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EFFECT OF GLUCOMANNAN SUPPLEMENTATION ON BODY WEIGHT IN OVERWEIGHT AND OBESE CHILDREN: PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

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EFFECT OF GLUCOMANNAN SUPPLEMENTATION ON BODY WEIGHT IN OVERWEIGHT AND OBESE CHILDREN: PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

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Key words: glucomannan, obesity, treatment, children, adolescents

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ABSTRACT

Introduction

Glucomannan (GNN), a water-soluble dietary fiber derived from the plant *Amorphophallus konjac*, is marketed for weight reduction. The exact mechanisms by which GNN might exert its actions are unclear. However, it has been shown that GNN slows gastric emptying by forming a viscous gel of large volume, which increases the feeling of satiety. Current evidence on the effectiveness of GNN for weight reduction is sparse, and well-designed trials performed in children are needed to assess the efficacy of this modality. We aim to systematically evaluate the efficacy of GNN consumption for the management of overweight and obesity in children.

Methods and analysis

Children aged 6 to 17 years with overweight and obesity (based on the WHO growth criteria) will be randomly assigned to receive GNN or placebo (maltodextrin) (both at a dose of 3 g/day) for 3 months and will be followed up for 3 months. Prior to the intervention, all children will receive dietetic advice, and they will be encouraged to engage in physical activity. The primary outcome measure will be the BMI-for-age z-score difference between the groups at the end of the intervention.

Ethics and Dissemination

The study was approved by the Ethics Committee of the Medical University of Warsaw. The findings of this trial will be submitted to a peer-reviewed journal (pediatric, nutrition, or gastroenterology). Abstracts will be submitted to relevant national and international conferences.

Trial registration:

ClinicalTrials.gov: NCT02280772

Protocol ver.1 19.11.2014

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomized, double-blind, placebo-controlled trial will help to resolve the uncertainty regarding the role of glucomannan (GNN), a water-soluble dietary fiber derived from the plant *Amorphophallus konjac,* if any, in the management of children with overweight and obesity, one of the most common problems worldwide.
- This study will be performed at a research center with experience in conducting independent, investigator-initiated, randomized controlled trials.
- The study is a single-center study. GNN is not available worldwide. The generalizability of the study findings will depend on the setting.

INTRODUCTION

Background and rationale

Obesity is a major global health challenge[1], and there is continuous research directed at identifying interventions that will effectively help in body mass reduction. The current recommendations for weight management offer comprehensive lifestyle interventions, including counseling and education, aimed at reducing weight[2]. However, in clinical practice, patients have difficulty complying with these lifestyle interventions. The lack of an effective standard care for overweight and obese children stimulates research for supportive modalities[3].

In many countries, glucomannan (GNN), a water-soluble dietary fiber derived from the plant *Amorphophallus konjac*, is marketed for weight reduction. The exact mechanisms by which GNN might exert its actions are unclear. However, it has been shown that GNN slows gastric emptying by forming a viscous gel of large volume, which increases the feeling of satiety[4, 5].

Recently, we carried out a systematic review of randomized controlled trials (RCTs) to evaluate the effects of GNN on body weight and body mass index (BMI) in otherwise healthy overweight or obese children and adults. Limited data suggest that, in the short term, GNN has the potential to reduce body weight, but not BMI, in adults. Data in children were too limited to allow one to draw any conclusions. The overall quality of the trials was moderate, with small study groups and short times for the intervention and follow-up[6]. Considering that current evidence on the effectiveness of GNN in children is sparse, well-designed RCTs performed in children are needed to assess the efficacy of this modality.

Study objective

The aim of the study is to determine the effectiveness of GNN administration on body weight and BMI of overweight and obese children.

METHODS

Study design/setting

This study is designed as a parallel group, superiority, randomized, double-blind, placebo-controlled, single-center trial, with allocation 1:1. The recruitment of the study subjects will take place in the Department of Paediatrics, The Medical University of Warsaw, Poland (academic hospital).

