2010). However, our study does not provide conclusive evidence for a specific mechanism and further research is needed.

Some reports indicate adverse effects of the antidiabetic drug metformin, including nausea, vomiting, stomach upset, diarrhea, weakness,

Table 5
Reported side effects in Study 1 and Study 2. Scores indicate the number of subjects and between () all days together that symptoms are registered daily in diary (Study 1) or weekly questionnaire (Study 2).

	Study 1		Study 2	
	CC	BG	CC	BG
Feeling of hypo	1 (2)	0	0	0
Oral allergy	1 (1)	0	0	0
Restless night	1 (1)	0	0	0
Common cold symptoms	1 (4)	1 (1)	5 (170)	5 (66)
More often to toilet	0	1 (1)	0	0
Difficult stool/obstipation	2 (6)	1 (2)	3 (86)	3 (37)
Feeling fatigue	2 (2)	1 (2)	0	0
Raised body temperature	1 (1)	0	0	0
Bloating/abdominal pain	2 (2)	0	2 (40)	4 (171)
Diarrhea/thin stools	1 (1)	0	3 (4)	4 (57)
Flatulence	0	0	5 (278)	7 (221)
Headache	0	0	9 (227)	5 (42)
Nausea	0	0	1 (1)	4 (66)

CC - cucumber control, BG - bitter gourd.

or a metallic taste in the mouth and gastrointestinal intolerance. However, these drawbacks are generally outweighed by the drug's benefits (Nasri and Rafieian-Kopaei, 2014). Subjects participating in both our intervention studies reported some side-effects, but these were seen in similar frequencies in both arms of the trials. Therefore, we consider the supplements, even at a dose of 3.6g/day for 12 weeks, safe and tolerable. This safety was also demonstrated by the liver and kidney markers analyzed. Recently, we performed a meta-analysis to evaluate the potential harm of BG-derived products using data from randomized controlled trials (Demmers et al., 2023). In that study, seventeen trials (including this Study 1) were included, resulting in the conclusion that BG interventions resulted in low risk for any adverse effect on ASAT, ALAT, creatine, reported adverse effects, reasons for drop out, and interaction with other treatments. An independently performed meta-analysis (Laczkó-Zöld et al., 2024) and the results of Study 2 are in line with this conclusion.

None of the subjects in Study 2 reverted from prediabetic FPG level (>5.6 mmol/l) to a normal level. To reverse T2DM without medication, a more comprehensive and multi-component diabetes intervention program is required, involving nutritional advice, exercise, and improvement of overall lifestyle (Pot et al., 2020; Goyal Mehra et al., 2022; Dagogo-Jack et al., 2022). BG-based supplements could add on to such program, providing the additional motivation needed for subjects to sustain lifestyle changes. Besides a supplement as used in this study, freshly prepared bitter gourd fruits in (bitter) dishes and meals, tea, and other bitter gourd-based beverages could be included in diets and tested in a more practice-oriented studies. The studies 1 and 2 clearly indicate that subjects must have increased fasting blood glucose levels at the start of the intervention and that effective intervention requires at least a treatment period of 12 weeks.

5. Conclusion

Bitter gourd supplementation in a prediabetic population can have a significant effect on glucose homeostasis. While some trends and effects can be observed after 4 and 8 weeks, interventions should ideally extend to 12 weeks or more before pronounced effects to manifest. Among the set of biomarkers related to glucose metabolism, the most significant improvements are seen in fasting plasma glucose and insulin levels, which also lead to better HOMA-IR values. The exact mechanism underlying these effects remains unclear. Although the effects are smaller compared to specific medications for T2DM, supplements derived from bitter gourd (as well as dishes, teas, or other products made from the fruit) may help improve fasting glucose and insulin levels in individuals who are prediabetic or otherwise healthy. These supplements, without any expected adverse side effects, could be an effective compliment to lifestyle interventions aimed to reverse early glucose dysregulation.

CRediT authorship contribution statement

Jurriaan J. Mes: Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Maartje van den Belt:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Sandra van der Haar:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Els Oosterink:** Methodology, Investigation, Formal analysis. **Teus Luijendijk:** Writing – review & editing, Investigation, Formal analysis. **Koen Manusama:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Lotte van Dam:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Tessa de Bie:** Methodology, Investigation, Formal analysis. **Renger Witkamp:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Diederik Esser:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Informed consent statement

All the patients signed informed consent agreements before the trial.

Institutional review board statement

The studies were conducted according to the principles of the Declaration of Helsinki (64th WMA Assembly, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO, 1998). Both studies were approved by the local ethical committee (Study 1: METC 19/09, NL70259.081.19; Study 2: METC, 2021–13237, NL79294.091.21) and registered at ClinicalTrials.gov (Study 1: NCT04090788; Study 2: NCT05215210).

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available because they contain sensitive data that can identify but are available from the corresponding author on reasonable request.

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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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2025.119756.

Data availability

Data will be made available on request.

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