Inclusion/exclusion criteria

At randomization, children eligible for the trial must comply with all of the following inclusion criteria:

- age 6-17 years;
- overweight or obesity based on the WHO growth charts/references (>+1 standard deviation [SD] or >+2 SD, respectively)

Exclusion criteria are as follows:

- drug therapy for a chronic disease (including drugs that influence appetite or body weight);

- type 1 or 2 diabetes;
- history of surgical treatment of obesity;
- participation in another program for treating obesity during the project and/or 3 months prior to recruitment;
- secondary causes of obesity;
- pregnancy.

Intervention

A summary of the trial is presented in **Table 1**. Eligible children will be randomly assigned to receive GNN or a comparable placebo (maltodextrin). Both products will be administered orally, at a dose of 3 g/d, for 3 months. Patients will be followed-up for the next 3 months to assess the retention of a possible effect.

The choice of maltodextrin as a placebo is based on the results of our systematic review[6] and a previous RCT carried out by our team[7].

The dose of GNN was based on the results of the systematic review by Sood et al.[8], which showed that a daily dose of 2-3 g was usually prescribed. In our systematic review[6], the only RCT performed in children showed no effect of GNN use (2 g/day) for 2 months. Therefore, we decided to use a dosage of GNN of 3 g/day (in three divided doses) for 12 weeks. The planned duration of the administration was based on the minimal time of an intervention for inclusion in the Cochrane Collaboration systematic review of interventions for treating obesity in children[9].

Both GNN and the placebo will be prepared by the hospital pharmacy in identical sachets. The contents of each sachet will need to be dissolved in water (approx. 200 ml). The administration of study products will start after a consultation with a dietitian (within 1 week after the enrollment visit).

The research team will monitor the study for acceptance of the study products and adverse events. If needed, discontinuation or modification of the treatment may be considered at the discretion of the physician.

A face-to-face adherence discussion will take place at the initial visit and at each study visit thereafter, emphasizing the importance of following study guidelines and the instructions about taking the study product. Participants will be asked to bring all remaining sachets (empty, half-empty, full) to each visit. To enhance validity of the data, sachets will be counted at each study visit. We will calculate the percentage adherence to therapy, based on the number of sachets consumed *vs.* anticipated sachet consumption.

Both groups will receive the same concomitant care.

1. Children and their caregivers will receive individually suited dietary advice based on the national daily allowances and physical activity levels. A dietician will perform a qualitative and quantitative analysis of the child's food intake, based on a 3-day food record (over 2 weekdays and 1 weekend day). This will be

then reviewed using the computer software DIETA 5.0; www.izz.waw.pl (2011, Warsaw, Poland). The Nutrition Standards for the Polish population will be used to calculate energy needs, considering the subject's age, sex, and level of physical activity[10]. No specific dietary plan, including calorie-restriction diets, will be prescribed. The consultation with a dietician is planned at the beginning of the study, at week 12, and at week 24.

2. All participants, at each program visit, will be encouraged to be physically active (with a goal of more than 60 min a day of a moderate-to-vigorous physical activity). However, otherwise, no specific physical activity plan will be advised.
3. Children and parents will be advised to limit sedentary/screen time to ≤ 2 hours a day[2].

Follow-up

All study participants will be followed up for the duration of the intervention (3 months) and then for an additional 3 months.

Outcomes

The *primary* outcome measure will be the BMI-for-age z-score difference (baseline *versus* end of the intervention) between the GNN and placebo groups at 12 weeks. According to Must and Anderson[11], this measure can be appropriately used as a comparison between group means and as a model of longitudinal weight trajectories.

BMI will be computed by dividing weight (kg) by height squared (m^2). The BMI-for-age z-score is the number of standard deviations by which the BMI in a child differs from the mean BMI of children of the same age and gender. It will be computed using the WHO AnthroPlus software v1.04. Body weight and height measurements will be obtained at the hospital at every study visit. Body weight (kg) will be measured using the Radwag digital scale to the nearest 0.1 kg without shoes, in light indoor clothing. Standing height (cm) will be measured using a stadiometer Holtain Ltd., to the nearest 0.1 cm, barefoot and the head positioned in the Frankfurt horizontal plane. For all measurements, we will ask the participants to visit a toilet before measurements.

The *secondary outcome measures* will include the following:

- *Body composition. Whole body fat, central body fat, fat-free mass (grams).* This outcome will be assessed by a dual energy X-ray absorption (DXA) technology, which is a valid and reliable methodology for quantifying body fat[12]. Participants will be positioned on the scanner table using standard procedures and total body cuts will be positioned as per standard manufacturer specifications. DXA scans will be performed at the baseline visit, and after the intervention period (week 13), using Lunar Prodigy (GE Healthcare, Little Chalfont, Buckinghamshire, UK) in the Department of Medical Imaging at the Children's Memorial Health Institute.
- *Change in BMI-for-age z-score between 0 and 24 weeks.*
- *Proportion of participants with dyslipidemia from baseline to week 12 and week 24* (mean change, SD).

- *Proportion of participants with impaired fasting plasma glucose (FPG), from baseline to week 12 and week 24* (mean change, SD).
  Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides in mg/dL) and fasting plasma glucose will be obtained at the baseline visit, at week 12, and at week 24 following an overnight fast in all participants with the use of standard methods at the hospital laboratory of the Medical University of Warsaw.
- *Energy intake (kJ/d) at baseline and at week 12, week 24.*
  Assessment will be based on self-written, 3-day food records (reviewed by a dietitian using the computer software DIETA 5.0; www.izz.waw.pl (2011, Warsaw, Poland)
- *Physical activity (h/w) at baseline and at week 12.*
  Physical activity will be assessed by the use of an accelerometer (Actigraph wGT3X-BT). Data will be analyzed using Actilife software (v.6; Actigraph).
- *Adverse events* (participants will be encouraged to report all possible adverse outcomes).

Sample size calculation

The primary endpoint is the difference in BMI-for-age z-scores between groups. Considering data from the literature[13], we assumed that the mean difference would be the value 0.17, with a standard deviation of 0.267. To detect this difference, with a power of 80% and a significance level of 5% and taking into account that 20% of the patients will be lost to follow up, we calculated that 48 patients will be needed to be studied in each group. The sample size calculation was performed using StatsDirect Ltd. StatsDirect statistical software (http://www.statsdirect.com. England: StatsDirect Ltd. 2013).

Recruitment

Participants will be recruited at the Department of Paediatrics. We will advertise our study among primary care physicians, targeting health care providers.

Our team has conducted a similar RCT, which enrolled 97 children over 23 months[7]. As the inclusion criteria are similar, we estimate 2 years will be sufficient for patient enrollment, and a further 3 months for data analysis. No incentives will be provided for study enrollment.

Sequence generation

Participants will be randomly assigned to either GNN or placebo groups with a 1:1 allocation by using a computer-generated randomization schedule stratified by gender and age (6 to 11 years, middle childhood; 12 to 17 years, early adolescence)[14] using permuted blocks of random sizes (the block size will be concealed until the end of the study). The randomization list will be developed by an independent investigator with no clinical involvement in the conduct of the trial.

Allocation concealment

Allocation concealment will be ensured using opaque, sealed, numbered envelopes. The study products will be weighed, packaged, and signed by consecutive numbers according to the randomization list by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the trial. The randomization sequence and codes will be secured until all participants have been recruited into the trial and all data have been analyzed.

Blinding

The study products (GNN and placebo) will be similar in terms of texture, smell, and color, and they will be packaged in identical sachets by the hospital pharmacy. All participants and investigators will be blinded to the assigned treatment throughout the study. Unblinding will occur after the final data analysis.

Statistical analysis

All analysis will be conducted on an intention-to-treat basis, including all patients in the groups to which they are randomized for whom outcomes will be available (including dropouts and withdrawals). Descriptive statistics will be used to summarize baseline characteristics. The Student t -test will be used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann–Whitney U test will be used. The X^2 test or Fisher exact test will be used, as appropriate, to compare percentages. The same computer software will be used to calculate the relative risk (RR), number needed to treat (NNT), and median difference (MD), all with a 95% CI. The difference between study groups will be considered significant when the P value is <0.05, when the 95% CI for RR does not include 1.0, or when the 95% CI for mean difference does not include 0. All statistical tests will be two tailed and performed at the 5% level of significance.

Ethics

The study protocol and the template consent forms were reviewed and approved of by the Ethics Committee of the Medical University of Warsaw. An informed written consent form will be signed by a parent or legal guardian (and patients ≥16 years) prior to the study enrollment. Any modifications to the protocol, which may impact the conduct of the study, potential benefits to the patients, or patient safety, including changes to the study design, will be reported to the Ethics Committee for all necessary amendments. All study-related information will be stored securely at the study site in locked cabinets, in an area with limited access (databases will be secured with a password-protected access system).

Dissemination

The findings of this RCT will be submitted to a peer-reviewed journal (pediatric, nutrition, or gastroenterology). Abstracts will be submitted to relevant national and international conferences.

CONCLUSIONS

The effectiveness of GNN for the management of overweight and obesity in children is still under discussion. A definitive answer has not yet been provided. Our study,

carried out at a research center with experience in conducting independent, investigator-initiated, randomized controlled trials, intends to address a gap in the field and tests the effectiveness of GNN for reducing body weight in overweight and obese children.

Authors' contributions

HS conceptualized the study. Both authors contributed to the design of the study and read and approved the manuscript. BZ developed the first draft of the manuscript. Both authors contributed to the development of the study protocol and approved the final draft of the manuscript.

Funding

This research will be fully funded by the Medical University of Warsaw.

Competing interest statements

BZ declares no conflict of interest. HS has participated as a speaker for Dicopharm, a manufacturer of GNN.

Table 1. Summary of the trial

	At enrollment	Randomization	Post-allocation				
Time-point		Start	Wk 6	Wk 12	Wk 13	Wk 18	Wk 24
Enrollment							
Eligibility screen	+						
Informed consent	+						
Randomization		+					
Product dispensation		+	+				
Interventions (week 0 – week 12)							
Follow–up (week 13 – week 24)							
Assessments							
Anthropometry	+	+	+	+		+	+
Body composition (DXA measurement)	+				+		
3-day food record	+			+			+
Dietician's assessment	+			+			+
Physical activity assessment	+			+			
Lipids and fasting plasma glucose	+			+			+
Return of unused study products			+	+			
Adverse events		+	+	+			

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1; 9
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4, 7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4, 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.1; 7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7/8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	-
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	-
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	In polish language
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Word count: 2653

ABSTRACT

Introduction

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Protocol ver. 2 26.01.2015

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- This randomized, double-blind, placebo-controlled trial will help to resolve the uncertainty regarding the role of glucomannan (GNN), a water-soluble dietary fiber derived from the plant *Amorphophallus konjac,* if any, in the management of children with overweight and obesity, one of the most common problems worldwide.
- This study will be performed at a research center with experience in conducting independent, investigator-initiated, randomized controlled trials.
- The study is a single-center study. GNN is not available worldwide. The generalizability of the study findings will depend on the setting.
- The dosing of GNN is not clearly established.
- There is no long-term follow-up.

INTRODUCTION

Background and rationale

Obesity is a major global health challenge,[1] and there is continuous research directed at identifying interventions that will effectively help in body mass reduction. The current recommendations for weight management offer comprehensive lifestyle interventions, including counseling and education, aimed at reducing weight.[2] However, in clinical practice, patients have difficulty complying with these lifestyle interventions. The lack of an effective standard care for overweight and obese children stimulates research for supportive modalities.[3]

In many countries, glucomannan (GNN), a water-soluble dietary fiber derived from the plant *Amorphophallus konjac*, is marketed for weight reduction. The exact mechanisms by which GNN might exert its actions are unclear. However, it has been shown that GNN slows gastric emptying by forming a viscous gel of large volume, which increases the feeling of satiety.[4, 5]

Recently, we carried out a systematic review of randomized controlled trials (RCTs) to evaluate the effects of GNN on body weight and body mass index (BMI) in otherwise healthy overweight or obese children and adults. Limited data suggest that, in the short term, GNN has the potential to reduce body weight, but not BMI, in adults. Data in children were too limited to allow one to draw any conclusions. The overall quality of the trials was moderate, with small study groups and short times for the intervention and follow-up.[6] Earlier systematic review, however including only RCTs carried out in adults, revealed a non-significant difference in weight loss between GNN and placebo groups.[7] Considering that current evidence on the effectiveness of GNN in children is sparse, well-designed RCTs performed in children are needed to assess the efficacy of this modality.

Study objective

The aim of the study is to determine the effectiveness of GNN administration on body weight and BMI of overweight and obese children.

METHODS

Study design/setting

This study is designed as a parallel group, superiority, randomized, double-blind, placebo-controlled, single-center trial, with allocation 1:1. The recruitment of the study subjects will take place in the Department of Paediatrics, The Medical University of Warsaw, Poland (academic hospital).

Inclusion/exclusion criteria

At randomization, children eligible for the trial must comply with all of the following inclusion criteria:

- age 6-17 years;
- overweight or obesity based on the WHO growth charts/references (>+1 standard deviation [SD] or >+2 SD, respectively)

Exclusion criteria are as follows:

- drug therapy for a chronic disease (including drugs that influence appetite or body weight);
- type 1 or 2 diabetes;
- history of surgical treatment of obesity;
- participation in another program for treating obesity during the project and/or 3 months prior to recruitment;
- secondary causes of obesity;
- pregnancy.

Intervention

A summary of the trial is presented in **Table 1**. Eligible children will be randomly assigned to receive GNN or a comparable placebo (maltodextrin). Both products will be administered orally, at a dose of 3 g/d, for 3 months. Patients will be followed-up for the next 3 months to assess the retention of a possible effect.

The choice of maltodextrin as a placebo is based on the results of our systematic review and a previous RCT carried out by our team.[7,8]

The dose of GNN was based on the results of the systematic review by Sood et al.,[9] which showed that a daily dose of 2-3 g was usually prescribed. In our systematic review,[7] the only RCT performed in children showed no effect of GNN use (2 g/day) for 2 months. Therefore, we decided to use a dosage of GNN of 3 g/day (in three divided doses) for 12 weeks. The planned duration of the administration was based on the minimal time of an intervention for inclusion in the Cochrane Collaboration systematic review of interventions for treating obesity in children.[10]

Both GNN and the placebo will be manufactured and supplied by Dicofarm SpA (Rome, Italy) as capsules in identical packing. The manufacturer had no role in the conception or design of the study, and will have no role in the conduct of the study, or in the analysis or interpretation of the data. The administration of study products will start after a consultation with a dietitian (within 1 week after the enrollment visit).

The research team will monitor the study for acceptance of the study products and adverse events. If needed, discontinuation or modification of the treatment may be considered at the discretion of the physician.

A face-to-face adherence discussion will take place at the initial visit and at each study visit thereafter, emphasizing the importance of following study guidelines and the instructions about taking the study product. Participants will be asked to bring all remaining capsules to each visit. To enhance validity of the data, capsules will be counted at each study visit. We will calculate the percentage adherence to therapy, based on the number of capsules consumed *vs.* anticipated capsules consumption.

Both groups will receive the same concomitant care.

1. Children and their caregivers will receive individually suited dietary advice based on the national daily allowances and physical activity levels. A dietician will perform a qualitative and quantitative analysis of the child's food intake, based on a 3-day food record (over 2 weekdays and 1 weekend day). This will be then reviewed using the computer software DIETA 5.0; www.izz.waw.pl (2011, Warsaw, Poland). The Nutrition Standards for the Polish population will be used to calculate energy needs, considering the subject's age, sex, and level of physical activity.[11] No specific dietary plan, including calorie-restriction diets, will be prescribed. The consultation with a dietician is planned at the beginning of the study, at week 12, and at week 24.
2. All participants, at each program visit, will be encouraged to be physically active (with a goal of more than 60 min a day of a moderate-to-vigorous physical activity). However, otherwise, no specific physical activity plan will be advised.
3. Children and parents will be advised to limit sedentary/screen time to ≤ 2 hours a day.[2]

At entry, maturity stage will be assessed according to the criteria of Tanner for secondary sexual characteristics.

Follow-up

All study participants will be followed up for the duration of the intervention (3 months) and then for an additional 3 months.

Criteria for discontinuing interventions

Participants may discontinue trial at their request or upon the occurrence of serious adverse events.

Outcomes

The *primary* outcome measure will be the BMI-for-age z-score difference (baseline *versus* end of the intervention) between the GNN and placebo groups at 12 weeks. According to Must and Anderson,[12] this measure can be appropriately used as a comparison between group means and as a model of longitudinal weight trajectories.

BMI will be computed by dividing weight (kg) by height squared (m^2). The BMI-for-age z-score is the number of standard deviations by which the BMI in a child differs from the mean BMI of children of the same age and gender. It will be computed using the WHO AnthroPlus software v1.04. Body weight and height measurements will be obtained at the hospital at every study visit. Body weight (kg) will be measured using the Radwag digital scale to the nearest 0.1 kg without shoes, in light indoor clothing. Standing height (cm) will be measured using a stadiometer Holtain Ltd., to the nearest 0.1 cm, barefoot and the head positioned in the Frankfurt horizontal plane. For all measurements, we will ask the participants to visit a toilet before measurements.

The *secondary outcome measures* will include the following:

- *Body composition. Whole body fat, central body fat, fat-free mass (grams).*

This outcome will be assessed by a dual energy X-ray absorption (DXA) technology, which is a valid and reliable methodology for quantifying body fat.[13] Participants will be positioned on the scanner table using standard procedures and total body cuts will be positioned as per standard manufacturer specifications. DXA scans will be performed at the baseline visit, and after the intervention period (week 13), using Lunar Prodigy (GE Healthcare, Little Chalfont, Buckinghamshire, UK) in the Department of Medical Imaging at the Children's Memorial Health Institute.

- *Change in BMI-for-age z-score between 0 and 24 weeks.*
- *Proportion of participants with dyslipidemia from baseline to week 12 and week 24* (mean change, SD).
- *Proportion of participants with impaired fasting plasma glucose (FPG), from baseline to week 12 and week 24* (mean change, SD).

  Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides in mg/dL) and fasting plasma glucose will be obtained at the baseline visit, at week 12, and at week 24 following an overnight fast in all participants with the use of standard methods at the hospital laboratory of the Medical University of Warsaw.
- *Blood pressure (systolic and diastolic, mean change, SD)*

  Three individual blood pressure measurements (mmHg) and pulse rates (bpm) will be taken in the sitting position on right hand according to the accepted standards at each study visit by use of automatic oscillometer.[14] Briefly, two readings will be taken at intervals of at least 1 minute, and the average of those readings will be used for analysis. However, when difference between the first and second reading will be ≥5 mm Hg additional (1 or 2) readings will be obtained. Mean change from baseline to week 12 and week 24 will be calculated as an outcome.
- *Energy intake (kJ/d) at baseline and at week 12, week 24.*

  Assessment will be based on self-written, 3-day food records (reviewed by a dietitian using the computer software DIETA 5.0; www.izz.waw.pl (2011, Warsaw, Poland)
- *Physical activity (h/w) at baseline and at week 12.*

  Physical activity will be assessed by the use of an accelerometer (Actigraph wGT3X-BT). Data will be analyzed using Actilife software (v.6; Actigraph).
- *Adverse events* (participants will be encouraged to report all possible adverse outcomes).

Sample size calculation

The primary endpoint is the difference in BMI-for-age z-scores between groups. Considering data from the literature,[15] we assumed that the mean difference would be the value 0.17, with a standard deviation of 0.267. To detect this difference, with a power of 80% and a significance level of 5% and taking into account that 20% of the patients will be lost to follow up, we calculated that 48 patients will be needed to be studied in each group. The sample size calculation was performed using StatsDirect Ltd. StatsDirect statistical software (http://www.statsdirect.com. England: StatsDirect Ltd. 2013). To assist in achieving this sample size, participants

will be offered flexible appointment times.

Recruitment

Participants will be recruited at the Department of Paediatrics. We will advertise our study among primary care physicians, targeting health care providers.

Our team has conducted a similar RCT, which enrolled 97 children over 23 months.[8] As the inclusion criteria are similar, we estimate 2 years will be sufficient for patient enrollment, and a further 3 months for data analysis. No incentives will be provided for study enrollment.

Sequence generation

Participants will be randomly assigned to either GNN or placebo groups with a 1:1 allocation by using a computer-generated randomization schedule stratified by gender and age (6 to 11 years, middle childhood; 12 to 17 years, early adolescence) using permuted blocks of random sizes (the block size will be concealed until the end of the study).[16] The randomization list will be developed by an independent investigator with no clinical involvement in the conduct of the trial.

Allocation concealment

Allocation concealment will be ensured using opaque, sealed, numbered envelopes. The study products will be weighed, packaged, and signed by consecutive numbers according to the randomization list by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the trial. The randomization sequence and codes will be secured until all participants have been recruited into the trial and all data have been analyzed.

Blinding

The study products (GNN and placebo) will be identically packaged capsules. All participants and investigators will be blinded to the assigned treatment throughout the study. Unblinding will occur after the final data analysis.

Statistical analysis

All analysis will be conducted on an intention-to-treat basis, including all patients in the groups to which they are randomized for whom outcomes will be available (including dropouts and withdrawals). Descriptive statistics will be used to summarize baseline characteristics. The Student t -test will be used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann–Whitney U test will be used. The X^2 test or Fisher exact test will be used, as appropriate, to compare percentages. The same computer software will be used to calculate the relative risk (RR), number needed to treat (NNT), and mean difference (MD), all with a 95% CI. The difference between study groups will be considered significant when the P value is <0.05, when the 95% CI for RR does not include 1.0, or when the 95% CI for mean difference does not include 0. All statistical tests will be two tailed and performed at the 5% level of significance.

Methods for additional analyses

Both the primary and secondary outcomes will be analyzed using analysis of covariance (adjusted for the baseline value). Potential effect modification (confounding) due to any chance imbalance in pubertal status, age, and sex will be counteracted by inclusion of these in a secondary analysis, using a multifactorial regression analysis.

Missing data

Every effort will be made to minimize missing baseline and outcome data. The amount of missing data will be reported for each randomized arm. If necessary, multiple imputation or Bayesian methods for missing data will be used as appropriate to address any missing data[17,18].

Ethics

The study protocol and the template consent forms were reviewed and approved of by the Ethics Committee of the Medical University of Warsaw. An informed written consent form will be signed by a parent or legal guardian (and patients ≥16 years) prior to the study enrollment. Any modifications to the protocol, which may impact the conduct of the study, potential benefits to the patients, or patient safety, including changes to the study design, will be reported to the Ethics Committee for all necessary amendments. All study-related information will be stored securely at the study site in locked cabinets, in an area with limited access (databases will be secured with a password-protected access system).

Dissemination

The findings of this RCT will be submitted to a peer-reviewed journal (pediatric, nutrition, or gastroenterology). Abstracts will be submitted to relevant national and international conferences. The results of the study will be available to the participants upon request during a face-to-face meeting.

CONCLUSIONS

The effectiveness of GNN for the management of overweight and obesity in children is still under discussion. A definitive answer has not yet been provided. Our study, carried out at a research center with experience in conducting independent, investigator-initiated, randomized controlled trials, intends to address a gap in the field and tests the effectiveness of GNN for reducing body weight in overweight and obese children.

Authors' contributions

HS conceptualized the study. Both authors contributed to the design of the study and read and approved the manuscript. BZ developed the first draft of the manuscript. Both authors contributed to the development of the study protocol and approved the final draft of the manuscript.

Funding

This research will be fully funded by the Medical University of Warsaw.

Competing interest statements

BZ declares no conflict of interest. HS has participated as a speaker for Dicopharm, a manufacturer of GNN.

Data sharing

No additional data available.

Table 1. Summary of the trial

	At enrollment	Randomization	Post-allocation				
Time-point		Start	Wk 6	Wk 12	Wk 13	Wk 18	Wk 24
Enrollment							
Eligibility screen	+						
Informed consent	+						
Maturity stage (the criteria of Tanner)	+			+			+
Randomization		+					
Product dispensation		+	+				
Interventions (week 0 – week 12)							
Follow–up (week 13 – week 24)							
Assessments							
Anthropometry	+	+	+	+		+	+
Body composition (DXA measurement)	+				+		
3-day food record	+			+			+
Dietician's assessment	+			+			+
Physical activity assessment	+			+			
Lipids and fasting plasma glucose	+			+			+
Blood pressure measurement	+		+	+		+	+
Return of unused study products			+	+			
Adverse events		+	+	+			

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1; 9
	5b	Name and contact information for the trial sponsor	n/a-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4, 7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6~~n/a~~
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4, 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.1; 7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7,8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	87
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7/8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6,7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not planned-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	No limits-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Comment: Harm from trial unlikely, post-trial care will be covered within mandatory health insurance	

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a~~-~~
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	no plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9 ~~In polish language~~
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.